Studies of the Lewis Acidity of Dicarbonyl Iodonium Ylides in Ionic and Photochemical Reactions

by

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Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Statement of Contributions

Islam was the sole author for Chapters 1, 2, and 3 which were written under the supervision of Prof. Graham Murphy and were not written for publication. I would like to acknowledge the work of Tristan Chidley who helped me with developing the theory in Chapter 2, also for being a big part of discovering S-H insertion reaction of thiols into iodonium ylides, and for synthesizing some of the products in Chapter 2 and some of the ylides in Chapter 3. Dr. Scott Hopkins performed ESP mapping of iodonium ylides in Chapter 2.

Abstract

Hypervalent iodine compounds have been established as useful reagents in synthetic chemistry due to their ease of handling and the diverse amount of chemical reactivity that can be accessed under mild reaction conditions. Iodonium ylides comprise an important class of hypervalent iodine reagents. They function as carbene transfer reagents with many different applications. They are also a safer alternative to diazo compounds. This thesis will focus on understanding the σ-holes in iodonium ylides and using this knowledge to develop new reactions. For this purpose, Chapter 1 introduces hypervalent iodine reagents and the synthesis and properties of iodonium ylides. Then, σ-holes are discussed with many examples of their applications in chemical reactions between iodonium ylides and nucleophiles.

In Chapter 2, computational analysis is used to view the σ-holes of iodonium ylides. Then a new theory is developed to understand the link between the existence of two σ-holes and the regioselectivity observed in the reactions of iodonium ylides with different nucleophiles. Understanding the Lewis-acidic nature of iodonium ylides and the presence of two σ-holes was used to promote O-H insertion of carboxylic acid and S-H insertion of thiols into the dicarbonyl motif of iodonium ylides. The halogen-bonding interactions between the iodine center of the ylide and the heteroatoms of the reaction partner (O or S) facilitate the transfer of hydrogen to the $\alpha-$carbon of the dicarbonyl motif of the ylide. Then, reductive elimination takes place to produce the final product. Both insertion reactions have wide substrate scope under mild conditions and give excellent yields.

In Chapter 3, the reaction between iodonium ylides and alkynes is investigated. In 2019, the Murphy Group discovered that blue light ($\lambda_{max} = 461$ nm) irradiation of a β-dicarbonyl-derived iodonium ylide and an alkene offers a highly chemoselective synthesis of doubly activated cyclopropanes, presumably via a diradical intermediate. Replacing alkenes with alkynes in this reaction resulted in furans, and using substituted iodonium ylides as substrates could result in the development of a metal-free method for the synthesis of substituted furans. This is important due to the countless occurrences of substituted furans in medicinal chemistry.

Acknowledgments

I would like to thank my supervisor, Dr. Murphy, for believing in me to work in his research group. His encouragement, support, and expectation of high standards pushed me to be the chemist I am today. For that opportunity, I am most grateful. I also appreciate all the things he did for me—sending me to conferences and encouraging me to seek opportunities. I also would love to extend my gratitude to my committee members, Dr. Eric Fillion and Dr. Michael Chong, for their valuable knowledge and help they provided me with. Dr. Scott Hopkins made a substantial impact on my work with his expertise in computational chemistry; many thanks to him for answering my questions and all his help.

The people I worked with were a big part of my growth. I appreciate the Murphy Group members for all their help. Special thanks to Tristan Chidley for teaching me a lot about laboratory techniques, organic reactions, and hypervalent iodine and for sharing with me critical tips and tricks for compound purifications. His knowledge offered to me cannot be repaid with anything. He was also a role model and someone I will always look up to. I also thank Avery To for all our interesting chemistry discussions and Fabio for his help with using mass spectrometer. Moreover, I am grateful to my co-op student, Cassio, for helping me with my research. I was thrilled to train him and was impressed by his work ethic and dedication.

The technicians who worked very hard behind the scenes to make this research possible at the University of Waterloo deserve much appreciation. A thank you is also extended to Jan Venne for helping me with the NMR spectroscopy, Dr. Richard Smith for his help with mass spectrometry, and Dr. Mónica Barra for providing access to UV-spectroscopy. Thank you to Catherine Van Esch and Kim Rawson for helping me apply to graduate school and their administrative assistance help. A big thank you to Hilly and Wayne, the janitors, for maintaining our building and checking up on me during my long nights at the laboratory.

Last but not least, my family is much deserving of my immense love and gratitude. No words can describe how much love and support they have given to me, they were my source of motivation and happiness.

Dedication

Dedicated to my family

My dad, Mohammed, my mum, Ashwak, my siblings, Duaa, Abdullah and Tuqa

And to the chemist Dr. Tristan Chidley

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List of Abbreviations

ABX	1-azido-1,2,benziodoxol-**3-**(1*H*)-one
Ac	acetyl
aq.	aqueous
Ar	aryl
Bn	benzyl
BO	bond order
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
BX	benziodoxole
Bz	benzoyl
C	Celsius
calcd	calculated
cat.	catalytic
cf.	confer (compare)
cm^{-1}	reciprocal centimetre
concd	concentrated
concn	concentration
d	doublet
dd	doublet of doublets
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulphoxide
dr	diastereomeric ratio
E	electrophilicity parameter
EDG	electron donating group
ee	enantio excess
e.g.	exempli gratia ("for example")
eq	equation
equiv.	equivalent(s)
ESI	electrospray ionization
Esp	α, α, α', α'- tetramethyl-1,3-benzenedipropionate)
Et	ethyl
et al.	et alia (and others)

etc	et cetera (and so forth)
EWG	electron withdrawing group
FCC	flash column chromatography
g	gram
GC	gas chromatography
Gem	geminal
GP	general procedure
h	hour
HMDSO	hexamethyldisiloxane
HOMO	Highest Occupied Molecular Orbital
HVI	hypervalent iodine
Hz	Hertz
i	iso
IBX	2-iodoxybenzoic acid
IR	Infrared Spectroscopy
i.e.	*id est* (that is)
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
$k20\ °C$	rate constant (determined at 20 °C)
k	rate constant
L	ligand
LED	Light-Emitting Diode
LG	leaving group
LUMO	lowest unoccupied molecular orbital
m	multiplet
m	meta
M	molar
*m*CPBA	*m*-chloroperbenzoic acid
Me	methyl
mg	milligram
MHz	megaHertz
min	minute(s)
mL	millilitre
mmol	millimole
MO	molecular orbital
mp	melting point
mol	mole
MS	mass spectrometry

m/z	mass to charge ratio
μL	microliter
μm	micrometre
μmol	micromole
nb	nonbonding
NMR	nuclear magnetic resonance
NR	no reaction
Nu	nucleophile
o	*ortho*
[O]	oxidation
OTf	trifluoromethanesulfonate
p	*para*
PFA	perfluoroalkoxy alkanes
Ph	phenyl
PIDA	phenyliodine diacetate
ppm	parts per million
Pr	propyl
py	pyridine
q	quartet
R	substituent
R_f	retention factor
rt	room temperature
s	singlet
SATP	symmetry-adapted perturbation theory
sept	septet
t	triplet
t	*tert*
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TLC	thin layer chromatography
THF	tetrahydrofuran
TMS	trimethylsilyl
UV	ultraviolet
v	volume
vs	versus
VSEPR	valence shell electron pair repulsion
wt	weight

X	electronegative group or atom
XB	halogen bonding

List of Symbols

Å	angstrom
~	approximately
δ	chemical Shift
°	degrees
=	equal to
ν	frequency
σ	sigma bonding orbital
σ*	sigma antibonding orbital
ρ	Hammett reaction constant
Δ	heat
μ	micro
π	Pi bond
π*	Pi anti-bond
h	Planck's Constant
Ψ	pseudorotation
λ	Wavelength

List of Schemes

بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

In the name of God, **Most Gracious**, **Most Merciful**

Chapter 1: Introduction

1.1   General Introduction

Iodine-containing compounds are among the most important building blocks in organic synthesis.[1] These compounds can undergo a variety of transformations via photo-initiated, thermal, or transition metal-catalyzed reactions, which allows for the synthesis of a variety of valuable organic compounds.[1] Many books have been dedicated to understanding and analyzing their reactivity, and over the last few decades there have been numerous discoveries in the field of hypervalent iodine chemistry. This chapter discusses hypervalent iodine chemistry in order to enable a better understanding of the research performed in the following chapters.

1.2   Iodine

During the Napoleonic Wars in the early 1800s the French chemist Bernard Courtois of Paris manufactured saltpeter (potassium nitrate, KNO_3), which is an important component in gunpowder.[2] After he ran out of wood ash as the source of potassium, he used seaweed (**Figure 1.1**).[3] During the manufacturing process he mistakenly added excess sulfuric acid that
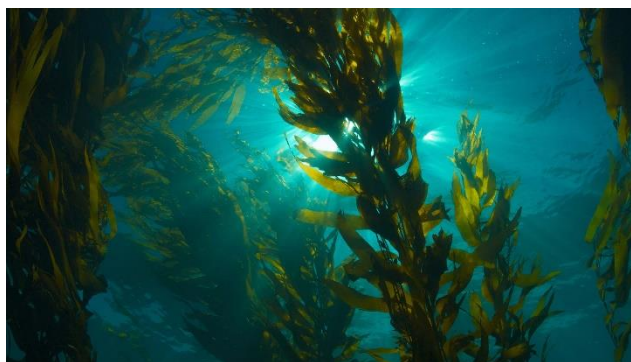
Figure 1.1. Seaweed

resulted in the emission of purple fumes which condensed to form crystals with a metallic luster. Courtois believed it to be a new element and he consulted physicists Charles-Bernard Desormes and Nicolas Clément who conducted a systematic investigation and confirmed that it indeed, was a new element.[4] In November 1813, iodine was introduced as a new element at the Imperial Institute in Paris. Joseph Gay-Lussac named it after the Greek word ἰώδης meaning "violet-colored."[5]
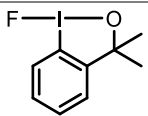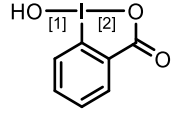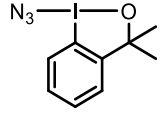
Iodine was found to be the heaviest, non-radioactive element in the periodic table, which is classified as a halogen. The formal electron configuration of iodine is $[Kr]d^{10}s^2p^5$ with seven electrons in its valence shell. Iodine is the largest, the least electronegative, and the most polarizable of all the halogens.[6] Due to its unique properties, iodine has been found to have many uses in its pure form (I_2)[7, 8] or contained within organic compounds, known as organoiodines.[9,10] For instance, I_2 can be used as a catalyst for many multicomponent reactions, enabling multiple bonds to form in one step, thereby reducing time and saving money, energy, and raw materials.[7] Catalytic loading of I_2 facilitates the synthesis of 2,4,6-triarylpyridines in a solvent-free multicomponent coupling reaction of aryl aldehydes and ammonium acetate to generate 2,4,6-triarylpyridines in moderate yields, as shown in **Scheme 1.1**.[7]
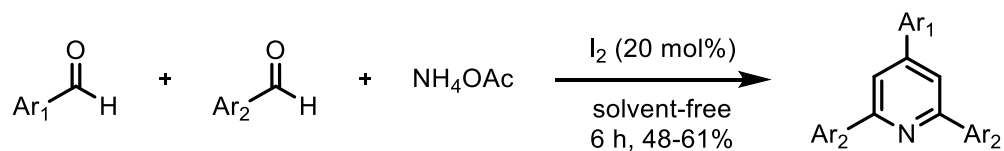
Scheme 1.1. Iodine catalyzed synthesis of the 2,4,6-triarylpyridines

Iodine-containing reactants are common in organic synthesis due to their ease of formation or cleavage of the C-I bond, which is the weakest of the carbon–halogen bonds. The bond dissociation energies (ΔHf_{298}) and bond length of iodine within various compounds are shown in **Table 1.1**.

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Table 1.1. Bond dissociation energies (ΔHf_{298}) and bond length for common iodine bonds in known compounds. ΔHf_{298} Values refer to the gaseous state and are given at 298 K.[11]

Covalent bond	ΔHf_{298}, kJ/mol	Bond length, Å	Compound
I-I	150.9	2.68[12]	I_2
I-C	213	2.14[13]	CH_3I
I-H	289.7	1.61[14]	HI
I-F	280(4)	2.05[15]	
I-O	184(21)	[1] 2.00 [2] 2.03[16]	
I-N	159(17)	2.18[17]	Zhdankin reagent

1.3   Hypervalency

In 1916 Gilbert N. Lewis introduced the "rule of eight" and this became a critical scientific concept which was later named the "octet rule."[18, 19] This rule states that "a stable arrangement is gained when the valence shell of an atom is surrounded by eight electrons, thereby attaining a similar electron configuration as the noble gases."[19] This octet is the sum of the atom's valance electrons and the electrons shared with other atoms. Thus, an atom continues to form bonds until an octet of electrons is made. The octet rule serves to help predict the position and bonding of the atoms and lone pairs of electrons that make up a molecule.[20] Although this theory is useful in understanding molecular bonding, it is not directly compatible with molecules containing atoms with expanded octets.[21,22,23,24]

In 1969 Jeremy I. Musher coined the term hypervalent to describe the ability of molecules to contain non-metallic elements within groups 15-18 with an expanded octet in their valence electron shell.[25,26] When iodine exists in higher oxidation states (+3, +5, and +7), it fits the hypervalency definition. When counting the electrons in the valance shell in hypervalent iodine

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compounds without considering the bond character, single or double bond, one may find an expanded octet, and thereby conclude that iodine is hypervalent in hypervalent iodine molecules.[27,28]

1.4   Iodine as a Hypervalent Element

Iodine's unique properties such as its electronic makeup and large atomic radius allow it to form stable poly-coordinate, multivalent compounds. Iodine is also able to form up to seven bonds (3, 5, or 7 bonds for neutral compounds, and 2, 4, or 6 bonds in charged species).[6] The bonding partners are commonly referred to as ligands. While iodine can exist in various oxidation states ranging from –1 to +7, it prefers to have an oxidation state of –1.[6] Iodine in hypervalent compounds is labeled as an oxidant,, which is considered incorrect in some cases when formally applying the reported electronegativity values. For example, carbon-centered ligands are less electronegative than iodine. Hence, the nomenclature of hypervalent compounds is based on their number of bonding interactions, instead of the oxidation states. Two different nomenclatures have emerged: the IUPAC and the *Martin-Arduengo* nomenclatures. The IUPAC rules designate λ as the non-standard bonding; thus, λ^3-iodine compounds possess three bonds, while the descriptors λ^5- and λ^7-iodine refer to five and seven bonds, respectively.[29] Polyvalent iodine species differ in *Martin-Arduengo* nomenclature (N-XL), where N is the number of valence electrons in the central atom, X is the central atom, and L is the total number of ligands.[30] *Martin-Arduengo* nomenclature is the most precise description of hypervalent compounds. According to the two forms of nomenclatures, IUPAC and *Martin-Arduengo,* PhI=O would be described as a λ^3-iodane or a 10-*I*-3 species, respectively. Similarly, Dess-Martin periodinane (DMP) would be a λ^5-iodane or a 12-*I*-5 compound, and IF_7 would be a λ^7-iodane or a 14-*I*-7 substance (**Figure 1.2**).

λ^3-Iodanes

10-I-3   10-I-3   8-I-2

λ^5-Iodanes

DMP: *12-I-5*   IBX: *12-I-4*

λ^7-Iodanes

IF$_7$
14-I-7
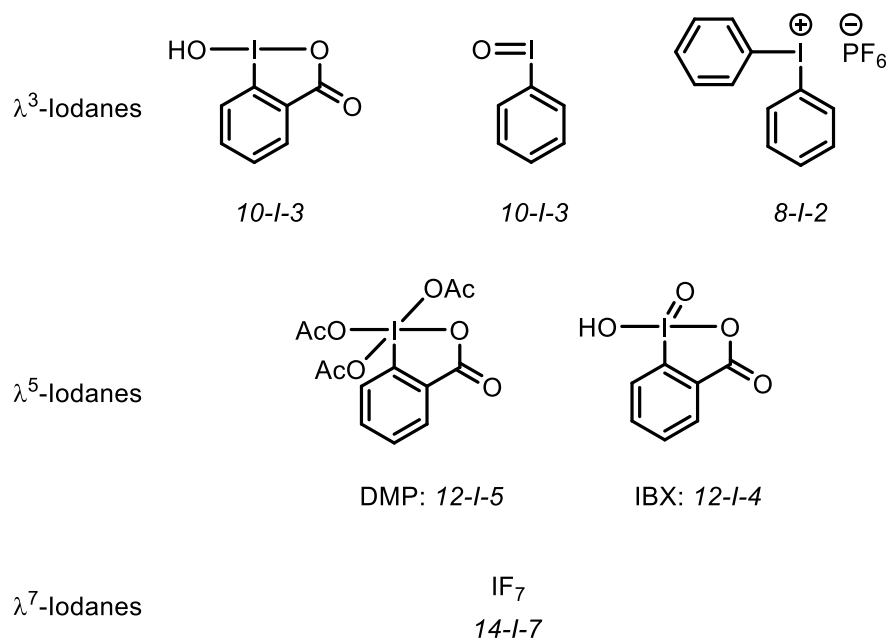
Figure 1.2. Examples of λ^3-, λ^5-, and λ^7-iodanes with their respective *Martin-Arduengo* nomenclature

Now that the formal nomenclature for hypervalent iodine compounds has been established, it has become more relevant to discuss their electronic and structural features. Owing to its large atom size, iodine's bond description differs from that of other light main group elements.[6] In hypervalent iodine molecules, the iodine center does not participate in forming double or triple bonds with lighter *p*-block elements because of the large difference in orbital sizes. The VSEPR model predicts that λ^3-iodine (*iodane*) compounds resemble a T-shaped structure with the two remaining electron pairs in equatorial positions. In the mid-twentieth century, G. C. Pimentel and R. E. Rundle independently proposed the concept of a three-center-four-electron (3C-4e) bond model based on the molecular orbital theory regarding λ^3-iodine compounds.[31,32] The fundamental description of the 3C-4e bond for L-X-L states that one pair of bonding electrons is delocalized to the two ligands, resulting in the charge distribution of almost -0.5 to each ligand and +1.0 to the central iodine atom.[6] In iodine (III) molecules, iodine's filled $5p$ orbital interacts with the half-filled orbitals of the two ligands at the apical position to form three molecular orbitals: bonding, nonbonding, and antibonding (**Figure 1.3**).[6] The iodine and aryl group contains overlapping orbitals that form a conventional two-center-two-electron (2C-2e) covalent, carbon-iodine σ-bond

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with $5sp^2$ hybridization. The highest occupied molecular orbital (HOMO) of the 3C-4e has a node at the central atom, hence, the hypervalent bond is highly polarized in nature. Therefore, the hypervalent molecule is arranged such that more electronegative atoms occupy the axial positions formed by the interaction of the orbitals of three collinear atoms.[6] The geometry of hypervalent iodine (III) is described as pseudotrigonal bipyramid with two electron pairs and the least electronegative carbon ligand in the equatorial position, while the two more electronegative ligands occupy the apical positions.[6] Neutral pentavalent iodine compounds (*periodinanes*) have a square pyramidal geometry with the description of two orthogonal 3C-4e bonds.
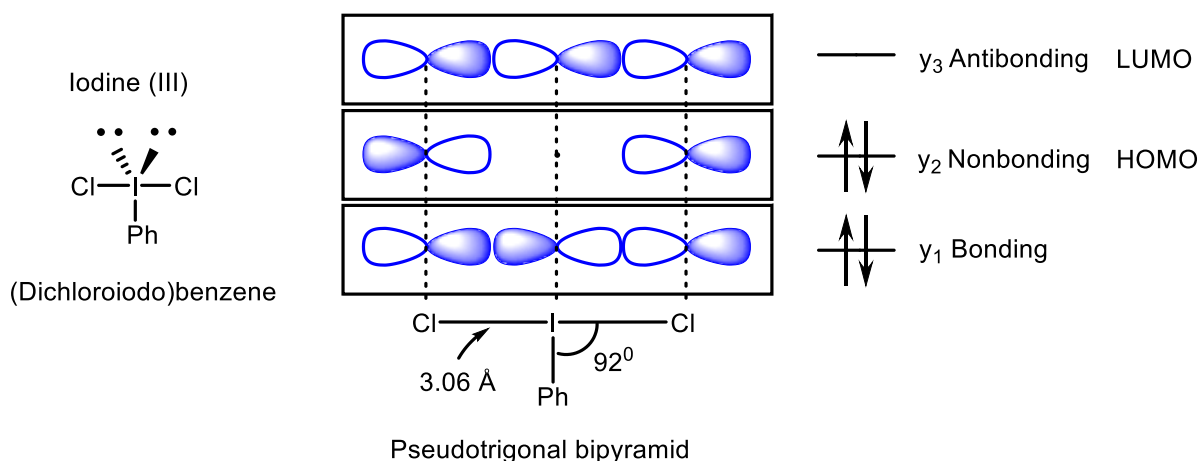
Figure 1.3. Molecular orbital description of the 3C-4e bond in hypervalent iodine(III) molecules

1.5   Reactivity Modes of Hypervalent Iodine Compounds

Hypervalent iodine reagents resemble transition metal salts in terms of reactivity, resulting from the strongly electrophilic properties of iodine that make it susceptible to nucleophilic attack. The reactions of hypervalent iodine-based reagents are commonly discussed using terms such as oxidative addition, ligand exchange, and reductive elimination (or ligand coupling) all of which are also typically used when working with transition metal salts. Homolytic and single-electron transfer (SET) pathways are also frequently observed under appropriate conditions. The hypervalent bonds in the apical position are easily cleaved due to the stability gained when

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reducing trivalent iodine, containing 10 electrons, into a more stable monovalent iodine with a full octet. Hence, the favorable reduction of the hypervalent iodine to normal valency (III → I) by reductive elimination of iodobenzene is the key driving force to its reactivity (**Scheme 1.2**).
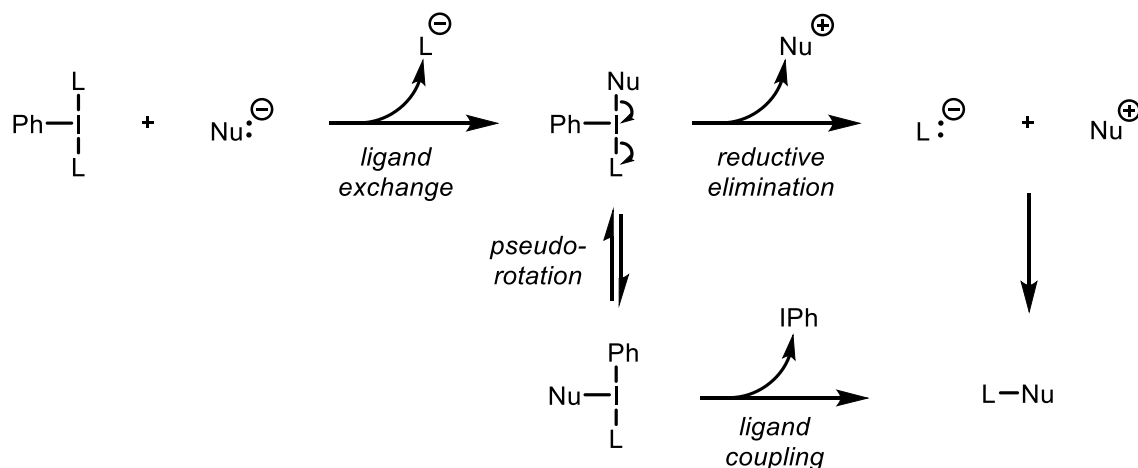
Scheme 1.2. A simplified description of the reaction of λ^3-iodanes with nucleophiles (Nu)

For hypervalent iodine reagents undergoing ligand substitution there are essentially two different reaction mechanisms, an associative pathway, and a dissociative pathway. The associative pathway of ligand exchange is initiated with the addition of a nucleophile to the partially positive iodine center of λ^3-iodanes that form *trans* hypervalent 12-*I*-4 square-planar species. The intermediate then isomerizes into the *cis* 12-*I*-4 square-planar intermediate and eliminates the ligand L to afford the final product (**Scheme 1.3**). This mechanism has been confirmed by the isolation of stable 12-*I*-4 species and analysis of their structures using X-ray.[33] For instance, tetrachloroiodate anion ICl_4, which is formed by the interaction of ICl_3 with chloride, has a distorted square-planar structure that was established using an X-ray analysis of the trichlorosulfonium salt Cl_3S^+ ICl_4^-.[33]

The dissociative pathway starts when the departing ligand leaves, generating a coordinatively unsaturated intermediate iodonium ion $[PhIL]^+$. An incoming ligand then enters the coordination sphere of iodine to generate the product. The dissociative pathway seems to be less likely to occur due to the low stability of the dicoordinated iodonium ion $[PhIL]^+$ involved in this

mechanism.[34] However, iodonium ions have been detected in the gas phase, for example, in mass spectrometry studies of protonated iodosobenzene [PhIOH]$^+$.[34] It was also observed that iodonium species in solution are coordinated with a counteranion that, in some cases, was a solvent molecule. In an aqueous solution the presence of cationic iodonium species has also been confirmed by spectroscopic measurements and potentiometric titrations of PhI(OH)OTs and PhI(OH).[35] The X-ray diffraction performed on aqueous solutions of hypervalent iodine reagents shows a T-shaped structure ligated with the water molecule at the apical site of the iodine(III) atom, with a near-linear O-I-O triad (173.96°) that is consistent with the λ^3-iodanes structure.[35]

Associative pathway:

12-I-4 (trans)   12-I-4 (cis)
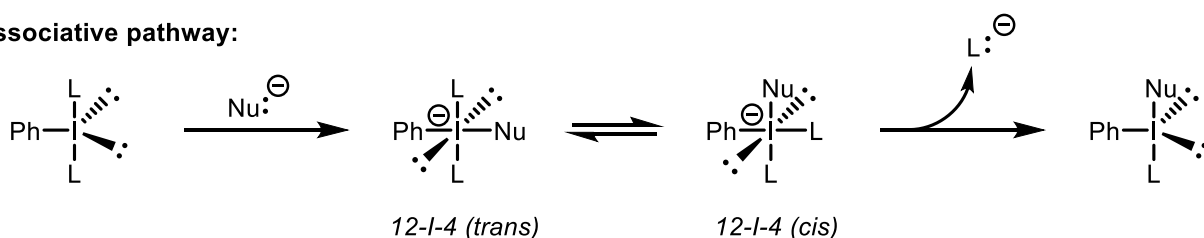
Dissociative pathway:
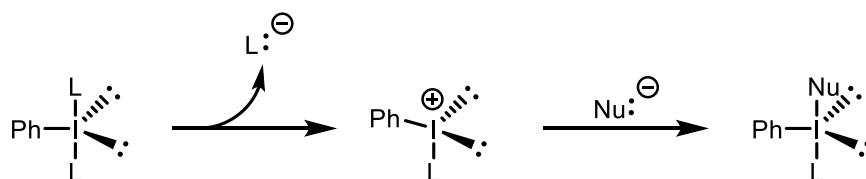
Scheme 1.3. Dissociative and associative pathways for the ligand exchange reactions of λ^3-iodanes with nucleophiles Nu

The second step of reactions of λ^3-iodanes with nucleophiles (**Scheme 1.2**) is the elimination of iodobenzene or other reduced iodine species. Ochiai has called the leaving group PhI (phenyliodonium) a "hypernucleofuge" which emphasizes the initial hypervalent stage and the excellent leaving ability of the PhI group.[36] In fact, PhI is an exceptional leaving group that is about a million times better than the triflate anion.[36] The elimination of PhI can occur through two processes, either reductive elimination or ligand coupling (**Scheme 1.2**). Reductive elimination results in the conversion of Nu$^-$ to Nu$^+$, which can be considered as a formal *umpolung* change in reactivity. This is a common process seen in various reactions of hypervalent iodine reagents; it can result in the formation of products of nucleophilic substitution, rearrangement, or

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fragmentation. The second elimination pathway is ligand coupling, which requires initial pseudorotation to bring ligands L and Nu to apical and equatorial positions that are favorable for coupling (**Scheme 1.2**). This pathway is mostly observed in the reactions of iodonium salts as a concerted process with retention of the configuration of the ligands.[6]

Free radical-based reactions usually occur under photochemical or thermal conditions. The small dissociation energies of λ^3-iodanes bearing chloro-, oxygen-, or nitrogen-ligands usually favor homolytic cleavage reactions. Depending on the reaction conditions, the homolytic cleavage could be followed by hydrogen atom abstraction of R'-H (**Scheme 1.4**), leading to C-H functionalization.[6] An alternative way to initiate radical reactions in hypervalent iodine reagents is by one-electron reduction using SET reagents. SET reagents include transition metals salts, photocatalysts, organic SET reductants, or electron-rich π-systems.
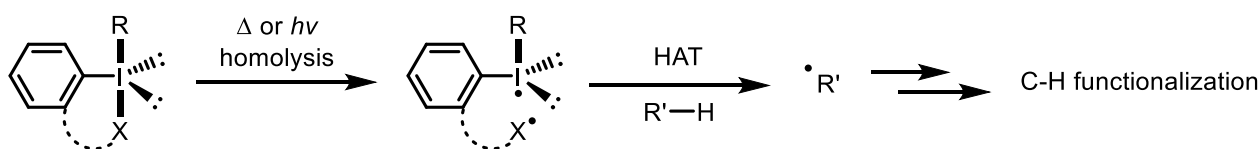
Scheme 1.4. Generation of radicals with λ^3-iodanes reagents vis homolysis
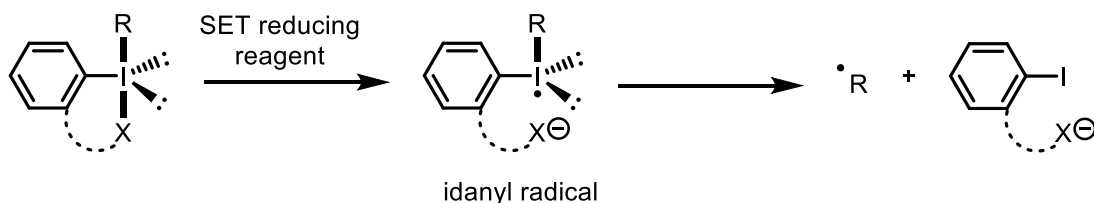
Scheme 1.5. Generation of radicals with λ^{3}-iodanes reagents vis SET

Generation of radicals with λ^3-iodanes reagents vis SET is usually used for transferring functional groups to an alkyne or an alkene. Some λ^3-iodane reagents that use this approach are Togni reagent, Zhdankin reagent, diaryliodonium salts, aryl iodonium ylides, iodonium ylides, aryl(cyano)iodonium triflates, and aryl(perfluoroalkyl)iodonium triflates.[6] An example of this type

of reactivity is the metal-free, single-electron reduction of Togni reagents with the use of the readily available sodium 2,2,6,6-tetramethylpiperidine-1-oxyl salt (TEMPONa) as an organic one-electron reductant. In the presence of alkenes as radical acceptors, vicinal trifluoromethyl products result via a sequence comprising of radical addition to the alkene and subsequent TEMPO trapping (**Scheme 1.6**). [37]
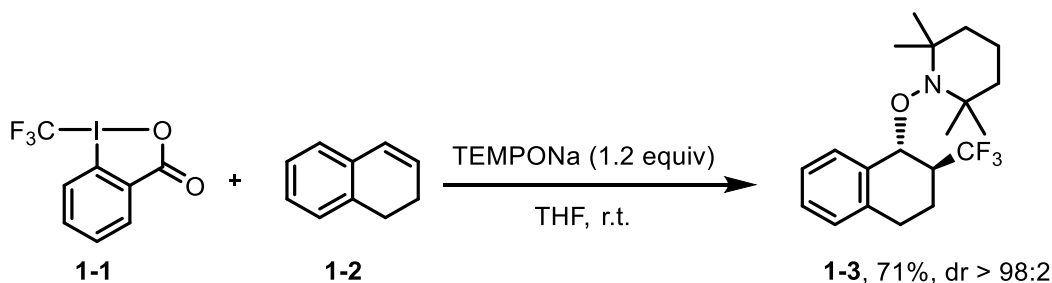
Scheme 1.6. Trifluoromethyl radical transfer to an alkene via SET through TEMPONa

1.6   Hypervalent Iodine Compounds Synthesis and Uses

Hypervalent iodine compounds have an extensive background and many fascinating applications in organic chemistry. They are useful reagents in modern organic chemistry, in particular, as oxidants, transfer agents, and carbene precursors.[6] (Dichloroiodo)benzene **1-5** was the first hypervalent λ^3-iodane species to be synthesized. This was done by Willgerodt in the nineteenth century and was achieved by the reaction of iodobenzene with chlorine gas (Cl_2).[38] The relatively low cost of this process compensated for the inconvenience of working with Cl_2 and made this method a viable option to be used for large-scale applications until the early 2000s.[39] Small laboratory-scale syntheses can be performed using a combination of an aqueous chloride solution (including HCl) and an oxidant (potassium permanganate, perchlorate, periodate, and perborates), as well as various forms of peroxides.[40]
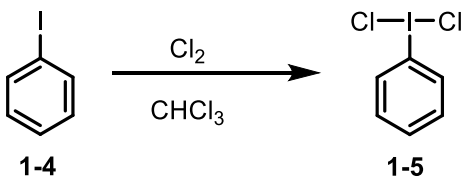
Scheme 1.7. Chlorination of iodoarenes using Cl_2

Hypervalent iodine compounds can be synthesized using two approaches, the direct introduction of the iodanyl group into an arene or the oxidation of an aryl iodide with the help of an appropriate oxidizing agent, as seen in the synthesis of iodobenzene diacetate (**Scheme 1.8.a**).[41,42] The latter is the more commonly used method (**Scheme 1.8.b**).[43]
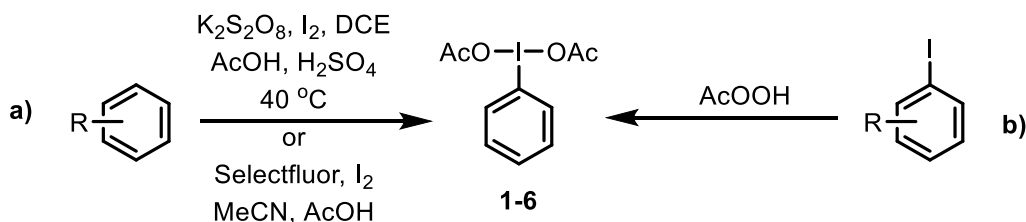
Scheme 1.8. Different methods of synthesizing iodobenzene diacetate

Once an aryl iodide is in the hypervalent form, interconversion to another hypervalent iodine species is possible by treating with mineral acid/acetic acid (**Scheme 1.9**).[44] The synthesis of common hypervalent iodine compounds is accomplished through the above-described ligand transfer process (**Scheme 1.2**).

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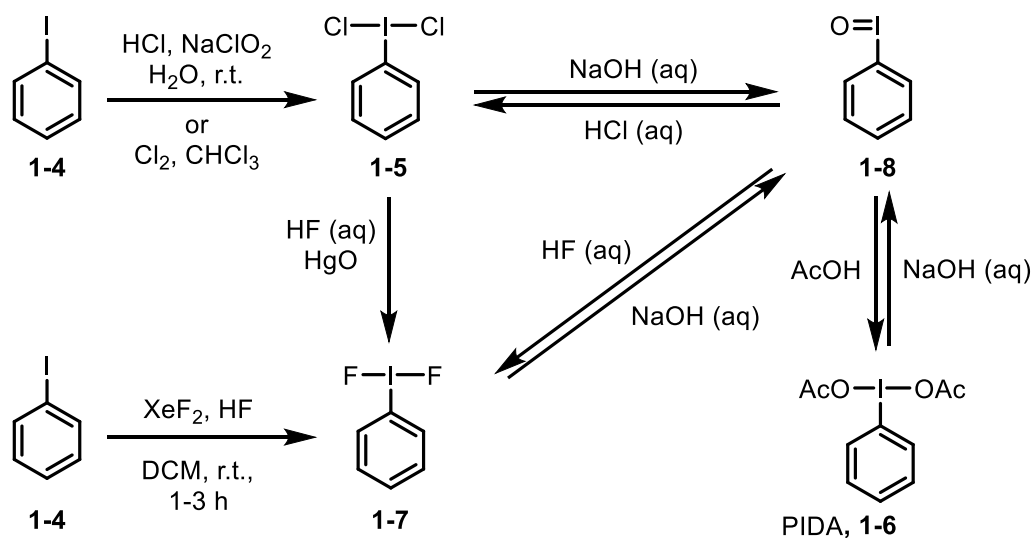
Scheme 1.9. Examples of the synthesis and interconversion to hypervalent iodine species using mineral acid/acetic acid

(Difluoroiodo)benzene **1-7** and derivatives are hygroscopic compounds which make their preparation and crystallization extremely difficult. A powerful but relatively expensive method is the treatment of iodoarenes with xenon difluoride in the presence of anhydrous hydrogen fluoride (HF).[45] Alternative methods include the treatment of iodosoarenes with HF in dichloromethane at room temperature (**Scheme 1.9**).[46] (Dichloroiodo)benzene **1-5** and (difluoroiodo)benzene **1-7** have been employed as halogenating reagents as well as oxidants in various organic transformations.[47]

Iodosobenzene **1-8** and derivatives are commonly prepared by alkaline hydrolysis of (diacetoxy)iodobenzene, (dichloroiodo)arenes, or (difluoroiodo)arenes (**Scheme 1.9**). They are often used as an oxygen-transferring reagent. The structure of iodosobenzene is often represented with a double bond between the iodine and the oxygen atoms, although iodosylarenes, in general, have a polymeric structure that results in its insolubility, thereby limiting their practical use.

Cyclic hypervalent iodine compounds with a heteroatom incorporated in the same five-membered ring are very important hypervalent iodine reagents that are used for various chemical reactions.[48] One of the best-known hypervalent iodine reagents in this class is Dess-Martin periodinane (DMP) **1-11**, which is a λ^5-iodane compound[49] and a soluble analog of 2-

iodoxybenzoic acid (IBX) **1-10**.[50] It is used as an oxidizing agent for alcohols giving the corresponding aldehydes or ketones. A convenient procedure of preparing DMP involves the oxidation of 2-iodobenzoic acid **1-9** with oxone, which results in the generation of IBX, then IBX is treated with acetic anhydride in the presence of TsOH generating DMP (**Scheme 1.10**).[51]
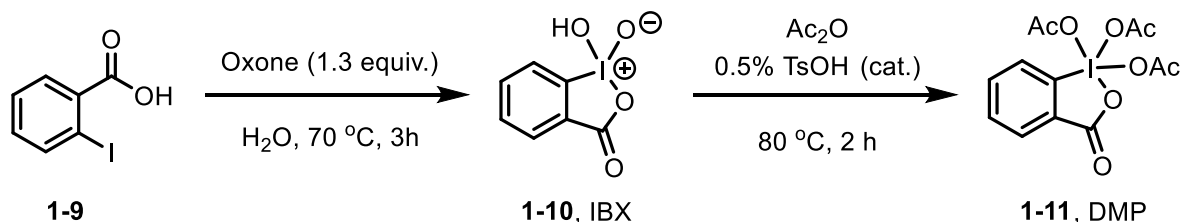
Scheme 1.10. Preparation of IBX and DMP

DMP is superior to chromium- and DMSO-based oxidants, as it offers many advantages including short reaction times, mild reaction temperature, high yields, high chemoselectivity, high tolerance of sensitive functional groups, and long shelf life. Nevertheless, industrial-scale use is not favorable due to its high cost and potentially explosive nature. The λ^5-iodane compound is reduced to a λ^3-iodane with the oxidation of the alcohol substrate. The reaction is usually very selective in the case of primary alcohols, preventing over-oxidation into the carboxylic acid. Hence, it is heavily used in natural product synthesis.[52] For example, DMP is used to oxidize the terminal alcohol in **1-12** to an aldehyde, a crucial step in the synthesis of the aziridine fragment **1-13** that is used for the synthesis of 7-*Epi* (+)-*FR900482* **1-14**, which is a compound known for its anti-cancer activity (**Scheme 1.11**).
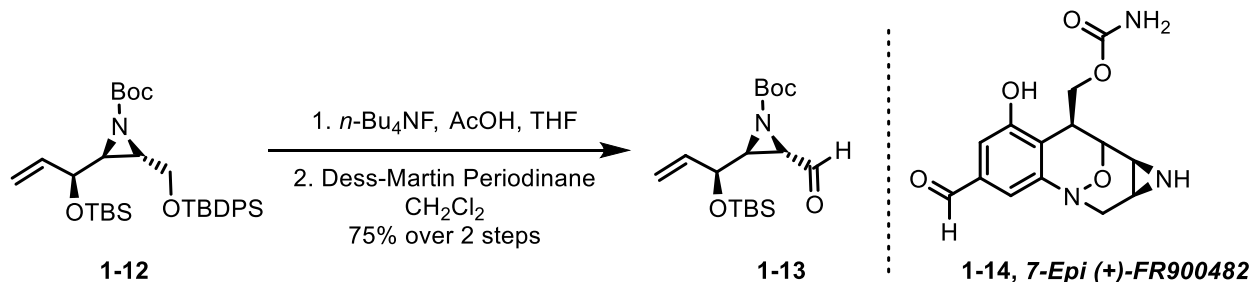
Scheme 1.11. The use of DMP as an oxidant for the synthesis of the aziridine fragment in the anti-cancer compound 7-Epi (+)-FR900482

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Another well-known hypervalent iodine reagent is iodobenzene diacetate (PIDA, **1-6**), which is a commercially available and bench stable HVI reagent. It is also a model example of showcasing the numerous reactions that HVI reagents are capable of facilitating under mild conditions, which otherwise would require the use of metal salts or harsh conditions. The following examples demonstrate the versatility in the reactions performed by PIDA. An example would be the one-pot metal-free direct transformation of amino acids into terminal diazirines using PIDA and ammonia (**Scheme 1.12.a**).[53] This method tolerates a broad range of functional groups and is operationally simple which can be scaled up to provide multigram quantities of diazirine. Another example is the decarboxylative bromination of sterically hindered aliphatic carboxylic acids using PIDA and potassium bromide (**Scheme 1.12.b**). This highly efficient reaction converts a broad range of carboxylic acids into the corresponding alkyl bromides in good to high yields.[54]
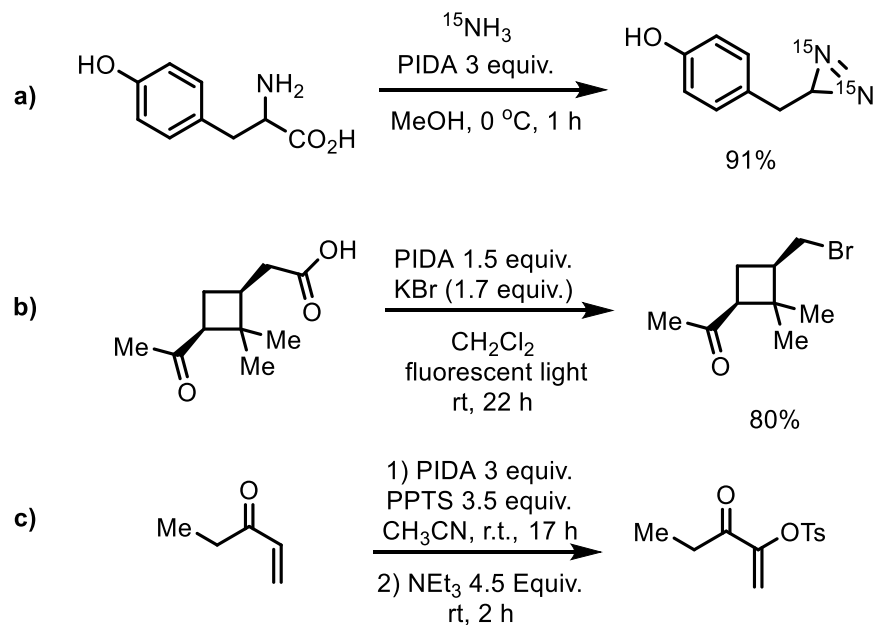
Scheme 1.12. Reactions of PIDA

Last but not the least, PIDA facilitates direct umpolung Morita-Baylis-Hillman reactions such as α-functionalization of enones via enolonium species,[55] giving direct access to α-chloro-enones, 1,2- diketones and α-tosyloxy-enones, which cannot be formed in a single step from enones in any other way (**Scheme 1.12.c**).[55]

1.7   Iodonium Ylides

An ylide is a neutral dipolar molecule that contains a negatively charged carbon atom that is directly bonded to a positively charged atom of sulfur, phosphorus, nitrogen, iodine, and others, where both charged atoms have complete octets. One of the classical examples of ylides are iodonium ylides, which are a key subset of HVI reagents (**Figure 1.4.**).
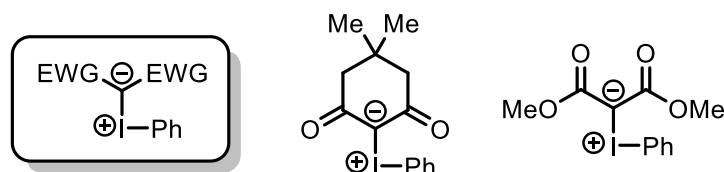
Figure 1.4. Structures of iodonium ylides

The most important and commonly encountered iodonium ylides is the phenyl iodonium ylide, PhI^+-$C^-(EWG)_2$, where X is an EWG, such as a carbonyl group or sulfonyl group (**Figure 1.4**). X-ray crystallography studies revealed that the geometry of aryliodonium ylides can be compared to that of iodonium salts, which have a C-I-C bond angle close to 90°.[56] For example, phenyliodonium ylide **1-15** has a geometry that is typical to that of an iodonium ylide with the I-C (ylidic) bond length of about 1.9 Å and a C-I-C bond angle of 98° (**Figure 1.5.**).[57]

1-15
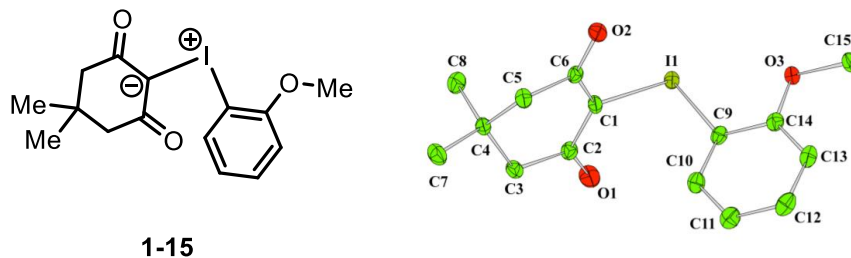
Figure 1.5. Crystal structure of iodonium ylide **1-15**[57]

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The nature and classification of hypervalent molecules have become a point of discussion over the years. In brief, when attempting to describe hypervalency using molecular orbital theory, one must include the contribution of d-orbitals, otherwise it would result in high energies and distorted geometries. However, the work of Magnusson concluded that the involvement of d-orbitals is not implicated in hypervalency,[58] and the concept itself was criticized by Gillespie in 2002[59] who concluded that there is no fundamental difference between the bonds of hypervalent and non-hypervalent molecules based on an analysis of electron localization functions. In iodonium ylides, a double bond is usually used to represent the bonding between iodine and the α−carbon. Having a double bond with the α−carbon results in 10 electrons around the iodine, making it a hypervalent compound.
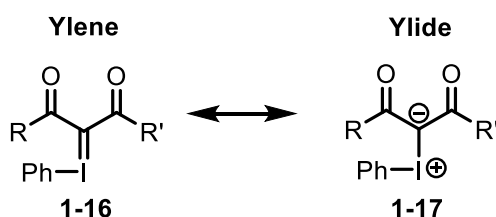
Figure 1.6. Resonance structures of general iodonium ylides

The existence of I=X double bonds, where X = O, N, or C in hypervalent iodine, was investigated by Zhdankin et al.[60] In their study, the adaptive natural density partitioning (AdNDP) was used to analyze the bonding of hypervalent iodine compounds. AdNDP is a powerful method that achieves a seamless description of systems, combining both Lewis and molecular orbital theories without invoking the concept of resonance.[61] The double bond character of the I=X bond was not observed in any of the species analyzed in this study (**Figure 1.7**), instead, the chemical bonding shows one dative I→X bond, and the octet rule is therefore followed in each case.
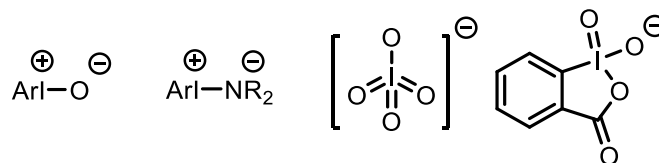
Figure 1.7. Common hypervalent iodine compounds that show one I→X dative bond

In particular, the chemical bonding picture of the iodonium ylide $PhICR_2$ ($R=CO_2Me$) shows one dative I→C bond with one 2C-2e bond between I and C of the Ph fragment and also between the I and C of the α−carbon.[60] The study suggested that a better way to describe the bonding in hypervalent iodine would be through donor-acceptor complexes. In the case of iodonium ylides, the electron donor or the Lewis base is (PhI) and the electron acceptor or the Lewis acid is $C^-(CO_2Me)_2$. Therefore, the positive charge on the iodine center is not conjugated with the dicarbonyl system, meaning that there is a prominent positive charge on the iodine potentially indicating that it may act as an electrophilic site or a Lewis acid. The phrase "hypervalent" will continue to be used throughout the thesis for convenience.

| 2C-2e dative I-C σ-bond | 2C-2e dative I-C σ-bond | 3C-2e dative C-C π-bond | Two 1C-2e lone pairs on I |
| ON = 1.96 \|e\| | ON = 1.97 \|e\| | ON = 1.80 \|e\| | ON = 1.96-1.99 \|e\| |
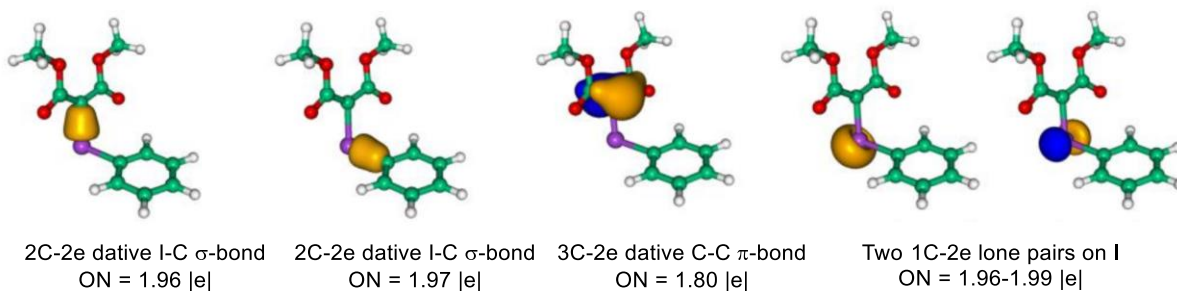
Figure 1.8. AdNDP bonding pattern of the $PhI=C(CO_2Me)_2$ molecule[60]

1.7.1 Preparation and Reactivity of Iodonium Ylides

Neiland and co-workers prepared the first stable iodonium ylide from (difluoroiodo)benzene **1-7** and dimedone in 1957.[62] Subsequently, many stable aryliodonium

ylides have been made and used as reagents in organic synthesis.[6] Iodonium ylides can be classified as monocarbonyl or dicarbonyl iodonium ylides, and many derivatives exits in both classes. Monocarbonyl iodonium ylides can only be synthesized and handled at low temperatures due to their low stability. However, dicarbonyl iodonium ylides derivatives, $PhI=C(COR)_2$, and disulfonyl derivatives, $PhI=C(SO_2R)_2$, have higher stability. Cyclic-dicarbonyl iodonium ylides can be stored in the fridge, whereas the majority of acyclic-dicarbonyl iodonium ylides must be stored in the freezer at -10 °C or below.[6] The general procedure used to prepare dicarbonyl iodonium ylides is the reaction of PIDA with the appropriate activated methylene compound in the presence of a base, as shown in **Scheme 1.13**.[6]
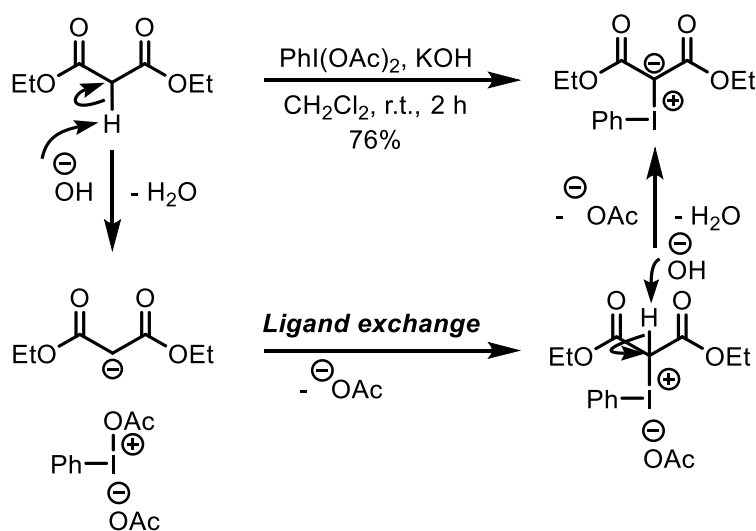
Scheme 1.13. Mechanism of the synthesis of iodonium ylides from dicarbonyl compounds

The solubility of iodonium ylides can cause serious limitations regarding their reactivity. Acyclic ylides such as **1-18** are generally limited in use due to their low solubility in most organic solvents, except DMSO. A significant improvement in both thermal stability and solubility is observed when introducing a coordinating substituent in the *ortho* position of the phenyl ring.[63] For example, 2-methoxyphenyliodonium ylide **1-19** has excellent solubility in organic solvents such as dichloromethane, chloroform, or acetone, and also has higher thermal stability, which permits its use in reactions with a wide variety of reaction conditions.[63]

Low solubility and stability   High solubility and stability
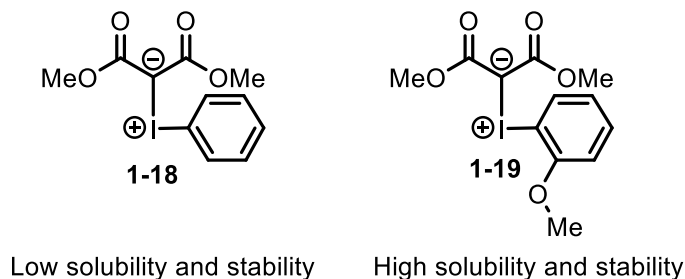
Figure 1.9. Comparison between soluble and insoluble iodonium ylides

In 2015, Stuart and co-workers synthesized several stable iodonium ylides containing a propan-2-ol group in the *ortho* position of the aryl iodide by the reactions of β-dicarbonyl compounds such as **1-20** with benziodoxole **1-21** in the absence of a base (**Scheme 1.14**). Owing to the intramolecular coordination of iodine with the hydroxyl group, the new iodonium ylides **1-22** are highly stable in comparison to acyclic iodonium ylides that do not contain an *ortho*-propan-2-ol group. Along with having high thermal stability, these ylides are also stable when purifying them by column chromatography on silica gel.[64] Perhaps, the strong coordination between the alcohol group and the iodine center in ylide **1-22** could lead to surprisingly high stability. This suggests a significant interaction between the Lewis acid (iodine center) and the Lewis base (lone pair of electrons on the oxygen), indicating that the iodine center in an iodonium ylide may act as a Lewis acid.

Ar = Ph or 4-MeOC$_6$H$_4$
R = OEt or Ph
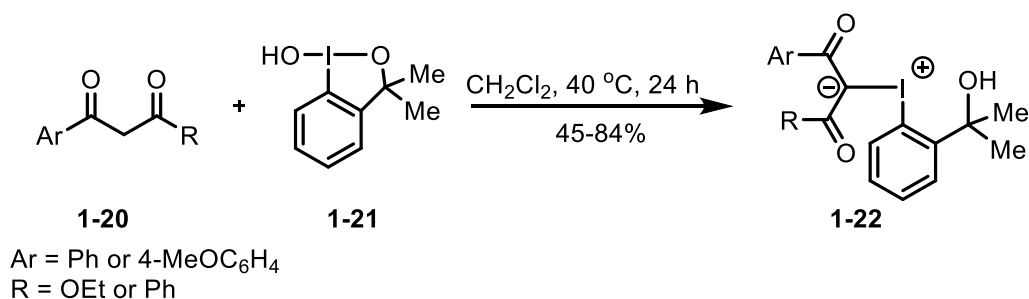
Scheme 1.14. Synthesis of alcohol-containing iodonium ylide

1.8   Sigma Holes

In halo organics, halogen atoms are well-established as sites of rich electron density due to their high electronegativity. Consistent with this understanding, it is generally recognized that halogen atoms function as electron donor sites (nucleophiles). The ability of some halogen-containing compounds to function as hydrogen bond acceptors was also discovered around the 1920s.[65] However, in compounds where halogen atoms are involved in the formation of one covalent bond, a region of lower electron density was observed in the halogen and was termed a sigma σ-hole.[66]

σ-holes are electron-deficient outer lobes of a half-filled *p* (or nearly *p*) orbital. They emerge from the anisotropic distribution of electron density in the atoms of group 14-17 elements while forming covalent bonds with EWGs.[66]

σ-holes were first discovered in 1992 when the analysis of the molecular electrostatic potential of halogenated methanes was first performed.[67] It has been observed that the electrostatic potential of the halogen shows positive and negative regions. The positive region was found to be an extension of the C-X bond, whereas the negative region constructs a belt of negative electrostatic potential that is orthogonal to the covalent C-X bond (where X = Cl, Br, or I). Since the positive region is an elongation of the σ bond of the halogen, it was named a σ-hole.[66]

A natural bond order B3LYP analysis of CF_3Y (where Y = F, Cl, Br, or I) was performed to better understand σ-holes. In three cases (where Y = Cl, Br, or I), it was observed that there is a negative belt of electron density around the C-Y bond and the σ-hole. Fluorine was an exception due to its high electronegativity and the significant *sp*-hybridization that resulted in an influx of electronic charge that neutralizes the σ-hole. The strength of the σ-hole is the most notable in I, followed by Br and Cl (**Figure 1.10**).[66]
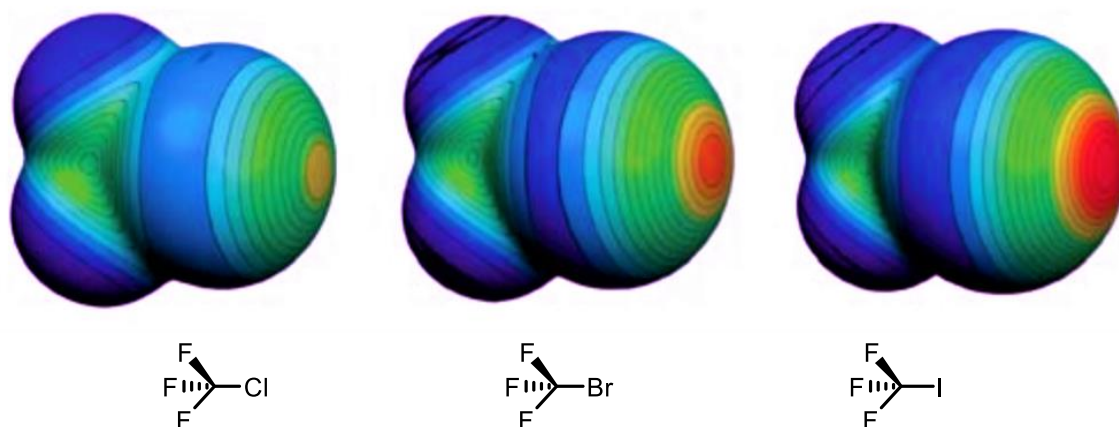
Figure 1.10. σ-holes in X-CF$_3$ compounds, X = Cl, Br, or I[66]

Halogen bonding is a subset of σ-hole interactions and an example of non-covalent interactions. It is characterized and named after the donor atom's group, which is the electrophilic region of one of the two interacting partners.[68] Halogen bonding refers to the non-covalent attractive interaction in the electrophilic region that is associated with a halogen atom (X) in an organic molecule (RX) with a negative site in another molecule. The halogen bond is shown below in the following diagram, where the dashed line indicates the interaction between the lone pair of electrons of the Lewis base (B) and the halogen atom (X):

$$R—X---B$$
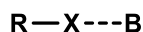
The angle of R—X---B is close to 180°, and in general, the strength of the interactions correlates well with the magnitudes of the positive and negative electrostatic potentials of the σ-hole and the negative site.[69] Hence, the strength of the halogen bond interaction increases with the decrease in the electronegativity of the halogen.

1.8.1   Sigma Holes in Hypervalent Iodine Compounds

Recently, a few computational studies have shed light on the importance of halogen bonding with nucleophiles in the complexes of λ^3-iodanes. The initial complex formed between

λ^3-iodanes and a nucleophile can be described as a non-covalent or σ-hole interaction. In hypervalent iodine species, DFT analysis shows the formation of a "nonclassical" σ-hole region with one or even two maxima. For example, when observing the molecular electrostatic potential (MEP) of Togni reagent derivative 3,3-dimethyl-1-(trifluoromethyl)-1-λ^3,2-benziodoxol **1-23**, it can be clearly seen that there is a positive region around the central iodine atom with a discernible σ-hole region of moderate strength that extends along the plane of the hypervalent region. SAPT analysis reveals the interaction between the iodine atom of a hypervalent species and the nucleophile is not always purely electrostatic in nature but may have a covalent component. The covalent component of the interaction may permit chemical transformations such as reductive eliminations and other processes.[70] This is crucial for understanding the chemical selectivity of iodonium ylides that will be described in the subsequent sections.
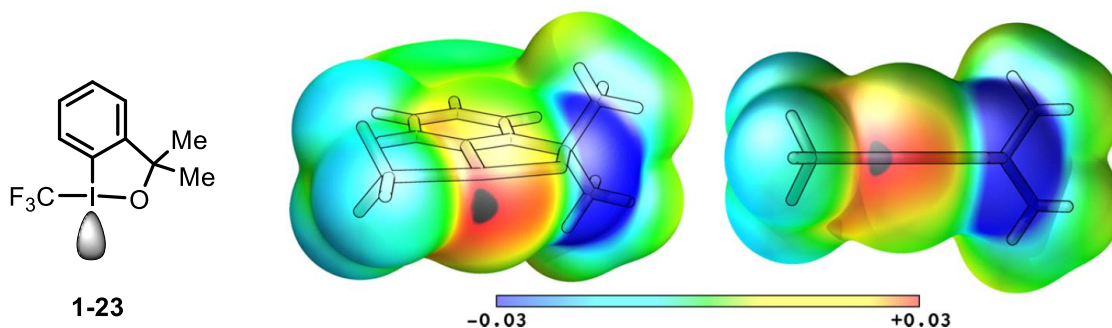
Figure 1.11. Two different views of the isopotential surface of the MEP of 3,3-dimethyl-1-(trifluoromethyl)-1-λ^3,2-benziodoxol[70]

In contrast to the neutral iodine(III) compounds with three substituents in a T-shaped geometry, both aryl iodonium salts and iodonium ylides have two substituents with a C-I-C angle that is close to 90°. In both cases, there are two electrophilic axes. The crystal structure of unhindered aryl iodonium salts **1-24** showed the formation of halogen bonds (XBs) along both axes with bromide ions (**Figure 1.12**). On the other hand, in an *ortho*-substituted derivative **1-25**, X-ray crystal structure confirms the absence of XB to potential substrates along the blocked electrophilic axis, suggesting that σ-holes can be blocked by steric effects.[71]
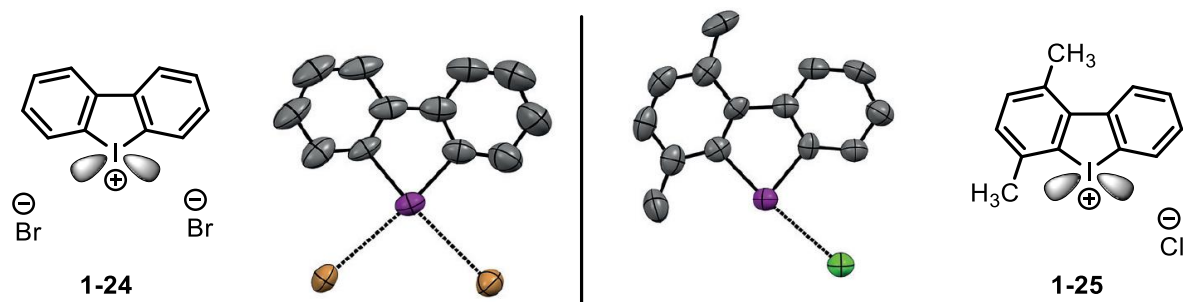
Figure 1.12. Excerpts of the X-ray structures of the XB complexes of **2-2** with bromide (left) and **2–3** with chloride (right). Ellipsoids are set at 50% probability. Hydrogen atoms are omitted for clarity[71]

1.8.2 Sigma Holes in Iodonium Ylides

Iodonium ylides also exhibit two σ-holes extending from the carbon(α)-iodine bond and from the carbon(phenyl)-iodine bonds, they will be termed **T** and **I**, respectively (**Figure 1.13**).[72] Having two σ-holes may explain the regioselectivity observed in some reactions of iodonium ylides with different nucleophiles.
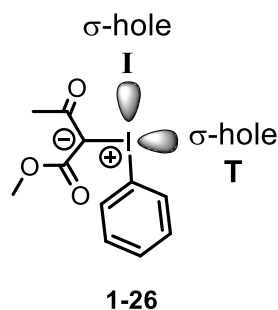
Figure 1.13. σ-Holes in iodonium ylides

Iodonium ylide reactions with nucleophiles almost always result in the substitution of the nucleophile to the β-dicarbonyl moiety, and this will be discussed in greater detail in section 1.8.2.1. One of the few exceptions can be found in the work of Satyamurthy and Barrio, who discovered that the reactions of iodonium ylides with nucleophiles (F⁻, Cl⁻, Br⁻, etc.) in polar

aprotic solvents such as acetonitrile, tetrahydrofuran, dimethylsulfoxide, dimethylacetamide, and dimethylformamide lead to a regioselective substitution of the nucleophile on the aromatic ring, instead of the β-dicarbonyl moiety.[73] For example, heating of phenyl iodonium ylides **1-27** with dried KFKryptofix (K$_{222}$) complex in dry DMF affords fluoroarenes **1-28** as the main product and hydrocarbon **1-29** as a by-product due to a radical channel competing with the nucleophilic substitution reaction (**Scheme 1.15**). The β-dicarbonyl moiety was observed to not undergo fluorination in this reaction.[74]

Ar = Ph, 4-MeC$_6$H$_4$, 2,4,6-Me$_3$C$_6$H$_2$, 2-MeOC$_6$H$_4$,
3-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$
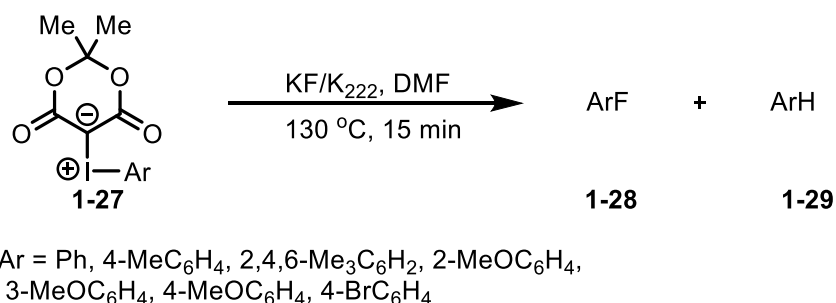
Scheme 1.15. The reaction of iodonium ylides with fluoride anion in DMF

1.8.2.1   Analysis of the Reaction between Soft Nucleophiles and Iodonium Ylides

There are many examples in the literature of the reactions between soft nucleophiles and iodonium ylides where the nucleophilic addition occurs on the β-dicarbonyl motif, for example, the reaction between thioamides and acyclic iodonium ylides.[72] DFT calculations suggested that the halogen bonding between a thioamide and an iodonium ylide is important in this chemoselective coupling reaction.[72] The thioamide could form halogen bonding with either σ-holes **I** or **T**, **1-30** and **1-31**, but stronger halogen bonding is observed with σ-hole **I**, *cis* to the α−carbon (**Figure 1.14**). Hydrogen bonding is also observed between the thioamide and the carbonyl of the iodonium ylide.
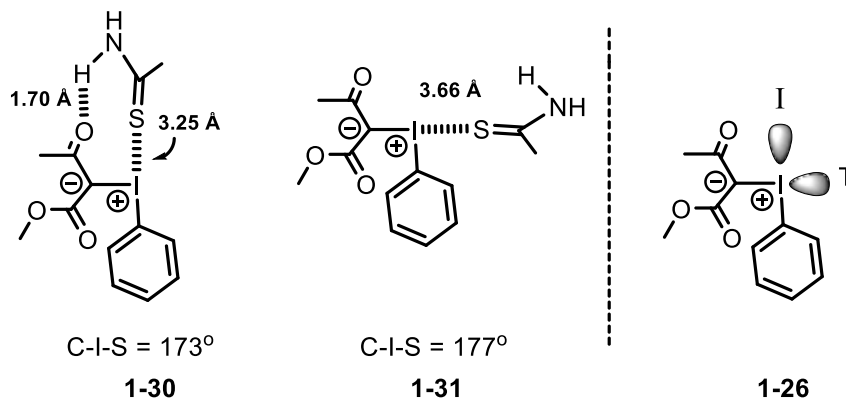
Figure 1.14. Coordination between thioamide and iodonium ylide σ-holes

The stronger interaction between the iodonium ylide's σ-hole **I** and thioamides leads to a selective nucleophilic addition to the β-dicarbonyl motif of the iodonium ylide (**Scheme 1.16**).[72]
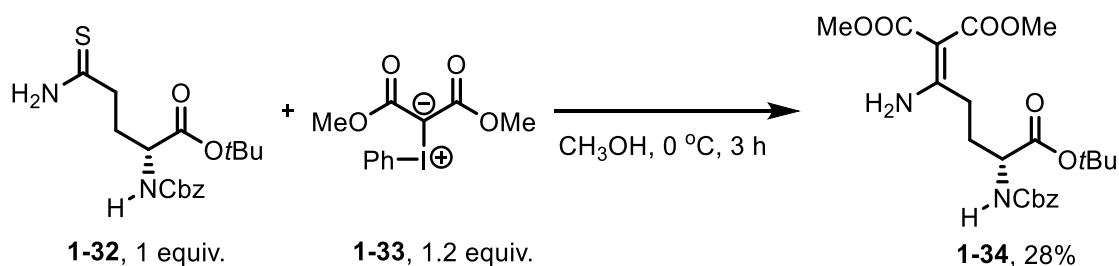
Scheme 1.16. The reaction of thioamide and iodonium ylide

Blocking σ-hole **T** with an *ortho* group on the aryl iodide leads to a stronger interaction between the soft nucleophile and σ-hole **I**. In the case of **1-35**, a strong interaction is established between the oxygen of the *ortho* nitro group and the iodine center that leads to a bond length of 2.83 Å, thereby blocking σ-hole **T,** which in turn, increases the yield of the product. The yield of product **1-34** increased when an *ortho* group is added on the iodonium ylide, 48% with *ortho*-NO_2 and 71% with *ortho*-CH_2OMe.[72]
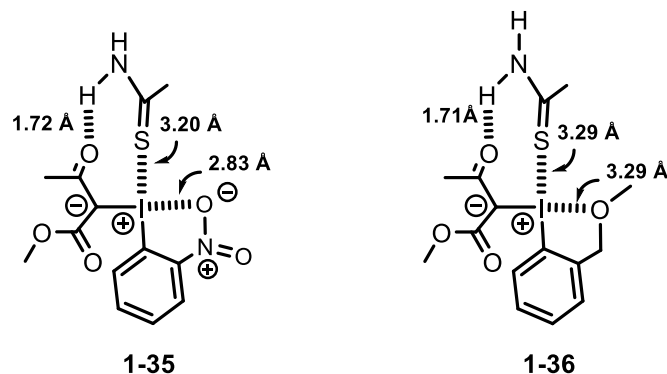
Figure 1.15. Halogen bonding and hydrogen bonding between the thioamide and the iodine center of iodonium ylide in the presence of an *ortho* σ-hole blocker

In the literature, there are numerous examples of the reactions between soft nucleophiles and iodonium ylides, and a regioselective addition onto the β-dicarbonyl motif is always observed as the only product. For example, the reaction between an acyclic iodonium ylide and isocyanates.[75]

R = Me or OEt
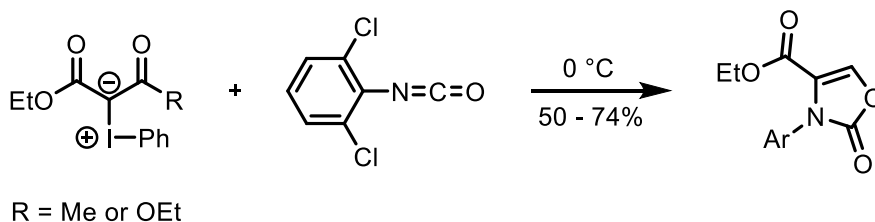
Scheme 1.17. Synthesis of oxazolin-2-ones from isocyanates and iodonium ylides

Iodonium ylides were shown to undergo a cyclization reaction with tertiary arylamines to afford *N*-heterocyclic products under metal-free conditions.[76] The reaction was also performed in the presence of CaH$_2$ (0.5 equiv.) for a selected number of examples giving slightly higher yields, but it was not a requirement for the reaction to work. The reaction was explained by the formation of a halogen bonding complex containing the combination of an iodonium ylide with a Lewis base.
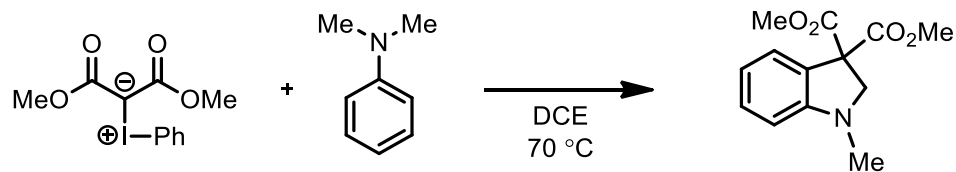
Scheme 1.18. Halogen-bond activated cyclization of iodonium ylides with arylamines

A simple method was developed by Wang in 2019 that enables the direct transformation of unprotected secondary aliphatic amines into functionalized N-heterocycles.[77] This metal-free reaction was conceived to operate through a halogen-bonding activation mode of iodonium ylides to induce a site-selective β-functionalization of secondary aliphatic amines for the construction of three σ-bonds and one π-bond in a single transformation.
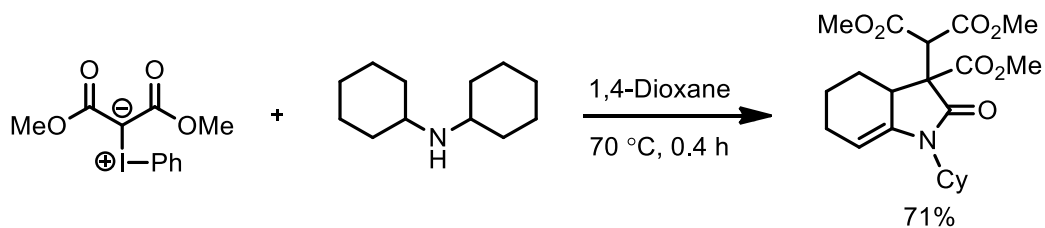
Scheme 1.19. Halogen-bond activated cyclization of iodonium ylides with aliphatic amines

Chapter 2: Iodonium Ylides as Lewis Acids for Metal Free O-H and S-H Insertion Reactions

2.1   Introduction

α-Functionalized carbonyl compounds are versatile intermediates for the synthesis of a variety of compounds of medicinal interest, natural products, and related compounds. An important functionalization reaction is the formation of a carbon-oxygen or carbon-sulfur bond on the α-carbon of the carbonyl substrate. A general and practical method for O-H and S-H bond insertion reactions of carboxylic acid and thiols into the α–carbon would thus constitute a valuable addition to the toolbox of synthetic chemistry. This chapter will discuss the utilization of iodonium ylide Lewis-acidity for the facilitation of S-H and O-H insertion reactions into the dicarbonyl motif of an iodonium ylide which could eliminate the use of salt-metal catalysts that are needed to perform similar insertion reactions into diazo compounds.

2.2   Diazo Compounds

Diazo compounds were discovered in 1894 by German chemist Hans von Pechmann through the synthesis of diazomethane, which is a yellow explosive gas in its pure form.[78] Diazo compounds are neutral organic molecules containing a diazo group that consists of two linked nitrogen atoms (azo) onto the organic framework. When the diazo group is bonded to an organic molecule, the general structural formula is $R_2C=N^+=N^-$, which is referred to as a diazonium ylide or diazoalkanes.

Following the discovery of the Wolff rearrangement in the early 20th century,[79] diazo compounds have been observed to act as nucleophiles in reactions such as the Buchner-Curtius-Schlotterbeck reaction and, most importantly, as carbene precursors. The formation of carbene intermediates allows access for many chemical transformations such as insertion reactions (C-H, N-H, S-H, O-H, Si-H), cyclopropanation, transylidation, and rearrangements. The decomposition of diazos into free carbenes is achieved by heat, or by light in the form of ultraviolet radiation or blue light. Using transition metal salts such as ruthenium, palladium, or copper in the presence of a diazo compound leads to the formation of a metallocarbene (**Figure 2.1**).
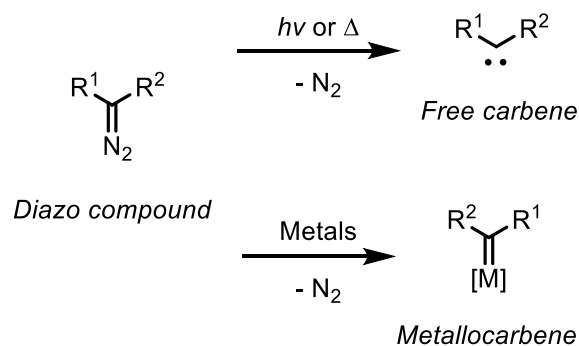
Figure 2.1. Generation of metallocarbenes and free carbenes from diazo compounds

The diversity of diazo compounds makes them extremely useful in organic transformations. However, there are many negative properties associated with diazo compounds as some are known to be toxic,[80] carcinogenic,[81] and explosive in nature.[82] Many diazonium salts are explosive when dry, while some others are explosive when moist.[83] An explosion may occur as a result of heat, friction, or impact, therefore, diazo compounds are slowly being replaced as safer alternatives become available.

2.2.1   Comparison between Iodonium Ylides and Diazonium Ylides

Iodonium ylides have been proposed as a safer alternative to diazo compounds. Both can serve as carbene precursors under thermal and photochemical conditions, or by the use of metal-salt catalysts derived from ruthenium, copper, or palladium. For example, the early work of Paul Müller and Daniel Fernandez (1995) showed a direct comparison between the Rh-catalyzed decomposition of diazo compounds and that of the corresponding iodonium ylides in different reactions.[84] It has been found that the metallocarbenes produced from the reaction between iodonium ylides with [Rh$_2$(OAc)$_4$] and the metallocarbenes produced from diazo and the same Rh-catalyst [Rh$_2$(OAc)$_4$] are identical in many reactions in terms of sensitivity and selectivity. For example, the sensitivity levels of the Rh-catalyzed in intermolecular cyclopropane formation from substituted styrenes and iodonium ylide (**2-1a**) or dimethyl diazomalonate (**2-2**) are identical.
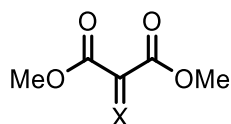
2-1a X = IPh
2-2 X = N$_2$

Figure 2.2. Structure of a diazo compound and an iodonium ylide

Iodonium ylides and diazo compounds afford the same products under [Rh$_2$(OAc)$_2$]-catalyzed cyclopropane formation, cycloaddition, and intramolecular CH insertion. They also exhibit identical chemoselectivity in intramolecular competitions for cyclopropane formation and insertion in the presence of a chiral catalyst (Rh$_2$(-)-(S)-ptpa$_4$). The intramolecular CH insertion of iodonium ylide **2-3** when carried out in the presence of chiral catalyst (Rh$_2$(-)-(S)-ptpa$_4$), results in the formation of **2-5,** having an *ee* of 67%, which is almost identical to the *ee* obtained using diazo compound **2-4** as seen in (**Scheme 2.1**).

2-3 X = IPh
2-4 X = N$_2$

2-5 = 78%, 67% *ee* (Iodonium ylide **2-3**)
2-6 = 89%, 69% *ee* (Diazo **2-4**)

Rh$_2$(-)-(S)-(ptpa)$_4$
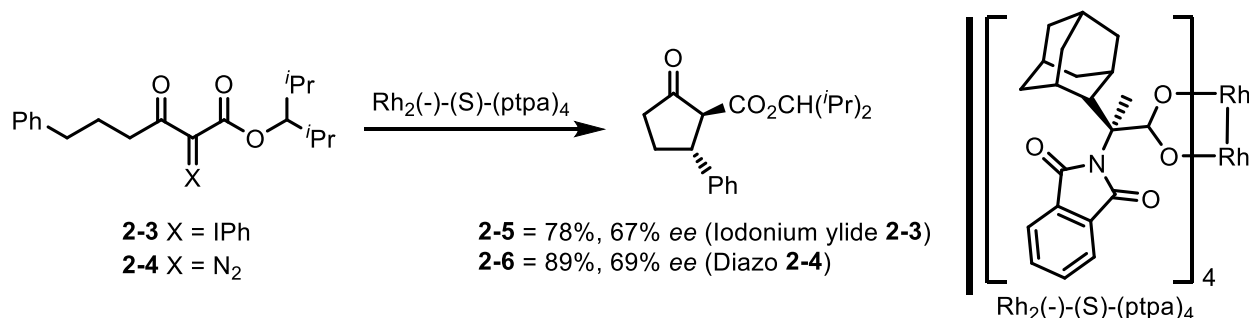
Scheme 2.1. Intramolecular CH insertion of ylide **2-3** and diazo **2-4** in the presence of a chiral catalyst

Although parallel reactivity is sometimes observed between diazo compounds and iodonium ylides under salt metal catalysis conditions, they have other modes of reactivities that are unique to each. The differences in reactivities between iodonium ylides and diazo compounds emerge from the inherent structural differences. The structural features of iodonium ylides can be found in Section **1.7**. In brief, an iodonium ylide is a neutral dipolar molecule containing a negatively charged carbon atom that is directly bonded to a positively charged iodine. Although iodonium ylides can been represented as containing two resonance structures, they have one

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dominant resonance structure (**Figure 2.3**). Studies by Zhdankin et al., employing adaptive natural density partitioning (AdNDP) to analyze the bonding of hypervalent iodine compounds, showed one dative I-C bond, and the octet rule was obeyed in the hypervalent iodine compounds investigated included iodonium ylides.[60] The double-bond character of the I=C bond was not observed in the iodonium ylides.
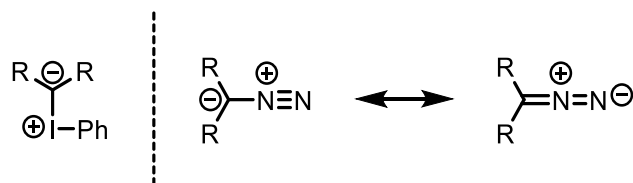
Figure 2.3. Structure and resonance of iodonium ylides and diazo compounds

Thus, there is a localized positive charge on the iodine center. Hence, it acts as an electrophilic site that coordinates with nucleophilic sites. This coordination between nucleophiles and the iodine center is discussed in Section 1.8.2.1. To summarize, iodonium ylides have two σ-holes, and according to previous mechanistic studies on the relationship between iodonium ylides and different nucleophiles, halogen bonding is observed between the iodine center and nucleophilic compounds. Even though iodonium ylides and diazo compounds are both classified as ylides, small differences in their structural properties allow for different modes of reactivities to be accessed.

2.3   Insertion Reactions of Diazo Compounds

X-H insertion reactions (where X = O, S, N, etc.) into diazo compounds can proceed through two different pathways depending on the nucleophilicity of the diazo compound and the acidity of the X-H compound used. For example, diazomethane is a potent methylating agent for carboxylic acids,[85] phenols,[86] some alcohols[87] and a multitude of other nucleophiles, such as nitrogen and sulfur-based compounds.[88] X-H insertion reactions with diazomethane are very fast and take place under mild conditions without the use of a metal-based catalyst (**Scheme 2.2**).
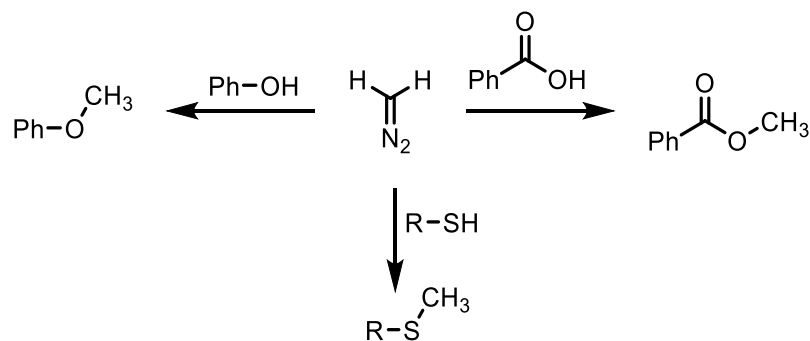
Scheme 2.2. Insertion reactions into diazomethane

The X-H insertion reactions with diazomethane are thought to proceed via proton transfer from the X-H compound. In the case of carboxylic acid reactions with diazomethane, the proton transfer results in the formation of a methyldiazonium cation, which then reacts with the carboxylate anion to give the methyl ester and nitrogen gas (**Figure 2.4**). Labeling studies indicate that the initial proton transfer is faster than the methyl transfer step.[89] Since proton transfer is required for the reaction to proceed, this reaction is selective for the more acidic carboxylic acids (pKa ~ 5) and phenols (pKa ~ 10) over aliphatic alcohols (pKa ~ 15).
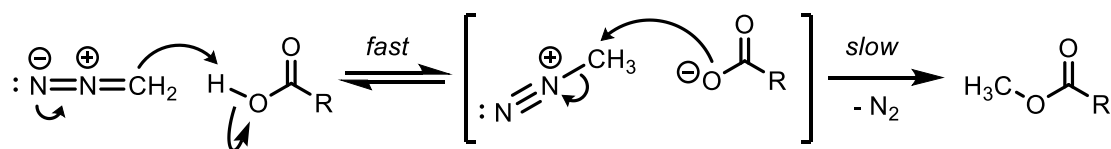
Figure 2.4. Reaction mechanism of the O-H insertion of carboxylic acids and diazomethane

Other highly nucleophilic diazo products also undergo fast X-H insertion reactions without the use of metal-based catalysts such as **2-5a**,[85-88] **2-5b**,[90] and **2-5c**[91] (**Figure 2.5**) through a similar mechanism as stated above (**Figure 2.3**). When moving to more conjugated diazo systems containing carbonyl groups such as ethyl ester diazo **2-5e**, **2-5f**, and the β-dicarbonyl diazo compound **2-5g**, the basicity of the diazo compounds decrease.[92] Consequently, the X-H insertion reactions will not occur through a nucleophilic attack. Instead, metal catalysts will be required to initiate the reaction through the formation of a metal-carbene intermediate.[93] The nucleophilicity of diazo **2-5d** allows for O-H insertions of carboxylic acids,[94] alcohols,[95] and phenols;[96] however, it requires a metal catalyst such as ruthenium, for the less acidic (N-H) insertion.[97]

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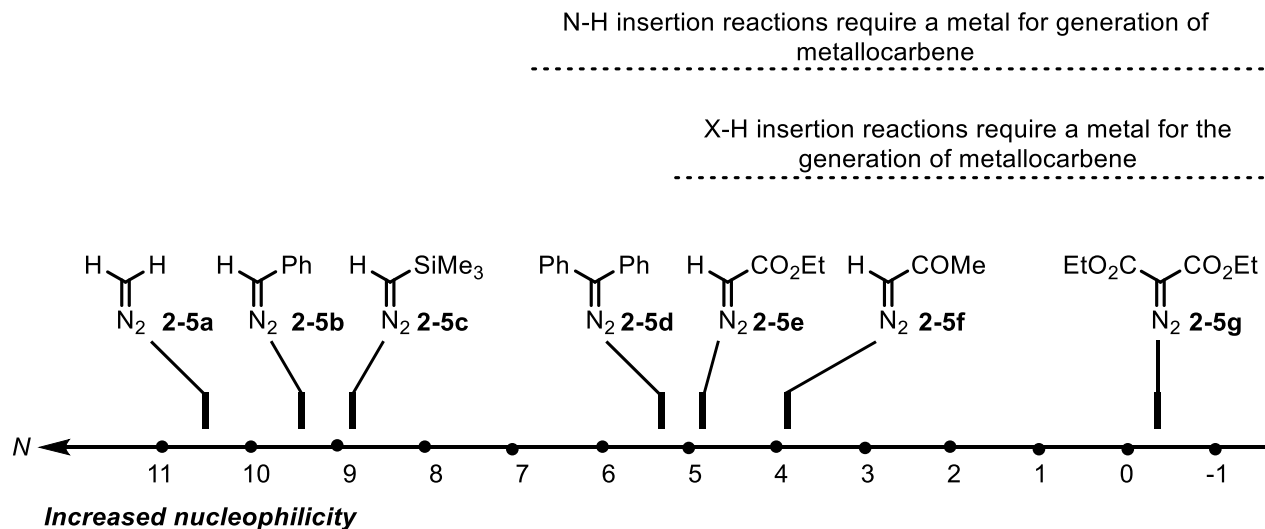
Figure 2.5. Nucleophilicity and slope parameters N/s of diazo compounds

2.3.1 O-H Insertion of Diazo Compounds

The reaction between β-dicarbonyl diazo compounds and carboxylic acids was reported by different groups under metal-salts catalysts such as ruthenium,[98] copper,[99] and palladium.[100] Many of the optimized procedures for O-H insertion reactions of carboxylic acids with diazos are not efficient (**A** and **B**, **Scheme 2.3**). For example, the procedure reported by Bertelsen and coworkers requires the use of carboxylic acids as solvents (**B**, **Scheme 2.3**). Other problems associated with this chemistry are the long reaction times that are often conducted under high temperatures, which may lead to many undesirable side reactions. These harsh conditions are not compatible with amino acids and other carboxylic acids comprising sensitive functional groups.[101] Recently, it was discovered that changing the catalyst to $Rh_2(esp)_2$ resulted in a more efficient O-H insertion reaction of a carboxylic acid into an acceptor–acceptor diazo. This procedure uses 1% catalytic loading of $Rh_2(esp)_2$, and the reaction was performed at room temperature, in a shorter reaction time than previously reported. It also generally gave higher yields of the desired product, with the occurrence of minimal side reactions (**C**, **Scheme 2.3**).[102]

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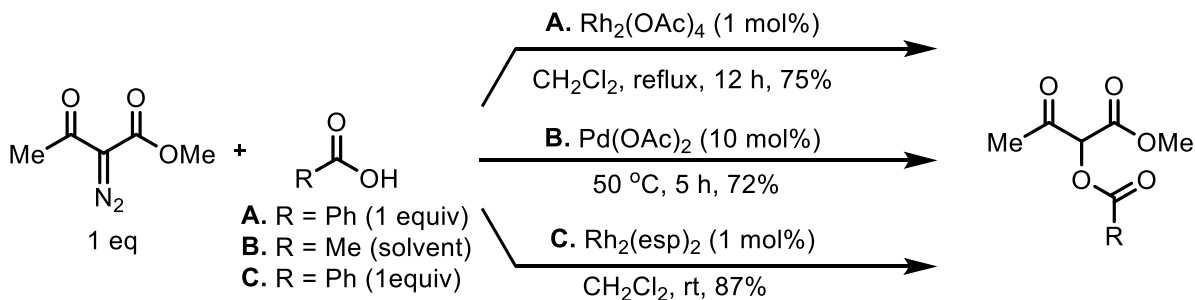
Scheme 2.3. O-H insertion reaction of carboxylic acids into diazo products

Although the previous method proceeds under mild conditions, a metal-catalyst is still relied upon to generate a metal carbene that is capable of performing the reaction. A metal carbene is highly reactive and may decompose in the presence of some functional groups, making this approach less desirable. Since metallocarbenes are known to undergo insertion reactions (O-H, S-H, N-H, Si-H, etc.) and cycloadditions, a beneficial approach that could yield the same product without going through a metallocarbene pathway would be of interest.

A detailed reaction mechanism was not provided in any of the previous examples. However, looking at similar reactions between phenols and diazo compounds to perform O-H insertion using a ruthenium catalyst may give some insights into the reaction mechanism.

The DFT calculations performed by Liang[103] and Liu et al.[104] demonstrate that metal catalysts could react with diazo compounds to release dinitrogen molecules and form active metal carbenes as precursors to the insertion reactions. In the case of the phenol-based substrate, the initial step is the formation of a metallocarbene. Subsequently, the oxygen atom of the phenol attacks the electrophilic carbene carbon atom of the metallocarbene, which leads to the formation of an oxonium ylide **Int-2-10** through transition state **TS-2-10**, with a modest energy barrier of 14.4 kcal/mol. Through hydrogen bonding between the carbonyl oxygen from the diazo precursor and the phenol hydrogen, the dicarbonyl motif gets protonated, forming enol isomer **Int-2-13**, followed by leaving of the metal. Keto-enol tautomerization leads to the formation of the more stable keto isomer **2-8** (

Figure 2.6).
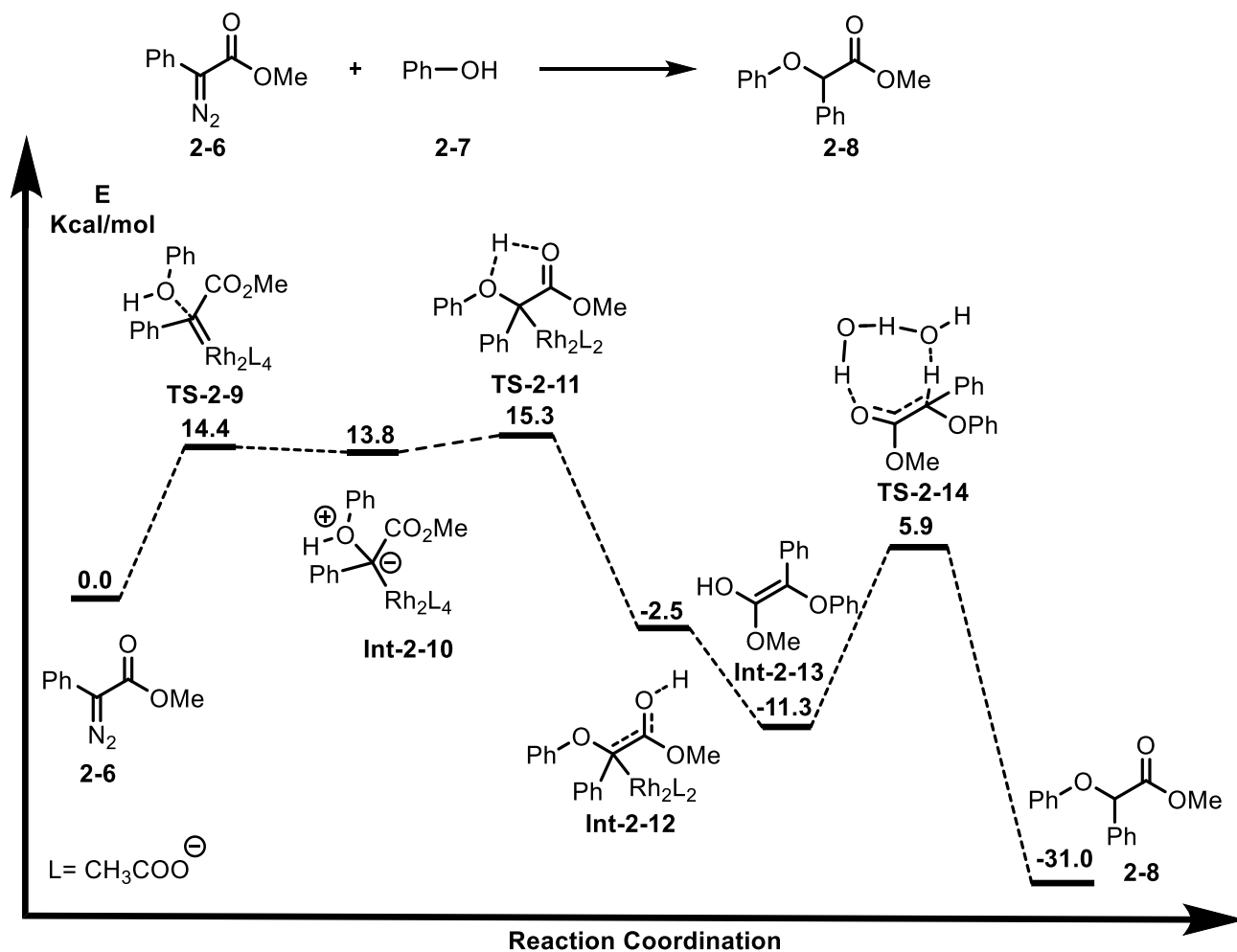
Figure 2.6. Reaction coordination diagram for the O-H insertion of phenol into diazo compounds

The reaction between diazo compounds and carboxylic acids in the presence of ruthenium salts may follow a similar pathway as the phenol-based substrate. Most likely, the reaction is initiated by the formation of a metallocarbene that switches the nucleophilic diazo to an electrophilic-based intermediate. Then, the formation of oxonium ylide may occur by an attack from the carboxylic acid oxygen onto the α–carbon of the metallocarbene, followed by protonation of the carbonyl oxygen, which then undergoes keto-enol tautomerization to produce the final product (**Scheme 2.4**).
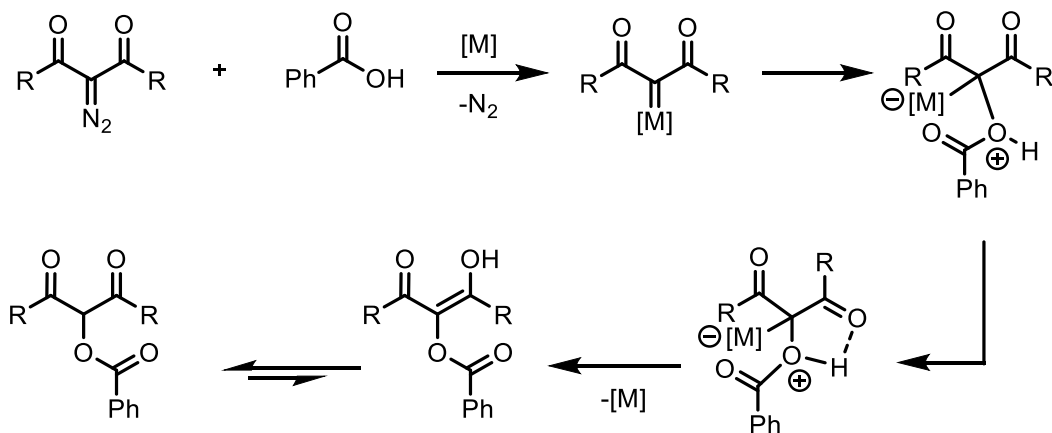
Scheme 2.4. Possible mechanism for the O-H insertion reaction of carboxylic acids and diazos

2.3.2   S-H Insertion of Diazo Compounds

Metal catalysts are shown to be efficient in facilitating the insertion of an S-H bond into α-diazoester. Some of the metal salt catalysts that were used are copper,[105] iridium,[106] ruthenium,[107] and iron (**Scheme 2.5**).[108] All of these reactions proceed under mild conditions and offer very high yields with low catalytic loading of the metal catalyst. The substrate scope of the reaction shows the use of substituted α-diazoester to be compatible with benzyl mercaptan and thiophenol.
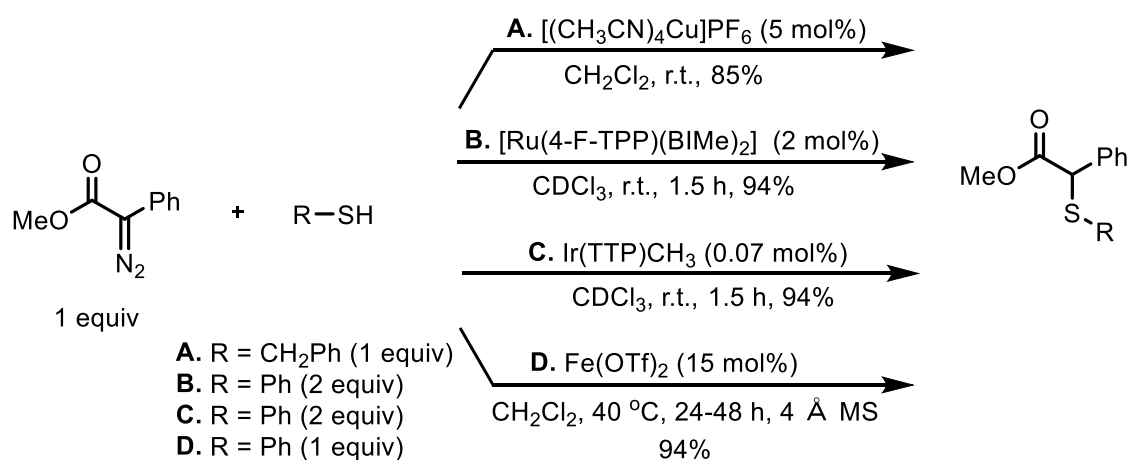
Scheme 2.5. Metal-catalyzed S-H insertion of thiols with diazos

The mechanism proposed for the reaction between α-diazoester and thiols to preform S-H insertion through the utilization of different transition metals catalysts follows similar mechanistic steps as metal-catalyzed O-H insertion reactions. First, there is an attack by the α-carbon of the diazo onto the metal catalyst to form metallocarbene intermediate **2-17** and release N_2 gas. Subsequently, the sulfur atom in R-SH attacks the electrophilic α-carbon of the metallocarbene. In the iridium catalyzed S-H insertion reaction, the negative Hammett ρ values suggest a buildup of positive charge on the sulfur atom during the S-H insertion reactions, which is consistent with the formation of metal-ylide species **2-19**. In analogy, a metal-bound ylide intermediate was recently suggested for a dirhodium-catalyzed S-H insertion with diazo reagents. In the case of iron-catalyzed S-H insertion, metal-ylide species or the release of metal catalysts to form sulfur ylide are both proposed as potential pathways. The last step is the protonation of the α-carbon of **2-29** and the release of the metal catalyst or the protonation of **2-20** to form the final product (**Scheme 2.6**).
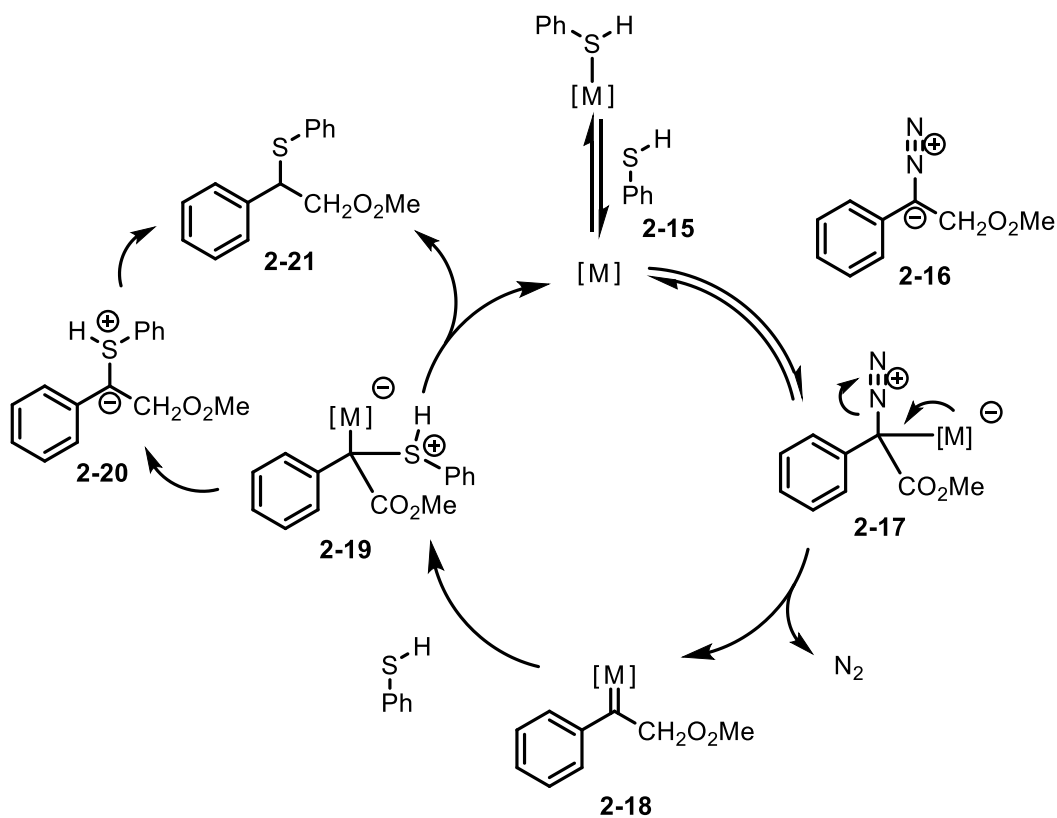
Scheme 2.6. Proposed mechanism for the S-H insertion reaction of thiols and diazos

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2.4   Proposal

The Lewis acidity of iodonium ylides will be investigated to perform X-H insertion (X = N, O, S) reactions into the α–carbon of iodonium ylides without the use of metal salts. This is unlike diazo compounds, for which the insertion reaction is only possible through the preformation of a metallocarbene intermediate. Electrostatic potential (ESP) mapping of iodonium ylides will be first generated to view the two σ-holes in iodonium ylides. A σ-hole on the iodine center of an iodonium ylide could coordinate with a heteroatom via halogen bonding. The electron-withdrawing power of the electrophilic iodine center may increase the Brønsted acidity of the coordinated acids, which may in turn, protonate the α–carbon through hydrogen transfer. A reductive elimination step may follow to remove iodobenzene and insert the heteroatom (X) into the α–carbon of the ylide.
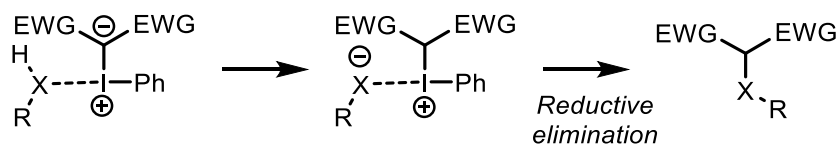
Scheme 2.7. Proposed mechanism of X-H insertion with iodonium ylides where (X = N, O, S)

2.5   Electrostatic Potential Mapping of Iodonium Ylides

The two σ-holes of iodonium ylides were investigated by the generation of ESP maps, which are also known as molecular electrical potential surfaces, and illustrate the charge distribution of molecules in 3D. These maps allow for the visualization of variably charged regions of a molecule. The knowledge of charge distributions can be used to locate potential sites of low electron densities such as σ-holes. Dr. Scott Hopkins performed these calculations.

ESP mapping showed the existence of two electrophilic sites in dimedone iodonium ylide **2-22** (**Figure 2.7**). The two σ-holes are different in terms of their electrophilic strength. The σ-hole extending from Ph-I bond (termed as σ-hole **I**) is weaker than the one extending from the R_2C^--I bond (R = EWG, $COR^{'}$), termed as σ-hole **T**.
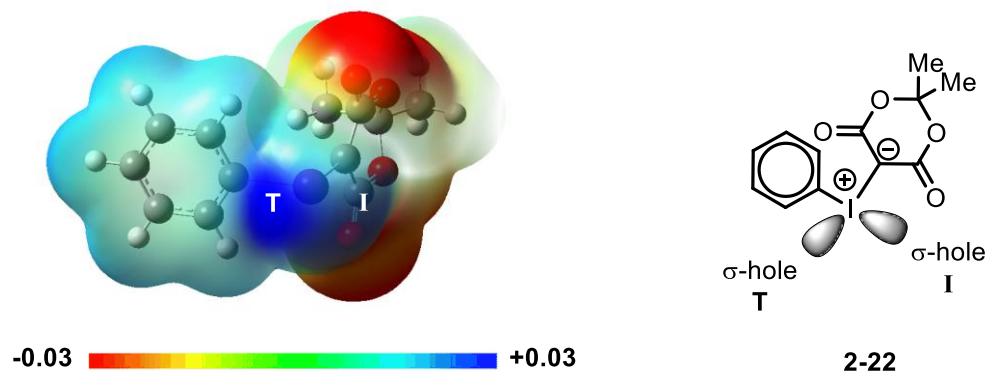
Figure 2.7. ESP mapping of ylide **2-22**

ESP calculations were also performed on a series of iodonium ylides, which showed that the strength of the sigma hole **T** slightly increases, from dimedone **2-23** to the ketoester **2–24**, to the Meldrum's acid diester **2-25** iodonium ylide. A stronger σ-hole may lead to the formation of a stronger halogen bond between the iodine center and an incoming nucleophile.
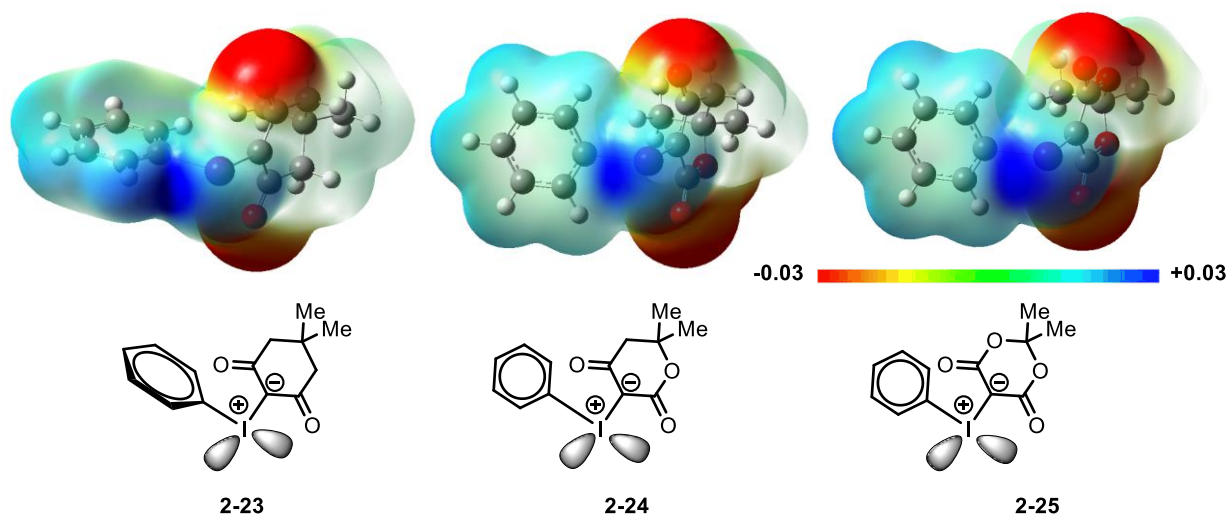
Figure 2.8. ESP mapping of iodonium ylides derived from dimedone **2-23,** ketoester **2-24**, and Meldrum's acid diester **2-25**

When changing the iodoarene group of a dimedone-derived iodonium ylide, the strength of the σ-holes also changed. For example, the σ-holes in the dimedone-derived iodonium ylide containing 1-naphthalene are less electropositive than the σ-holes in the dimedone-derived iodonium ylide containing 2,6-dimethoxy-4-methylphenyl (**Figure 2.9**).
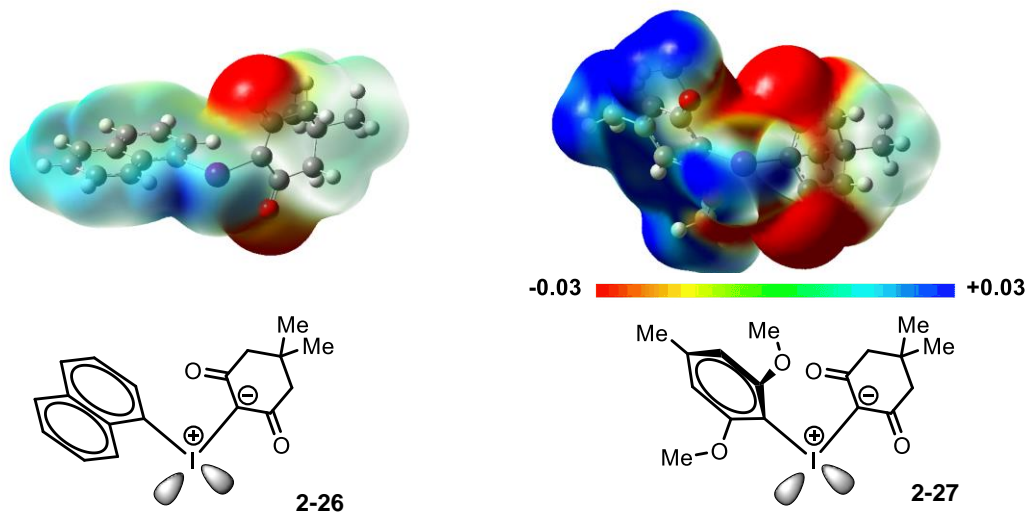
Figure 2.9. ESP mapping of iodonium ylides derived from dimedone

2.5.1 Analysis of the two σ-holes in iodonium ylides

The strength of the σ-holes may explain the regioselectivity observed when iodonium ylides react with soft vs. hard nucleophiles, as discussed in Chapter 1. As stated earlier, the work of Satyamurthy and Barrio shows that hard nucleophiles are regioselectively substituted on the aromatic ring of an iodonium ylide.[73] In contrast, the reactions of iodonium ylides with soft nucleophiles leads to substitution on the β-dicarbonyl section.[109]

Taking into consideration the two different σ-holes in iodonium ylides and the regioselective nature of some iodonium ylide reactions, an explanation into the observed selectivity may be attributed to the fact that each σ-hole has its own unique properties. The established reactivity of iodonium ylides involves two critical steps: ligand coupling and reductive elimination. In the first step, the nucleophile might be in an equilibrium between the two σ-holes, however, an interaction with a specific σ-hole may contain a significant covalent component that

facilitates the next step of reductive elimination. For any two coupling partners to undergo reductive elimination, they must be in a mutually *cis* orientation. Hence, the regioselectivity of the reactions of iodonium ylides with different nucleophiles can be attributed to the σ-holes that the nucleophile interacts the most strongly with. For example, ligand coordination to σ-hole **I** will lead to an addition occurring to the β-dicarbonyl moiety. On the other hand, when the coordination happens at the σ-hole **T**, the addition will occur on the phenyl ring (**Scheme 2.8**). The stronger σ-hole is predicted to react with hard nucleophiles is termed σ-hole **T**. On the other hand, the weaker σ-hole, according to ESP, that is termed as σ-hole **I** is the one anticipated to react with soft nucleophiles.
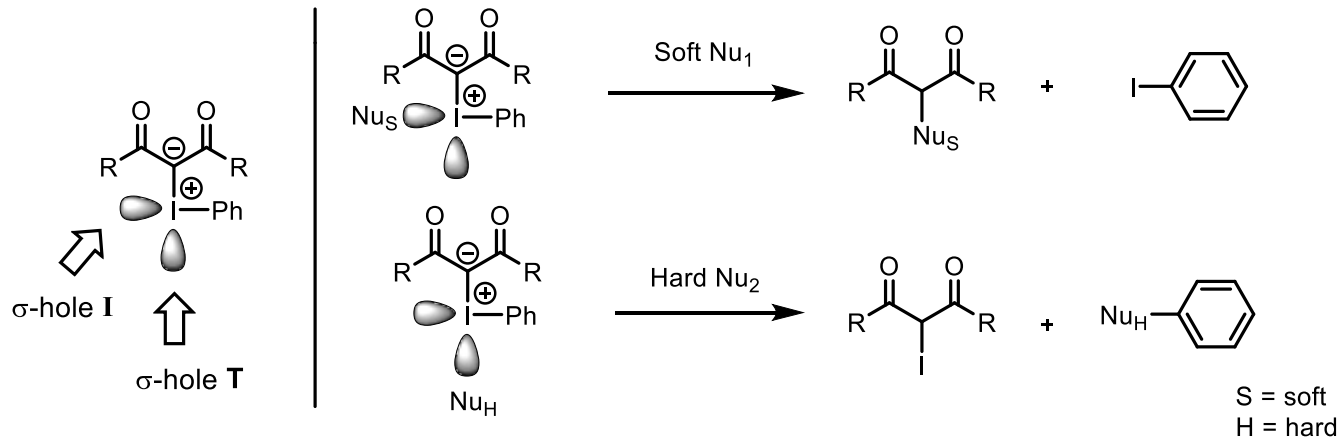
Scheme 2.8. Nucleophile selectivity of iodonium ylides

O-H insertion reactions of carboxylic acids and S-H insertion reactions of thiols into iodonium ylides may initiate through the coordination of the heteroatom to the σ-holes as the first step required for the reaction to take place. Since the heteroatoms may function as soft nucleophiles, a more predominate interaction may occur with σ-hole **I** via halogen bonding. The Lewis acidity of the iodine center may decrease the pKa of the heteroatom's hydrogen leading to protonation of the α-carbon. The last step is reductive elimination which leads to the final product (**Scheme 2.9**).
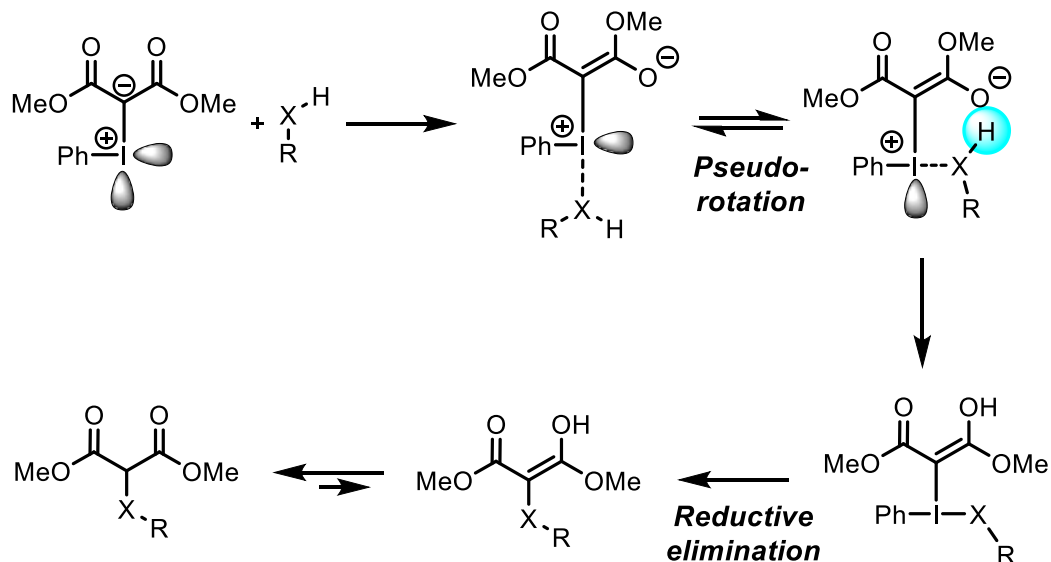
Scheme 2.9. Proposed mechanism for X-H insertion reactions into iodonium ylides that involves the use of σ-holes (X = S or O)

2.6   Reaction optimization

2.6.1   Reaction Optimization of O-H Insertion into Iodonium Ylides

Alkyl alcohols, phenols, and carboxylic acids were investigated to perform O-H insertion into the α−carbon of iodonium ylides. First, the reaction between carboxylic acids and iodonium ylides was investigated. The model substrate chosen for insertion reaction studies was benzoic acid and iodonium ylide **2-1b**. Iodonium ylide **2-1b** was easily synthesized and has very high solubility in various organic solvents. The initial optimization of the O-H insertion reaction of carboxylic acids and iodonium ylides included solvent screening and equivalents screening (**Table 2.1**).

Table 2.1. Optimization reaction of O-H insertion of carboxylic acid into iodonium ylide
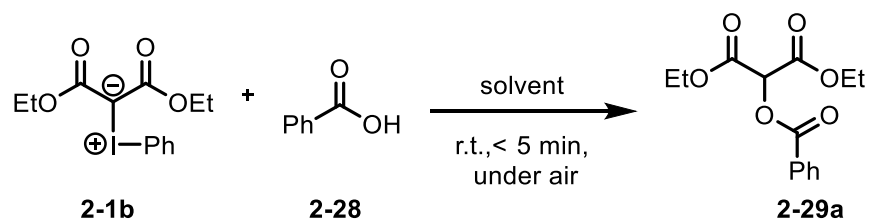
Entry	Equiv. of 2-1b	Equiv. of 2-28	Solvent	Yield (%)[a] 2-29a
1	1	2	DCM	97
2	2	1	DCM	99
3	1	1	DCM	95
4	1	1	MeCN	90
5	1	1	Toluene	89
6	1	1	DCE	90
7	1	1	Chloroform	88
8	1	1	MeOH	75

[a]Yield was determined by ^{1}H NMR using 10 μL of HMDSO as an internal standard.

The reaction appears to be completed after several minutes in very high yields. The reaction tolerates the use of different solvents, there is no need to use any of the reagents in excessive amounts to achieve a high yield. In the development of a new methodology, it is important to demonstrate the compatibility of the method with various substrates. Thus, a panel of carboxylic acids and iodonium ylides was subjected to the optimized O-H insertion conditions, employing 1:1 equivalent of acyclic iodonium ylide to carboxylic acid. The O-H insertion product was isolated as the sole product in excellent yields in a wide variety of carboxylic acids and iodonium ylides. The reaction accommodates carboxylic acids with varying functionalities, including amino acids with absolute chemoselectivity to carboxylic acids. In addition, the reaction tolerates a broad range of stable iodonium ylides (**Scheme 2.10**).
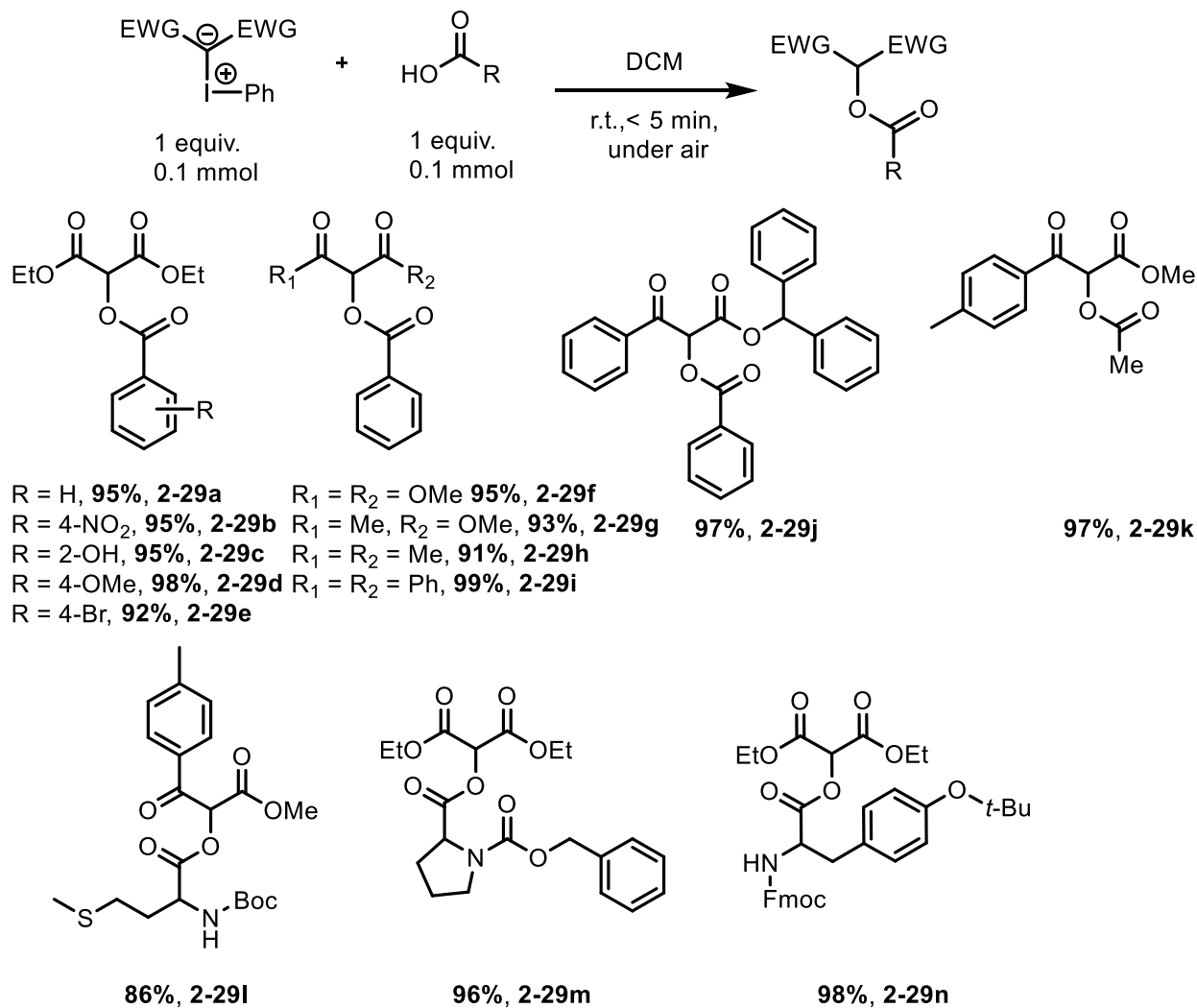
Scheme 2.10. Scope of the O-H insertion reaction between carboxylic acids and iodonium ylides

Next, the O-H insertion reaction between phenols and iodonium ylides was investigated. The reaction between iodonium ylide **2-1a** and phenol **2-30** resulted in 16% yield of the O-H insertion product **2-31**. The reaction time was 5 minutes and under an atmosphere of air. When the reactants were mixed, the solution turned brown, and the disappearance of the ylide was observed through TLC analysis. The ^{1}H NMR analysis showed the formation of other side products. Reduction of the β-dicarbonyl motif of the ylide was observed in 30% yield. The utilization of different solvents and equivalents of the starting materials did not improve the reaction yield. The use of additives did not increase the reaction yield as well (**Table 2.2**).
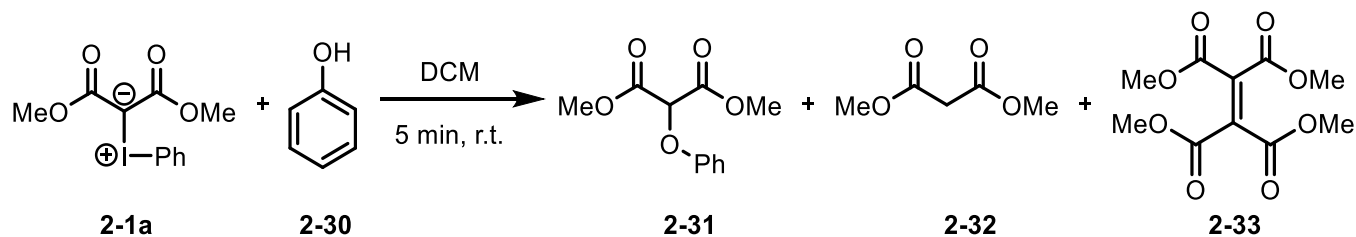
Table 2.2. Optimization of conditions for the reaction of iodonium ylides and phenols

Entry	Equiv. of 2-1a	Equiv. of 2-30	Solvent	Yield (%)[a] 2-31:2-32:2-33 [b]
1	1	2	DCM	16:30:15
2	2	1	DCM	20:24:10
3	1	1	DCM	10:20:17
4	1	1	MeCN	16:30:15
5	1	1	Toluene	16:30:15
6	1	1	DCE	16:30:15
7	1	1	Chloroform	16:30:15
8	1	1	MeOH	16:30:15

[a]Yield was determined by ^{1}H NMR using 10 μL of HMDSO as an internal standard.
[b]50% Theoretical yield.

Finally, the reaction of iodonium ylides with alcohols was investigated. Alcohols are ubiquitous and widely used as raw starting materials with broad applications in organic chemistry. Therefore, the functionalization of alcohols is a valuable reaction in synthetic organic chemistry. The O-H insertion reaction of an alcohol into an iodonium ylide was first performed using iodonium ylide **2-1b** and alcohol **2-34** in DCM at room temperature, but this reaction did not result in the anticipated O-H insertion product **2-35** (entry 1, **Table 2.3**). Different solvents, equivalents, and additives were tested, but none of the conditions resulted in the desired O-H insertion product (**Table 2.3**). Perhaps, the coordination between the oxygen of alcohol **2-34** and the iodine center of iodonium ylide **2-1b** did not lead to a significant drop in the Brønsted-Lowry acidity of alcohol hydrogen to protonate the dicarbonyl motif.
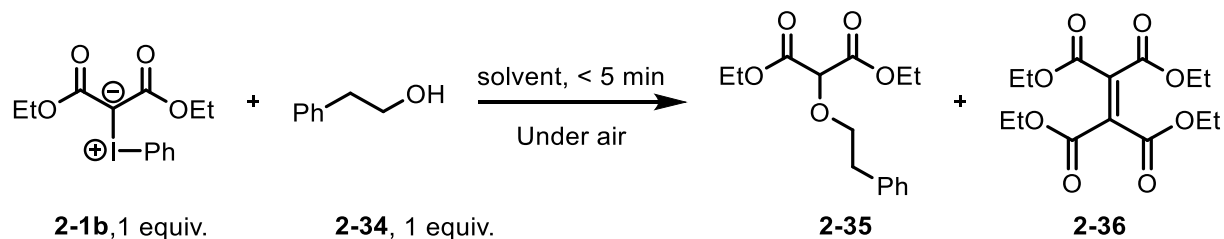
Table 2.3. Optimization of conditions for the reaction of iodonium ylides and alcohol

Entry	Equiv. of 2-1b	Equiv. of 2-34	Solvent	Additive	Temp.	Yield of 2-35[a]	Yield of 2-36[a,b]
1	1	2	DCM	-	r.t	-	50%
2	2	1	DCM	-	r.t	-	50%
3	1	1	DCM	-	r.t	-	50%
4	1	1	MeCN	-	80°C	-	50%
5	1	1	Toluene	-	r.t	-	50%
6	1	1	DCM	1 eq. MeSO$_3$H	r.t	-	50%
7	1	1	CHCl$_3$	N-Succinimide	r.t	-	50%

[a]Yield was determined by ^{1}H NMR using 10 μL of HMDSO as an internal standard.
[b]50% Theoretical yield.

Failing to achieve O-H insertion of alcohol into iodonium ylides under metal-free conditions led to investigating the use of light. When irradiating a mixture of iodonium ylides with alcohols, O-H insertion may occur. Blue light irritation of iodonium ylides leads to the formation of diradical intermediate, which then may abstract a hydrogen from the alcohol. The reductive elimination step follows, in order to form the final product **2-35** and eliminate iodobenzene (**Scheme 2.11**).
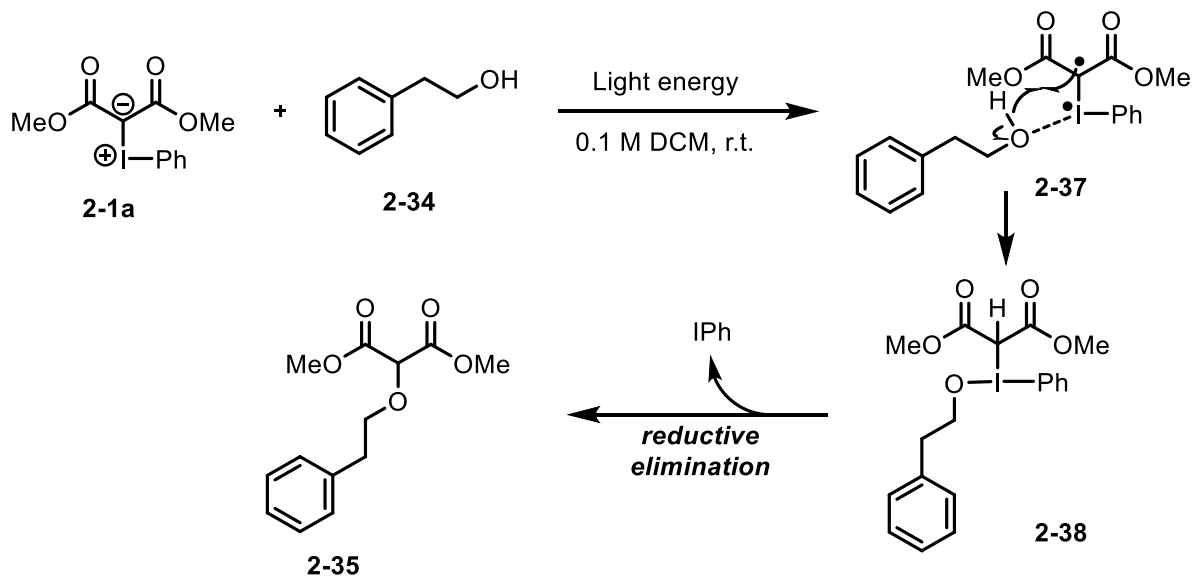
Scheme 2.11. Proposed reaction mehcanism for O-H insertion of phenol into iodonium ylides under blue light irridiation

The reaction between iodonium ylide **2-1a** and alcohol **2-34** under blue light irradiation did not result in O-H insertion product **2-35**. The major product was β-dicarbonyl dimer **2-36**.

Scheme 2.12. O-H insertion reaction of alcohol into iodonium ylides under blue light irradiation

2.6.2 Reaction Optimization of S-H Insertion into Iodonium Ylides

In the past few decades, hypervalent iodine compounds have been developed as selective reagents for oxidative transformations and the construction of carbon-heteroatom and carbon-

carbon bonds. Hypervalent iodine reagents are thiophilic in nature and have been shown to activate sulfur atoms in compounds such as thioethers, thioamides, thioureas, and thiols.[110] An investigation into the activation of simple thiols by hypervalent iodine reagents have been reported by Rattanangkool and coworkers.[111] The reaction involves ligand exchange between PIDA **2-39** and thiol, leading to the formation of sulfenyl iodide intermediate **2-40**. A second molecule of thiol then undergoes ligand exchange with **2-40** to produce the disulfide product **2-41**. This process is facilitated by the reductive elimination that generates iodobenzene, which is a well-known reaction for hypervalent iodine compounds.
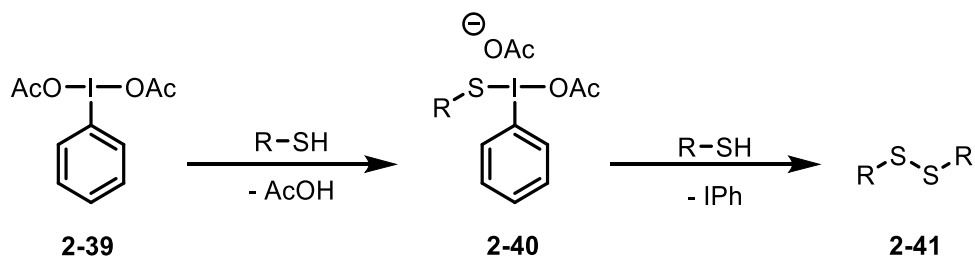
Scheme 2.13. Reaction mechanism for disulfide bond formation using PIDA and thiols

Many other hypervalent iodine reagents facilitate the formation of the disulfide product. Therefore, when investigating the S-H insertion reaction of thiols into iodonium ylide, a disulfide product was anticipated as a side product. The study began with the reaction of **2-1a** and readily **2-42** (2 equiv.) in DCM at room temperature (**Table 2.4**). Although S-H insertion was observed in 20% yield, the major product was the S-S bond formation, which consumes the thiols in the reaction mixture. Altering the conditions to two equivalents of thiols slightly increased the S-H insertion product to 28% yield. The addition of two equivalent of the iodonium ylide did not increase the reaction yield. Hypervalent iodine is known to facilitate S-S bond formation readily, and it is observed as the major product in this reaction. In order to solve this problem, the use of an additive that slows down sulfur dimerization was investigated. First, the use of acids to protonate the thiols before the addition of the iodonium ylide was evaluated. To our delight, it was discovered that in the presence of the organic methanesulfonic acid, the reaction smoothly afforded the desired S−H bond insertion product **2-43a** in good yield (entries 1-3 and 6-10, **Table 2.4**).
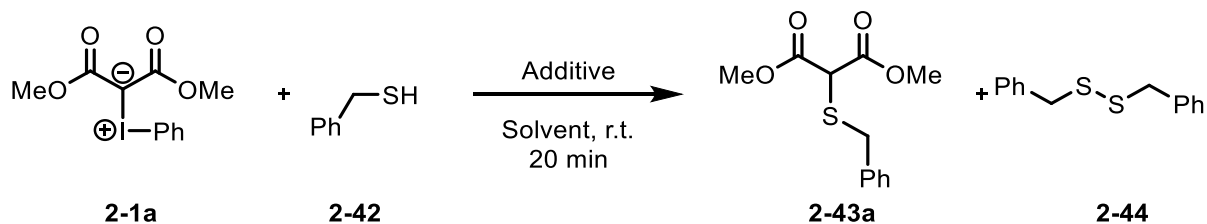
Table 2.4. Optimization of conditions for the reaction of iodonium ylides and benzyl mercaptan

Entry	Equiv. of 2-1a	Equiv. of 2-42	Solvent	Additive	Temp.	Yield (%)[a] 2-43a:2-44[b]
1	1	1	DCM	-	rt	16:40
2	2	1	DCM	-	rt	23:37
3	1	2	DCM	-	rt	28:30
4	1	2	Toluene	20% Succinimide	70 °C	40:23
5	1	2	Toluene	20% Succinimide	rt	38:24
6	1	2	DCM	20% Succinimide	rt	35:25
7	1	1	DCM	100% Succinimide	rt	45:15
8	1	1	DCM	50% MeSO$_3$H	rt	50:11
9	1	1	DCM	100% MeSO$_3$H	rt	80:5

[a]Yield was determined by ^{1}H NMR using 10 μL of HMDSO as an internal standard.
[b]50% Theoretical yield.

The S-H bond insertion reactions into iodonium ylides succeeded under the optimal reaction conditions using 1 equivalent of MeSO$_3$H in dichloromethane at room temperature with various substituted thiophenols (**Scheme 2.14**). High yields were obtained using substituted thiophenols containing EDGs, such as methyl and EWGs in the *para*-position, such as Br (**Scheme 2.14**).
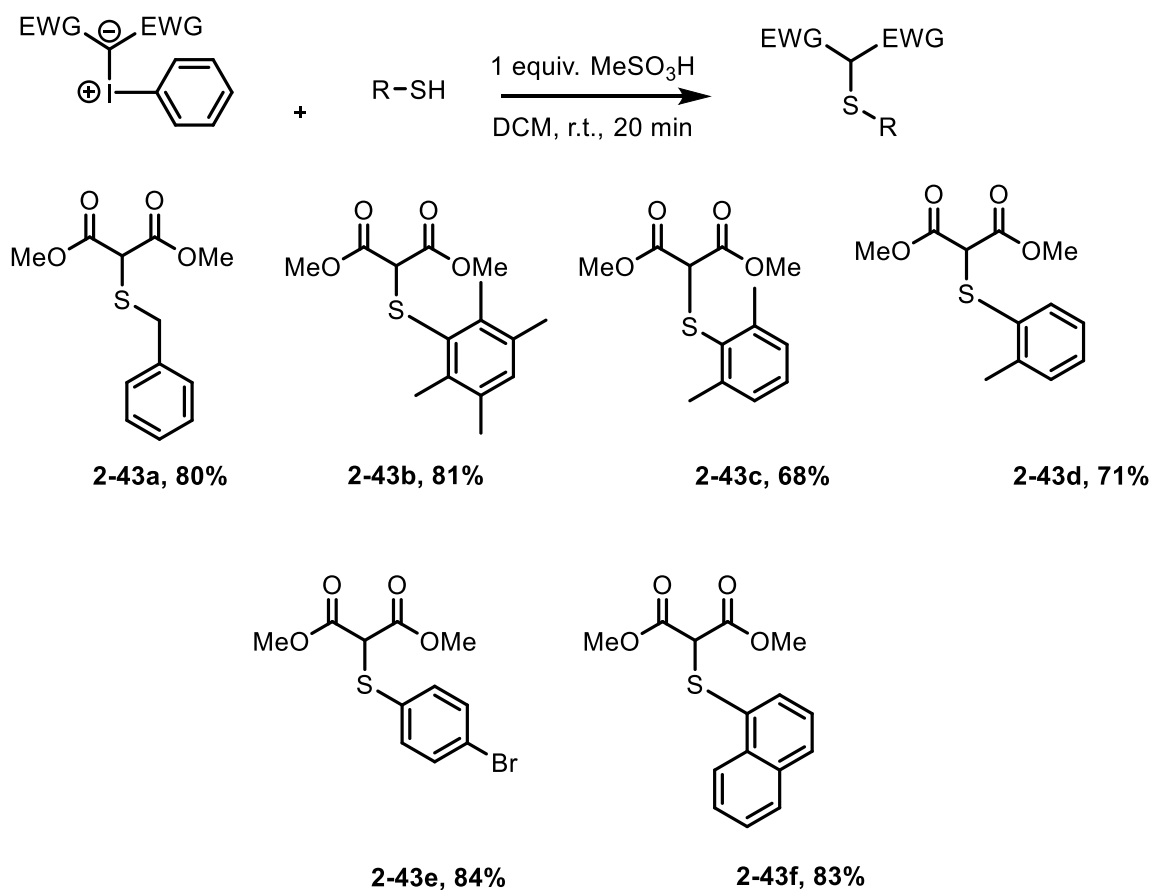
Scheme 2.14. Examples of S-H insertion of thiols into iodonium ylides

2.6.2.1   Mechanistic study

To further understand the insertion reaction between X-H (X= S, O) and iodonium ylides, a series of competition experiments were conducted (**Table 2.5**, 4–6). First, I tested the effects of increasing the partially negative charge on the carbonyl of the carboxylic acids. The use of carboxylic acid with an EDG could increase the coordination between the carbonyl and the iodine center, leading to a faster conversion to products with higher yields. On the other hand, upon adding an EWG, the Brønsted-Lowry acidity of the carboxylic acid would increase, making it easier for the proton to protonate the α-carbon of the dicarbonyl motif of iodonium ylides.
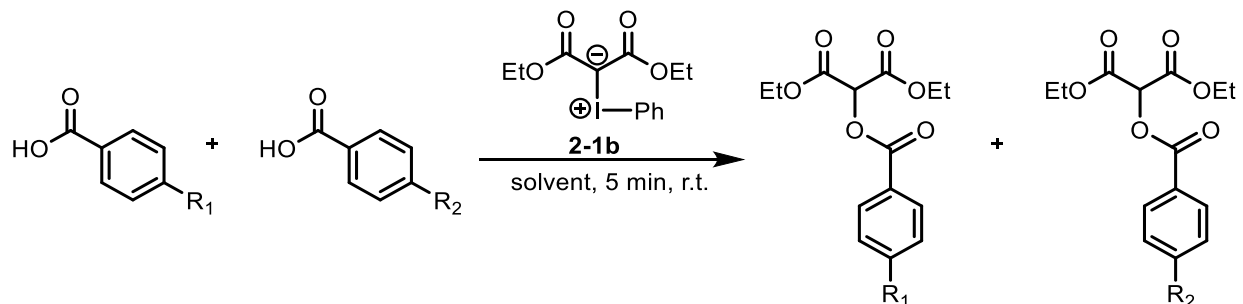
Table 2.5. Competition reaction of the O-H insertion reaction of *para*-substituted benzoic acids and iodonium ylides

Entry	R_1	R_2	Solvent	Yield (%)[a] R_1:R_2
1	H (**2-28**)	OMe (**2-45**)	DCM	34:66
2	H (**2-28**)	NO$_2$ (**2-47**)	DCM	30:60
3	OMe (**2-45**)	NO$_2$ (**2-47**)	DCM	10:80
4	CF$_3$ (**2-46**)	OMe (**2-45**)	MeOH	70:30

[a] Yield was determined by ^{1}H NMR using 10 µL of HMDSO as an internal standard.

The addition of EDG or EWG on the *para*-position of benzoic acid resulted in a higher yield of the O-H insertion into iodonium ylide when running competition reactions (**Table 2.5**, entries 1 and 2). This may suggest that both factors the Brønsted-Lowry acidity, and the partially negative charge on the carbonyl group of the carboxylic acid affect the reaction yield. Mechanistically it is proposed that the coordination between the carbonyl group and iodine center of the ylide causes the acidic proton on the carboxylic acid to increase in acidity enabling the reaction to proceed. Both entries 1 and 2 (**Table 2.5**) do not contradict the proposed mechanism. When performing a competition reaction between a benzoic acid with *para*-substituted EWG and a benzoic acid with *para*-substituted EDG (**Table 2.5**, entries 3 and 4), the O-H insertion reaction favors the benzoic acid with a *para*-substituted EWG. This could imply that the Brønsted-Lowry acidity of the carboxylic acid plays a bigger part in the reaction mechanism.

The use of iodonium ylide with an EWG on the aryl iodide increases the Lewis acidity of the ylide, which may lead to stronger interactions with the Lewis base (the carbonyl group of the carboxylic acid). A control reaction was performed where 1 equiv. iodonium ylide with an EDG in the *para*-position is mixed with 1 equiv. iodonium ylide not substituted with any groups. To this mixture, 1 equiv. carboxylic acid was added. After five minutes, ^{1}H NMR analysis of the mixture showed the presence of 100% of aryl iodide **2-48** and 50% of the aryl iodide **2-49**. Unfortunately,

the results were inconclusive due to the fast decomposition of the ylide. The reaction was performed four times at 0 ℃, and similar results were obtained for each instance. The outcomes were not conclusive.
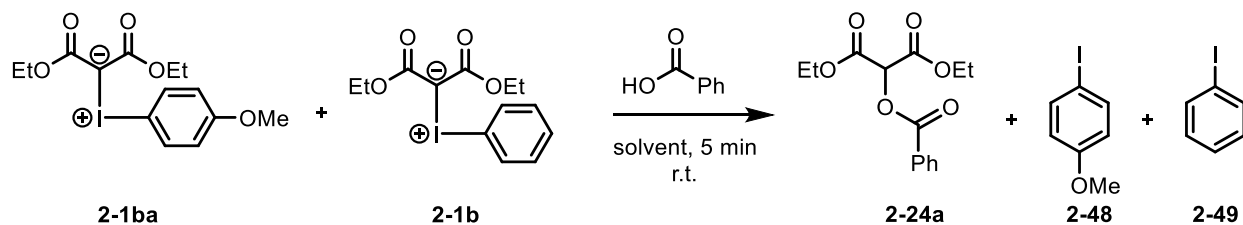
Scheme 2.15. Control competition reaction between **2-1b** and **2-1ba** to perform O-H insertion reaction with benzoic acid

The reaction between carboxylic acids and iodonium ylides and the reaction of thiols (without additives) and iodonium ylides may follow the same mechanistic steps. Halogen bonding between the iodine center and an electronegative atom may initiate the insertion reactions. Pseudorotation of the nucleophilic center and two sigma holes of the iodonium ylide is believed to occur; however, since thiols and carbonyl groups are considered to be weak nucleophiles (**Scheme 2.16** and **Scheme 2.17**), the more predominate coordinate is believed to occur for sigma holes **I**. Therefore, a proton transfer on the carbonyl oxygen or the α-carbon of the ylide may occur. Lastly, a reductive elimination is responsible for the formation of the final product.
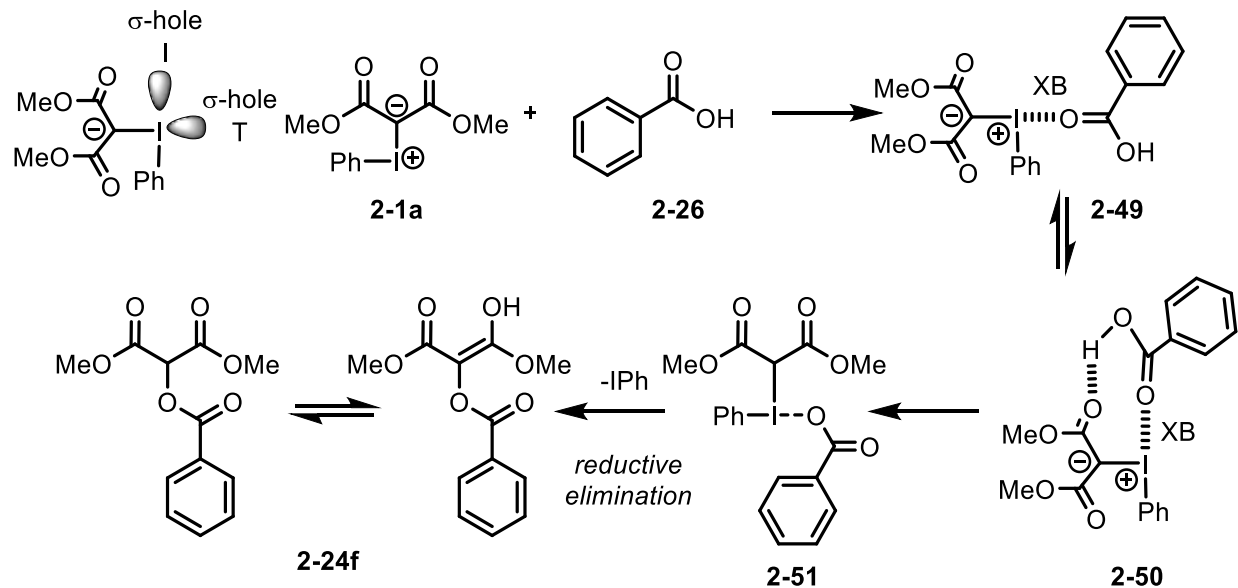
Scheme 2.16. The proposed reaction mechanism for the O-H insertion reaction of carboxylic acids into iodonium ylides
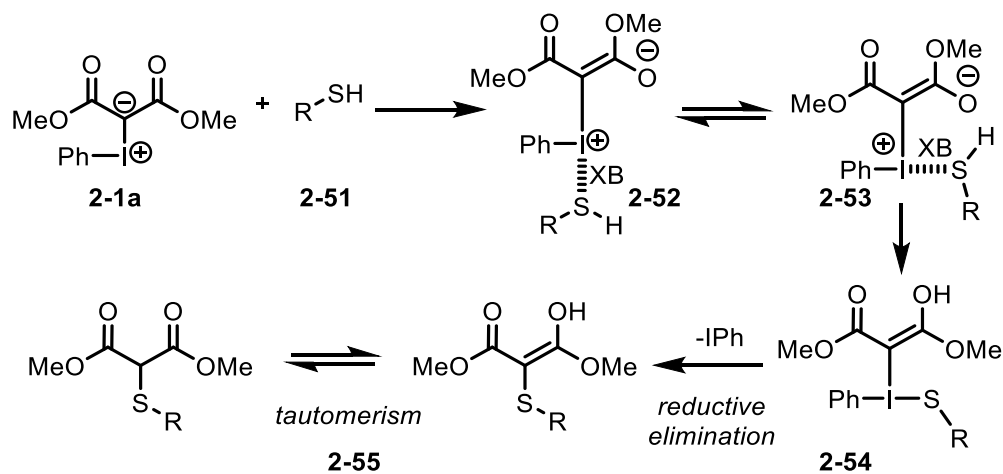
Scheme 2.17. The proposed reaction mechanism for the S-H insertion reaction of thiols into iodonium ylides

2.7 Conclusion

To sum up, the development of an efficient metal-free insertion reaction of iodonium ylides into S-H and O-H bond of thiols and carboxylic acids, respectively, was successfully achieved. A wide range of carboxylic acids was used with good to excellent yields. For the first time, the insertion of iodonium ylides into S-H bond of thiols in the presence of methanesulfonic acid has been reported. The desired products were obtained in excellent and short reaction times. The metal-like properties of iodine allow for the occurrence of these reactions under metal-free conditions. The iodine center in an iodonium ylide is a Lewis acidic site with two sigma holes. The coordination between a heteroatom and the σ-holes on the iodine center of the iodonium ylide via halogen bonding is thought to be the key for the observed reactivity. The use of iodonium ylides as organic Lewis-acids should be investigated further in order to reveal their potential of activating cyclization reactions, or aldol reactions.

2.8   Supporting Information

All reactions were carried out in flame-dried glassware. Solvents were either obtained from a JC Meyer solvent purification system or purified according to the Purification of Laboratory Chemicals handbook. All reagents were purchased from Sigma-Aldrich and used without further purification. ^{1}H NMR spectra were recorded on Bruker instruments at 300 MHz, and were referenced to residual ^{1}H shift in CDCl$_3$ (7.24 ppm). ^{13}C NMR were recorded at 75 or 125 MHz, and CDCl$_3$ (77.0 ppm) was used as the internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br s = broad singlet, m = multiplet. Reactions were monitored by thin-layer chromatography (TLC) on commercial silica pre-coated plates with a particle size of 60 Å and viewed by UV lamp (254 nm) or by ^{1}H NMR. Flash chromatography was performed using 60Å (230-400 mesh) silica gel. InfraRed (IR) data was recorded using an ATR-FTIR (Attenuated Total Reflection Fourier Transform InfraRed) instrument. The following abbreviations were used to explain the IR peak intensities: (s) = strong, (m) = medium, (w) = weak. Positive ion electrospray ionization (ESI) was performed with a Thermo Scientific Q-Exactive hybrid mass spectrometer. Accurate mass determinations were performed at a mass resolution of 70,000. For ESI, samples were infused at 10 µL/min in 1:1 CH$_3$OH/H$_2$O + 0.1% formic acid or CH$_3$OH/H$_2$O + 0.1% formic acid or or CH$_3$OH/H$_2$O + 0.1% LiOAc.

2.8.1   General Procedure 1- Synthesis of Phenyliodonium Ylides of Acyclic 1,3-Dicarbonyl Compounds (GP1)

The following procedure was based upon a protocol reported by Lick.[112] To a cooled (–5 °C) 50 mL round bottom flask containing a stirring solution of acyclic 1,3-dicarbonyl compound (5.0 mmol) in MeOH (3.5 mL) was added 30% (wt/v) KOH/MeOH (3.5 mL) solution over 1 minute. To this mixture, iodobenzene diacetate (5.0 mmol) in MeOH (8 mL) was added slowly to ensure the reaction temperature remained < 0 °C. After allowing the mixture to stir for 30–60 min, the resulting reaction mixture was poured onto ice (~100 mL), diluted with water (30 mL), and then transferred to a separatory funnel and extracted with DCM (30 mL × 3). The combined organic extracts were dried over MgSO4, filtered, and then concentrated to ~20% of their original

volume using a rotary evaporator. The resulting solution was treated with solvent (e.g., Et$_2$O and/or hexanes) and cooled to 0 °C to induce precipitation of the ylide. The solid was collected via suction filtration and dried in vacuo to yield the phenyliodonium ylides as typically white amorphous solids and were either used immediately or stored in a –20 °C freezer.
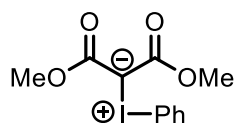
Dimethyl 2-(phenyl-λ^3-iodaneylidene)malonate (**2-1a**): Iodonium ylide **2-1a** was prepared according to Charette's literature procedure[113] from dimethyl malonate (0.693 mL, 6.0 mmol, 1 equiv.), KOH (2.0 g, 36 mmol, 6 equiv.) and (diacetoxyiodo)benzene (2.13 g, 6.0 mmol, 1 equiv.) in CH$_3$CN (20 mL) for 2 h at 0 °C. Purification by trituration (CH$_2$Cl$_2$:Et$_2$O 1:10) led to the title compound isolated as a white solid (1.51 g, 75% yield). The characterization data matches what has already been reported in the literature.[115] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.72 (d, J = 8.3 Hz, 2 H), 7.52 (t, J = 7.5 Hz, 1 H), 7.40 (t, J = 7.6 Hz, 2 H), 3.73 (s, 6 H).
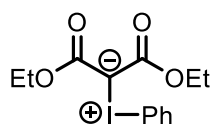
Diethyl 2-(phenyl-λ^3-iodaneylidene)malonate (**2-1b**): Iodonium ylide **2-1b** was prepared according to Charette's literature procedure[113] from diethyl malonate (0.76 mL, 5.0 mmol, 1 equiv.), KOH (1.68 g, 30 mmol, 6 equiv.) and (diacetoxyiodo)benzene (1.60 g, 5.0 mmol, 1 equiv.) in MeOH (15 mL) for 2 h at 0 °C. Purification by trituration (CH$_2$Cl$_2$:Et$_2$O 1:10) led to the title compound isolated as a white solid (1.11 g, 70% yield). The characterization data matches what has already been reported in the literature.[114] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.75-7.70 (m, 2 H), 7.53-7.47 (m, 1 H), 7.41-7.34 (m, 2 H), 4.16 (q, J = 7.1 Hz, 4 H), 1.25 (t, J = 7.1 Hz, 6 H).
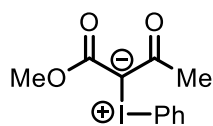
Methyl 3-oxo-2-(phenyl-λ^3-iodaneylidene)butanoate (**2-1c**): Iodonium ylide **2-1c** was prepared according to Charette's literature procedure[113] from methyl acetoacetate (0.53 mL, 5.0 mmol, 1 equiv.), KOH (1.68 g, 30 mmol, 6 equiv.) and (diacetoxyiodo)benzene (1.60 g, 5.0 mmol, 1 equiv.) in MeOH (15 mL) for 2 h at 0 °C. Purification by trituration (CH$_2$Cl$_2$:Et$_2$O 1:10) led to the title compound isolated as a white solid (1.11 g, 70% yield). The characterization data matches what has already been reported in the literature.[115] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.76 (d, J = 8.1 Hz, 2 H), 7.52 (t, J = 7.6 Hz, 1H), 7.37 (t, J = 7.8 Hz, 2 H), 3.67 (s, 3 H), 2.58 (s, 3 H).
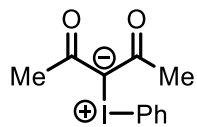
3-(Phenyl-λ^3-iodaneylidene)pentane-2,4-dione (**2-1d**): Iodonium ylide **2-1d** was prepared according to Charette's literature procedure[113] from pentane-2,4-dione (0.51 mL, 5.0 mmol, 1 equiv.), KOH (1.68 g, 30 mmol, 6 equiv.) and (diacetoxyiodo)benzene (1.60 g, 5.0 mmol, 1 equiv.) in MeOH (15 mL) for 2 h at 0 °C. Purification by trituration (CH$_2$Cl$_2$:Et$_2$O 1:10) led to the title compound isolated as a white solid (0.775 g, 50% yield). The characterization data matches what has already been reported in the literature.[116] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.82 (d, J = 8.7 Hz, 2 H), 7.51 (t, J = 8.7 Hz, 1 H), 7.35 (t, J = 8.7 Hz, 2 H), 2.51 (s, 6 H).
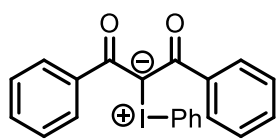
1,3-Diphenyl-2-(phenyl-λ^3-iodaneylidene)propane-1,3-dione (**2-1e**): Iodonium ylide **2-1e** was prepared according to Charette's literature procedure[113] from 1,3-diphenylpropane-1,3-dione (1.12 g, 5.0 mmol, 1 equiv.), KOH (1.68 g, 30 mmol, 6 equiv.) and (diacetoxyiodo)benzene (1.60 g, 5.0 mmol, 1 equiv.) in MeOH (15 mL) for 2 h at 0 °C. Purification by trituration (CH$_2$Cl$_2$:Et$_2$O 1:10) led to the title compound isolated as a yellow solid (1.49 g, 70% yield). The characterization data matches what has already been reported in the literature.[112] ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.04-8.06 (m, 2 H), 7.55-7.59 (m, 2 H), 7.41-7.34 (m, 2 H), 7.23-7.26 (m, 4 H), 7.08-7.13 (m, 1 H), 6.92-7.96 (m, 4 H).

Benzhydryl 3-oxo-3-phenyl-2-(phenyl-λ^3-iodaneylidene)propanoate (**2-1f**): Iodonium ylide **2-1f** was formed via GP1 using benzhydryl benzoylacetate (1.27 g, 5.0 mmol). Following the concentration of the organic extracts, the solution containing the crude iodonium ylide has precipitated the addition of Et$_2$O and hexanes. Vacuum filtration yielded the title compound as a white amorphous solid (1.52 g, 57% yield). The characterization data matches what has already been reported in the literature.[112] **^{1}H NMR** (500 MHz, CDCl$_3$): δ 7.80 (d, J = 7.8 Hz, 2 H), 7.59 (d, J = 7.1 Hz, 2 H), 7.52 (t, J = 7.5 Hz, 1 H), 7.42 (t, J = 7.3 Hz, 1 H), 7.37-7.32 (m, 4 H), 7.24-7.21 (m, 6 H), 7.07-7.03 (m, 4 H), 6.80 (s, 1 H).
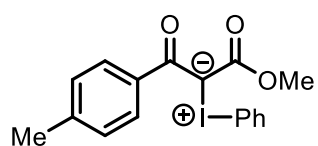
Methyl 3-oxo-2-(phenyl-λ^3-iodaneylidene)-3-(p-tolyl)propanoate (**2-1g**): Iodonium ylide **2-1g** was synthesized via GP1 using methyl (4-toluoyl)acetate (1.15 g, 5.0 mmol). A solution of the title compound dissolved in DCM was treated with Et$_2$O, cooled to 0 °C, and the resulting precipitate was collected using suction filtration to yield the title compound as a white amorphous solid (1.18 g, 60% yield). The characterization data matches what has already been reported in the literature.[112] **^{1}H NMR** (500 MHz, CDCl$_3$) δ 7.85 (d, $J = 7.6$ Hz, 2 H), 7.52 (t, $J = 7.4$ Hz, 1 H), 7.46 (d, $J = 7.5$ Hz, 2 H), 7.39 (t, $J = 7.4$ Hz, 2 H), 7.14 (d, $J = 7.5$ Hz, 2 H), 3.49 (s, 3 H), 2.36 (s, 3 H).

2.8.2 General Procedure 2 - O-H Insertion of Carboxylic Acids into Iodonium Ylides (GP2)

Into a dry round bottom flask (10.0 mL) was added iodonium ylide (0.1 mmol, 1 equiv.), CH$_2$Cl$_2$ (1.0 ml, 0.1 M), and benzoic acid (0.1 mmol, 1 equiv.). The mixture was stirred at room temperature until the reaction was observed to be complete by TLC or NMR analysis. The mixture was then evaporated to dryness and purified by column chromatography, eluting with mixtures of ethyl acetate and hexanes. The use of column chromatography can be avoided when using high vacuum to remove iodobenzene.
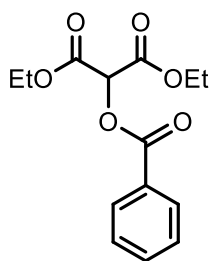
Diethyl 2-(benzoyloxy)malonate (**2-29a**): Synthesized according to GP2 using iodonium ylide **2-1b** (0.036 g, 0.10 mmol, 1 equiv.), benzoic acid (0.012 g, 0.10 mmol, 1 equiv.), DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 8:1) led to the title compound isolated as a white oil (0.027 g, 95% yield). R$_f$ = 0.65 (hexanes:EtOAc 3:1). The characterization data matches what has already been reported in the literature.[102] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 8.10–8.15 (m, 2 H), 7.58–7.61 (m, 1 H), 7.44–7.50 (m, 2 H), 5.76 (s, 1 H), 4.30-4.37 (m, 4 H), 1.33 (t, $J = 7.2$ Hz, 6 H).
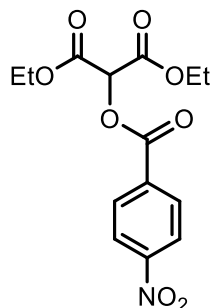
Diethyl 2-((4-nitrobenzoyl)oxy)malonate (2-29b): Synthesized according to GP2 using iodonium ylide **2-1b** (0.036 g, 0.10 mmol, 1 equiv.), 4-nitrobenzoic acid (0.017 g, 0.10 mmol, 1 equiv.), DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white oil (0.031 g, 95% yield). R_f = 0.55 (hexanes:EtOAc 3:1). The characterization data matches what has already been reported in the literature.[102] **¹H NMR** (300 MHz, CDCl$_3$): δ 8.33 (s, 4 H), 5.79 (s, 1 H), 4.31-4.41 (m, 4 H), 1.36 (t, *J* = 7.1 Hz, 6 H).
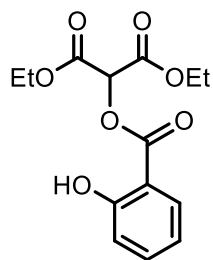
Diethyl 2-((2-hydroxybenzoyl)oxy)malonate (2-29c): Synthesized according to GP2 using iodonium ylide **2-1b** (0.036 g, 0.10 mmol, 1 equiv.), salicylic acid (0.014 g, 0.10 mmol, 1 equiv.), DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a clear oil (0.028 g, 95% yield). R_f = 0.61 (hexanes:EtOAc 3:1). The characterization data matches what has already been reported in the literature.[102] **¹H NMR** (300 MHz, CDCl$_3$): δ 10.15 (br. s, 1 H), 8.02 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.50–7.56 (m, 1 H), 7.00-7.03 (dd, *J* = 7.9 Hz, 1.6 Hz, 1 H), 6.92–6.98 (m, 1 H), 5.76 (s, 1 H), 4.32-4.40 (m, 4 H), 1.35 (t, *J* = 7.1 Hz, 6 H).
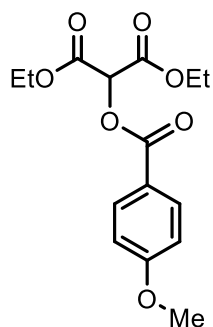
Diethyl 2-((4-methoxybenzoyl)oxy)malonate (2-29d). Synthesized according to GP2 using iodonium ylide **2-1b** (0.036 g, 0.10 mmol, 1 equiv.), 4-methoxybenzoic acid (0.015 g, 0.10 mmol, 1 equiv.), DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a clear oil (31 g, 98% yield). R_f = 0.50 (hexanes:EtOAc 3:1). The characterization data matches what has already been reported in the literature.[9] **¹H NMR** (300 MHz, CDCl$_3$): δ 8.07 (d, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 5.72 (s, 1 H), 4.27-4.36 (m, 4 H), 3.87 (s, 3 H), 1.32 (t, *J* = 7.1 Hz, 6 H).
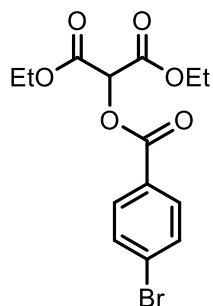
Diethyl 2-((4-bromobenzoyl)oxy)malonate (**2-29e**). Synthesized according to GP2 using iodonium ylide **2-1b** (0.036 g, 0.10 mmol, 1 equiv.), 4-bromobenzoic acid (0.015 g, 0.10 mmol, 1 equiv.), DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white crystals (0.033 g, 95% yield). R_f = 0.60 (hexanes:EtOAc 3:1). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.61-7.99 (AA'BB', 4 H), 5.75 (s, 1 H), 4.33-4.36 (m, 4 H), 1.34 (t, J = 7.1 Hz, 6 H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 164.4, 164.3, 131.9, 131.6, 129.1, 127.4, 72.9, 62.6, 14.0. **IR** (**ATR**): 2919.1 (w), 1760.7 (m), 1743.7 (m), 1723.9 (s), 1230.4 (s), 1117.9 (s) cm^{-1}. **HRMS** (**ESI**): Calculated for C$_{14}$H$_{15}$^{79}BrO$_6$Li (M+Li)$^+$ 365.0216, found 365.0207. Calculated for C$_{14}$H$_{15}$^{81}BrO$_6$Li (M+Li)$^+$ 367.0195, found 367.0186.
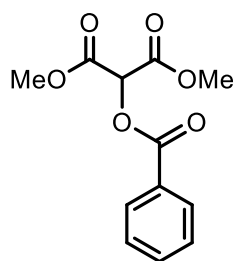
Dimethyl 2-(benzoyloxy)malonate (**2-29f**): Synthesized according to GP2 using iodonium ylide **2-1a** (0.033 g, 0.10 mmol, 1 equiv.), benzoic acid (0.012 g, 0.10 mmol, 1 equiv.), DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white oil (0.023 g, 91% yield). R_f = 0.24 (hexanes:EtOAc 3:1). The characterization data matches what has already been reported in the literature.[117] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 8.14–8.17 (m, 2 H), 7.61–7.66 (m, 1 H), 7.47–7.52 (m, 2 H), 5.83 (s, 1 H), 3.89 (s, 6 H).
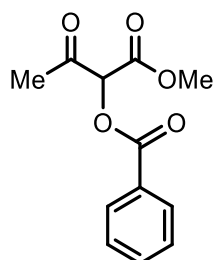
1-Methoxy-1,3-dioxobutan-2-yl benzoate (**2-29g**): Synthesized according to GP2 using iodonium ylide **2-1c** (0.032 g, 0.10 mmol, 1 equiv.), benzoic acid (0.012 g, 0.10 mmol, 1 equiv.), DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white oil (0.020 g, 85% yield). R_f = 0.75 (hexanes:EtOAc 3:1). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 8.14 (d, J = 8.7 Hz, 1 H), 7.63-7.67 (t, J = 8.6 Hz, 2 H), 7.48-7.53 (t, J = 8.6 Hz, 2 H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 197.6, 165.1, 133.9,

130.1, 128.6, 128.4, 78.0, 53.2, 27.3. **IR** (**ATR**): 3064.9 (w), 1759.5 (m), 1716.4 (s), 1100.3 (s), 1255.9 (s), 711.3 (s) cm^{-1}. **HRMS** (**ESI**): Calculated for $C_{12}H_{12}O_5Li$ (M+Li)$^+$ 243.08295, found 243.08393.
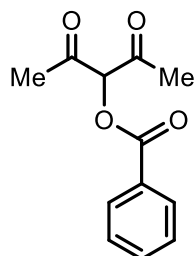
2,4-Dioxopentan-3-yl benzoate (**2-29h**): Synthesized according to GP2 using iodonium ylide **2-1d** (0.030 g, 0.10 mmol, 1 equiv.), benzoic acid (0.012 g, 0.10 mmol, 1 equiv.), DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white oil (20 mg, 91% yield). R_f = 0.67 (hexanes:EtOAc 3:1).[117] The characterization data matches what has already been reported in the literature. **^{1}H NMR** (300 MHz, CDCl$_3$): Mixture of keto:enol (2.6:1) δ 8.16–8.2 (m, 0.85 H, enol), 8.13–8.15 (m, 2 H, keto), 7.63–7.68 (m, 1.5 H, keto and enol), 7.49–7.57 (m, 3 H, keto and enol), 5.75 (s, 1 H, keto), 2.41 (s, 6 H, keto), 2.08 (s, 2.25 H, enol).
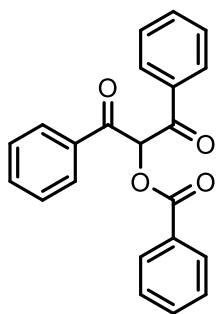
1,3-Dioxo-1,3-diphenylpropan-2-yl benzoate (**2-29i**): Synthesized according to GP2 using iodonium ylide **2-1e** (0.043 g, 0.10 mmol, 1 equiv.), benzoic acid (0.012 g, 0.10 mmol, 1 equiv.), DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white oil (0.034 g, 99% yield). R_f = 0.70 (hexanes:EtOAc 3:1). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 8.14 (d, J = 8.6 Hz, 4 H), 8.09 (d, J = 8.6 Hz, 2 H), 7.60-7.66 (m, 3 H), 7.44-7.54 (m, 6 H), 7.22 (s, 1 H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 191.1, 164.9, 134.4, 134.2, 133.8, 130.1, 129.6, 128.8, 128.6, 128.6, 80.7. **IR** (**ATR**): 2949.7 (w), 1770.8 (m), 1728.1 (s), 1700.5 (s), 1444.6 (m), 1871.7, 784.8 (m) cm^{-1}. **HRMS** (**ESI**): Calculated for $C_{22}H_{16}O_4Li$ (M+Li)$^+$ 351.1215, found 351.1203.
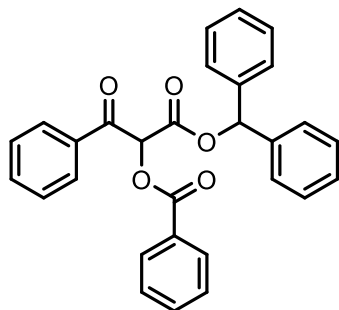
1-(Benzhydryloxy)-1,3-dioxo-3-phenylpropan-2-yl benzoate (**2-29j** Synthesized according to GP2 using iodonium ylide **2-1f** (0.053 g, 0.10 mmol, 1 equiv.), benzoic acid (0.012 g, 0.10 mmol, 1 equiv.), DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white oil (0.044 g, 99% yield). R_f = 0.70 (hexanes:EtOAc 3:1). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 8.12 (d, J = 7.8 Hz, 2 H), 8.06 (d, J = 7.1 Hz, 2 H), 7.60-7.67 (m, 2 H), 7.45-7.52 (m, 4 H), 7.20–7.36 (m, 8 H), 7.13–7.16 (m, 2 H), 6.98 (s, 1 H), 6.70 (s, 1 H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 189.5, 165.1, 164.2, 139.0, 138.9, 134.5, 134.2, 133.8, 130.2 (2), 129.3 (2), 128.8 (2), 128.54 (2), 128.51 (2), 128.4 (2), 128.2, 128.1, 127.1 (2), 126.9 (2), 79.2, 75.1. **IR (ATR)**: 2952.1 (w), 1766.6 (m), 1718.1 (s), 1701.6 (s), 1446.4 (m), 1234.6 (s), 1121.9, 694.5 (s) cm^{-1}. **HRMS (ESI)**: Calculated for C$_{29}$H$_{22}$O$_5$Li (M+Li)$^+$ 457.1595, found 457.1615.
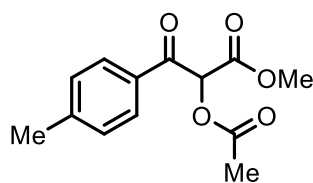
Methyl 2-acetoxy-3-oxo-3-(*p*-tolyl)propanoate (**2-29k**): Synthesized according to GP2 using iodonium ylide **2-1g** (0.039 g, 0.10 mmol, 1 equiv.), acetic acid (0.006, 0.10 mmol, 1 equiv.), DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white oil (0.024 g, 95% yield). R_f = 0.65 (hexanes:EtOAc 3:1). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.30-7.91 (AA'BB', 4 H), 6.35 (s, 1 H), 3.80 (s, 3 H), 2.45 (s, 3 H), 2.24 (s, 3 H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 189.0, 169.5, 165.8, 145.5, 131.6, 129.5 (2), 129.4 (2), 74.3, 53.1, 21.8, 20.5. **IR (ATR)**: 2956.5 (w), 1748.1 (s), 1698.5 (s), 1372.1 (m), 1207.5 (s), 1084.3 (m) cm^{-1}. **HRMS (ESI)**: Calculated for C$_{13}$H$_{14}$O$_5$Li (M+Li)$^+$ 257.0988, found 257.0996.
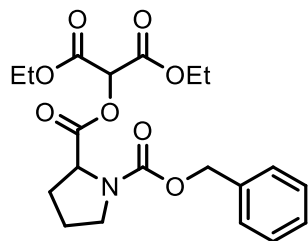
1-Benzyl 2-(1,3-diethoxy-1,3-dioxopropan-2-yl) pyrrolidine-1,2-dicarboxylate (**2-29l**): Synthesized according to GP2 using iodonium ylide **2-1b** (0.036 g, 0.10 mmol, 1 equiv.), ((benzyloxy)carbonyl)proline (0.025 g, 0.10 mmol, 1 equiv.), DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white oil (0.039 g, 96% yield). R_f = 0.46 (hexanes:EtOAc 3:1). Mixture of rotemers (A: B: 1:1). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.76-7.80 (m, 2 H), 7.55-7.65 (m, 2 H), 7.31-7.44 (m, 4 H), 5.61 (s, 1 H), 5.46 (s, 1 H), 4.44-4.54 (m, 1 H), 4.13-4.38 (m, 2 H), 3.65-3.74 (m, 7 H), 3.50-3.59 (m, 1 H), 2.30-3.34 (m, 2 H), 1.95-2.19 (m, 3 H), 1.24-1.36 (m, 7 H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 171.1, 171.1, 164.3, 164.1, 164.0, 163.9, 154.9, 154.3, 144.5, 144.1, 143.9, 143.8, 141.3, 141.3, 141.2, 127.7, 127.7, 127.6, 127.0, 127.0, 125.2, 125.1, 124.9, 120.0, 119.9, 119.9, 71.9, 71.9, 67.6, 62.6, 62.5, 58.9, 58.5, 47.2, 47.2, 47.0. 46.5, 30.9, 29.8, 24.2, 23.2, 13.9, 13.9. **IR** (**ATR**): 2981.6 (w), 1748.0 (s), 1704.0 (s), 1450.2 (m), 1414.9 (s), 1347.8 (m), 1156.9 (s) cm^{-1}.
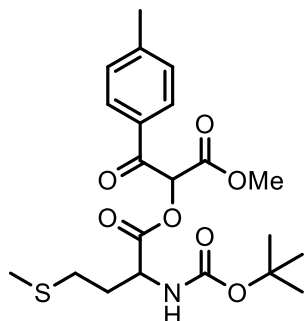
1-Methoxy-1,3-dioxo-3-(p-tolyl)propan-2-yl (tert-butoxycarbonyl)methioninate (**2-29m**): Synthesized according to GP2 using iodonium ylide **2-1g** (0.036 g, 0.10 mmol, 1 equiv.), (tert-butoxycarbonyl)methionine (0.025 g, 0.10 mmol, 1 equiv.), DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a clear oil (0.036 g, 86% yield). R_f = 0.51 (hexanes:EtOAc 3:1). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.28-7.89 (AA'XX', 4 H), 6.33-6.35 (m, 1 H), 5.12-5.14 (m, 1 H), 4.54-4.55 (m, 1 H), 3.78 (s, 3 H), 2.55-2.65 (m, 2 H), 2.43 (s, 3 H), 2.20-2.27 (m, 1 H), 2.01-2.11 (m, 4 H) 1.39-1.43 (m, 9 H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 188.4, 171.2, 171.0, 165.5, 165.2, 145.7, 145.6, 131.5, 131.4, 129.6, 129.6, 129.5, 129.3, 129.3, 74.8, 74.6, 53.2, 53.2, 31.8, 29.7, 29.7, 28.3, 28.2, 21.8, 15.4, 15.3. **IR** (**ATR**): 3381.6 (w), 2976.5 (w), 1751.7 (m), 1692.2 (s), 1605.8 (m), 1154.9 (s) cm^{-1}. **HRMS** (**ESI**): Calculated for C$_{21}$H$_{30}$NO$_7$S (M+H)$^+$ 440.1717, found 440.1738.

Diethyl 2-((2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-(tert-butoxy)phenyl)propanoyl)oxy)malonate (**2-29n**): Synthesized according to GP2 using iodonium ylide -- (0.032 g, 0.10 mmol, 1 equiv.), 2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-(tert-butoxy)phenyl)propaneperoxoic acid (0.048 g, 0.10 mmol, 1 equiv.), DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white solid (62 g, 99% yield). R_f = 0.25 (hexanes:EtOAc 3:1). **¹H NMR** (300 MHz, CDCl$_3$): δ 7.77 (d, J = 8.7 Hz, 2 H), 7.56-7.59 (m, 2 H), 7.40-7.44 (m, 2 H), 7.30-7.35 (m, 2 H), 7.10-7.13 (m, 2 H), 6.92-6.95 (m, 2 H), 5.61 (s, 1 H), 5.26-5.28 (m, 1 H), 4.83-4.89 (m, 1 H), 4.27-4.44 (m, 7 H), 4.20-4.24 (t, 1 H), 3.27-3.34 (m, 1 H), 3.10-3.17 (m, 1 H), 1.31-1.36 (m, 15 H). **¹³C NMR** (75 MHz, CDCl$_3$): δ 170.4, 164.0, 163.9, 155.5, 154.6, 143.8, 143.7, 141.3, 130.1, 129.9, 127.7, 127.1, 125.1, 124.2, 120.0, 78.4, 72.1, 67.1, 63.2, 62.7, 54.5, 47.1, 37.1, 28.8, 14.0, 13.9. **IR** (**ATR**): 3365.0 (w), 2974.9 (w), 1750.3 (s), 1700.3 (s), 1395.8 (m), 1188.2 (m) cm^{-1}. **HRMS** (**ESI**): Calculated for C$_{35}$H$_{40}$NO$_9$ (M+H)$^+$ 618.2667, found 618.2698.

2.8.3   General Procedure 3 - S-H Insertion of Thiols into Iodonium Ylides (GP3)

Into a dry round bottom flask was added iodonium ylide (0.1 mmol, 1 equiv.), CH$_2$Cl$_2$ (1.0 ml, 0.1 M) and methanesulfonic acid (0.1 mmol, 1 equiv.) was added in one portion. The reaction mixture was stirred at room temperature for 2 minutes, then thiols (0.1 mmol, 1 equiv.) was added in one portion. reaction was observed to be complete by TLC or NMR analysis after 5 min. The mixture was then evaporated to dryness and purified by column chromatography, eluting with mixtures of hexane and ethyl acetate 3:1. The use of column chromatography can be avoided when using high vacuum to remove iodobenzene.
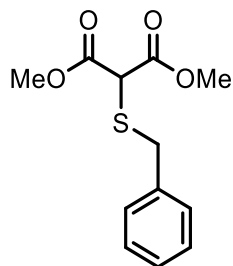
Dimethyl 2-(benzylthio)malonate (**2-43a**): Synthesized according to GP3 using iodonium ylide **2-1a** (0.033 g, 0.10 mmol, 1 equiv.), benzyl mercaptan (0.012 mL, 0.10 mmol, 1 equiv.), methanesulfonic acid (0.006 mL, 0.1 mmol, 1 equiv.) in DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white oil (0.020 g, 80% yield). R_f = 0.70 (hexanes:EtOAc 3:1). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.27-7.38 (m, 5 H), 4.09 (s, 1 H), 3.93 (s, 2 H), 3.76 (s, 6 H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 167.1, 136.4, 129. 2, 128.6, 127.5, 53.2, 49.7, 35.9. **IR** (**ATR**): 3029.2 (w), 2953.4 (w), 1730.7 (s), 1434.0 (m), 1242.1 (m), 1141.7 (m) cm^{-1}. **HRMS** (**ESI**): Calculated for C$_{12}$H$_{14}$O$_4$SLi (M+Li)$^+$ 261.0765, found 261.0765.
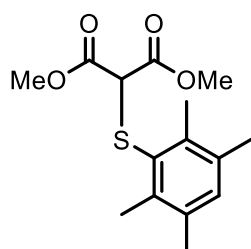
Dimethyl 2-((2,3,5,6-tetramethylphenyl)thio)malonate (**2-43b**): Synthesized according to GP3 using iodonium ylide **2-1a** (0.033 g, 0.10 mmol, 1 equiv.), 2,3,5,6-tetramethylbenzenethiol (0.017 mL, 0.10 mmol, 1 equiv.), methanesulfonic acid (0.006 mL, 0.1 mmol, 1 equiv.) in DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as white crystals (0.020 g, 81% yield). R_f = 0.75 (hexanes:EtOAc 3:1). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.00 (s, 1 H), 4.18 (s, 1 H), 3.75 (s, 6 H), 2.50 (s, 6 H), 2.25 (s, 6 H). **^{13}C NMR** (75 MHz, CDCl$_3$)**:** δ 167.0, 139.2, 134.6, 133.1, 130.8, 54.7, 53.1, 30.9, 20.9, 18.2. **IR** (**ATR**): 2942.1 (w), 1764.7 (s), 1740.5 (m), 1720.0 (s), 1256.4 (m), 1115.9 (s) cm^{-1}. **HRMS** (**ESI**): Calculated for C$_{15}$H$_{30}$O$_4$SLi (M+Li)$^+$ 303.1248, found 303.1237.
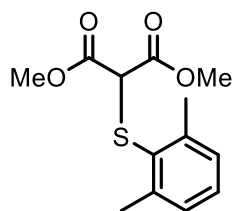
Dimethyl 2-((2,6-dimethylphenyl)thio)malonate (**2-43c**): Synthesized according to GP3 using iodonium ylide **2-1a** (0.033 g, 0.10 mmol, 1 equiv.), 2,6-dimethylbenzenethiol (0.014 mL, 0.10 mmol, 1 equiv.), methanesulfonic acid (0.006 mL, 0.1 mmol, 1 equiv.) in DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to

the title compound isolated as a white oil (0.018 g, 68% yield). R_f = 0.70 (hexanes:EtOAc 3:1). The characterization data matches what has already been reported in the literature.[118] **¹H NMR** (300 MHz, CDCl₃): δ 7.11–7.17 (m, 1 H), 7.11 (d, J = 6.7 Hz, 2 H), 4.29 (s, 1 H), 3.75 (s, 6 H), 2.55 (s, 6 H).
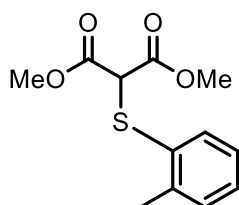
Dimethyl 2-(*o*-tolylthio)malonate (**2-43d**): Synthesized according to GP3 using iodonium ylide **2-1a** (0.033 g, 0.10 mmol, 1 equiv.), 2-methylbenzenethiol (0.012 mL, 0.10 mmol, 1 equiv.), methanesulfonic acid (0.006 mL, 0.1 mmol, 1 equiv.) in DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white oil (0.018 g, 71% yield). R_f = 0.70 (hexanes:EtOAc 3:1). The characterization data matches what has already been reported in the literature.[118] **¹H NMR** (300 MHz, CDCl₃): δ 7.50 (d, J = 7.6 Hz, 1 H), 7.24 (d, J = 4.0 Hz, 2 H), 7.15–7.21 (m, 1 H), 4.51 (s, 1 H), 3.77 (s, 6 H), 2.50 (s, 3 H).
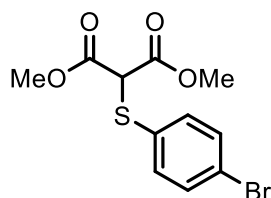
Dimethyl 2-((4-bromophenyl)thio)malonate (**2-43e**): Synthesized according to GP3 using iodonium ylide **2-1a** (0.033 g, 0.10 mmol, 1 equiv.), 4-bromobenzenethiol (0.019 g, 0.10 mmol, 1 equiv.), methanesulfonic acid (0.006 mL, 0.1 mmol, 1 equiv.) in DCM (1.0 mL). The reaction was stirred for 5 min at 25 °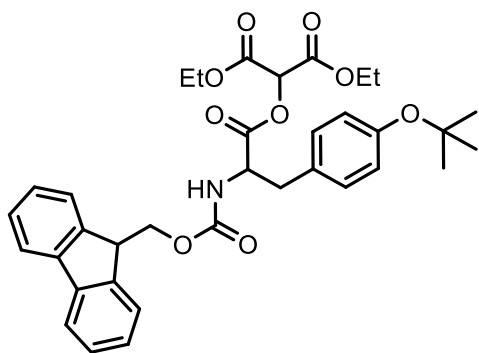C until the starting materials were consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white oil (0.027 g, 84% yield). R_f = 0.75 (hexanes:EtOAc 3:1). The characterization data matches what has already been reported in the literature.[119] **¹H NMR** (300 MHz, CDCl₃): δ 7.41-7.50 (AA'BB', 4 H), 4.52 (s, 1 H), 3.78 (s, 6 H).
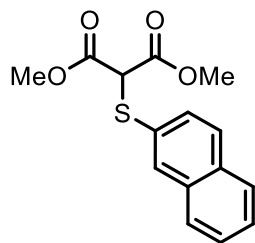
Dimethyl 2-(naphthalen-1-ylthio)malonate (**2-43f**): Synthesized according to GP3 using iodonium ylide **2-1a** (0.033 g, 0.10 mmol, 1 equiv.), naphthalene-2-thiol (0.016 g, 0.10 mmol, 1 equiv.), methanesulfonic acid (0.006 mL, 0.1 mmol, 1 equiv.) in DCM (1.0 mL). The reaction was stirred for 5 min at 25 °C until the starting materials were consumed as indicated

by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white oil (0.024 g, 83% yield). R_f = 0.75 (hexanes:EtOAc 3:1). The characterization data matches what has already been reported in the literature.[119] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 8.06 (s, 1 H), 7.81-7.86 (m, 3 H), 7.56-7.71 (m, 1 H), 7.51-7.54 (m, 2 H), 4.67 (s, 1 H), 3.78 (s, 6 H).

Chapter 3: Synthesis of Substituted Furans via the Irradiation of Iodonium Ylides and Alkynes with Blue Light

3.1 Introduction

Furans are important structural motifs that exist in a wide array of pharmaceuticals, natural products, and biologically active compounds. There are many methods for furan synthesis and in this chapter, a new method for the synthesis of substituted furans will be investigated. This method utilizes the photochemical activation of iodonium ylides with blue LED light to perform a new reaction with alkynes. To understand the reaction mechanism, controlled reactions were performed, and an in-depth analysis was conducted of all the side-products that were formed in addition to the furans. Thus, the focus of this chapter is the synthesis of substituted furans by the reaction of iodonium ylides with alkyne under blue light irradiation.

3.2 Furans

Furan is a five-membered aromatic ring with four carbon atoms and one oxygen atom. Furans represent one of the most versatile classes of five-membered heterocyclic compounds, and constitute core entities frequently found in food, pharmaceuticals, natural products, drugs, and some selected examples shown below in **Figure 3.1**.[120] The wide range of applications displayed by furans and their derivatives have made progressive impacts over approximately the last nine decades to the field of chemistry.

Selective inhibitor of MetAP   Angelone   *NCGC00189258-01*
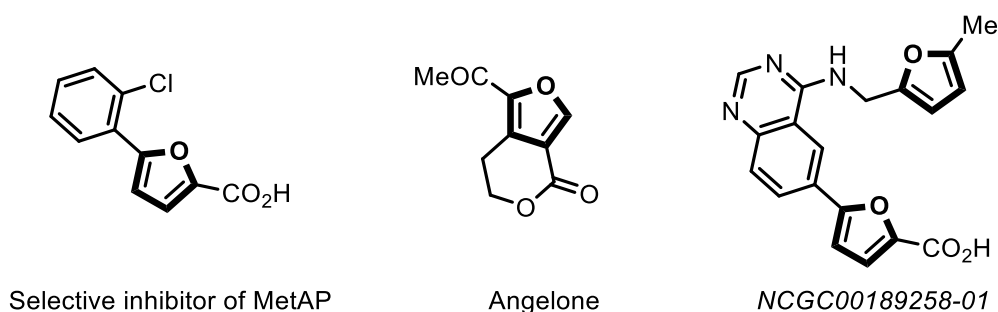
Figure 3.1. Some furan derived natural products and drugs.

One of the modifications that increases the value of furans is the addition of a trifluoromethyl (CF_3) group. Studies have shown that the fluorination of organic molecules can greatly affect their biological properties. For example, the incorporation of a fluorine atom or a trifluoromethyl group can alter both the pharmacodynamic and pharmacokinetic properties of that molecule. Properties that make fluorination of organic molecules an attractive and beneficial strategy include increases the lipophilicity of the molecule which can modify absorption into cells and improve metabolic stability.[121] Consequently, trifluoromethylated compounds have been increasingly used in medicinal chemistry,[122] agrochemicals,[123] and materials science.[124] Trifluoromethyl-substituted furan derivatives are among the valuable trifluoromethylated compounds, with many of them being patented as drug molecules. For example, a large number of reported pharmacologically-active compounds contain a furan subunit with a CF_3 substituent (**Figure 3.2**), and have been used for treatment of various diseases such as cancer,[125] HIV,[126] obesity,[127] diabetes,[128] and numerous others.[129] The established medicinal benefits of substituted furan drugs have provided an enormous amount of motivation for chemists to discover new methods for synthesizing these valuable moieties.

Treatment of obesity, diabetes type II and metabolic syndrome

Cancer treatment

Calcium or sodium channel blockers
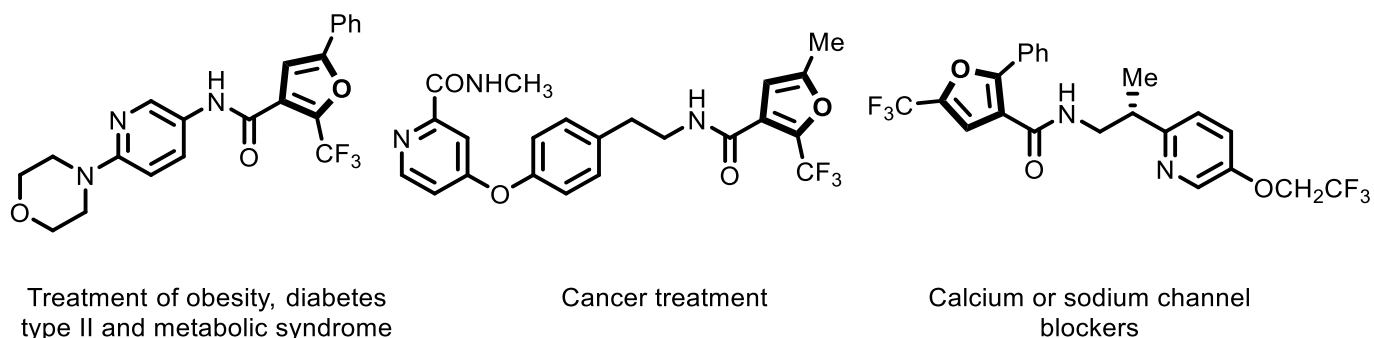
Figure 3.2. Examples of biologically active CF_3-substituted furan derivatives.

3.2.1 Synthesis of Substituted Furans

The Paal-Knorr reaction, first discovered in 1884, is an acid-catalyzed cyclization of 1,4-dione to furans.[130] Different acid catalysts can be used in this reaction such as sulfuric acid, phosphorus (V) oxide, and zinc chloride. The original conditions required prolonged heating in acid which introduced major limitations to this reaction when dealing with sensitive functionalities in the 1,4-dione precursors. Hence, new procedures were developed such as using microwave

irradiation to decrease the reaction time (**Scheme 3.1**).[131] Newly established methods for the synthesis of 1,4-dione broadened the synthetic utility of the Paal-Knorr reaction.[132]
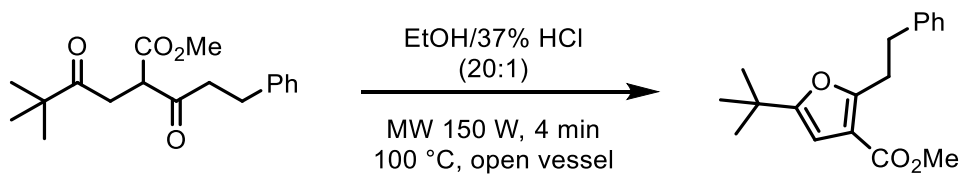
Scheme 3.1. Furan synthesis using Paal-Knorr reaction

Another well-known reaction aimed at synthesizing furans is the Feist-Benary reaction.[133] The Feist-Benary reaction is a cyclocondensation reaction between an α−halogenated carbonyl compound and a 1,3-dicarbonyl compound catalyzed by amines such as ammonia or pyridine.
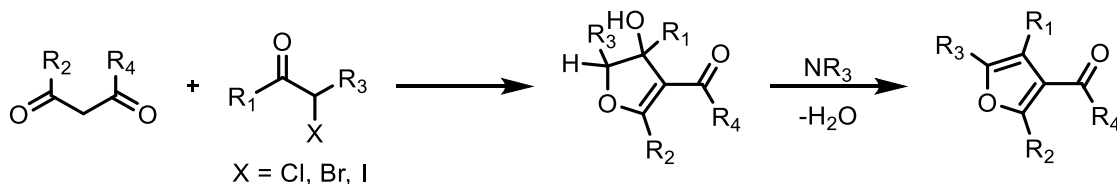
Scheme 3.2. General reaction route for the synthesis of furans by the Feist–Benary reaction

Other methods used for generating substituted furans include the cyclization of acyclic precursors, such as an exo-cyclization reaction utilizing triple bonds, or allenyl ketones.[134] These methods are usually performed under milder conditions using metal salts as catalysts. Palladium or platinum salts are commonly used to catalyze exo-cyclization reaction.[134] Recently, gold and silver catalysts emerged as a better replacement for the previously used metal salts, due to their allowance for greater flexibility of the reaction scope. For example, low catalytic loading of gold and silver salts allowed for intramolecular dehydrative cyclizations of 3-alkyne-1,2-diols to trisubstituted furans (**Scheme 3.3**). This procedure was also used later for the synthesis of pyrroles and thiophene in high yields.[135]
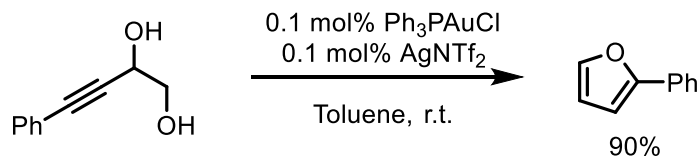
Scheme 3.3. Gold catalyzes intramolecular cyclization of 3-alkyne-1,2-diols to furan

Among the many methods that are employed, the cycloaddition of α–carbonyl diazo compounds with alkynes are widely used due to it being a convenient method for the construction of diversely substituted furan molecules. Metallocarbene intermediates are generated from the activation of α-diazocarbonyls with transition metals such as rhodium or copper. The metallocarbene then undergoes a cycloaddition reaction with alkynes affording furans.[136] The synthesis of trifluoromethylated furans was reported via a $Rh_2(OAc)_4$ catalyzed [3+2] cycloaddition reaction of trifluoromethylacetyl diazo compound **3-5** and terminal alkynes. This reaction yields two structural isomers containing furan rings **3-7** and **3-8**.[137]
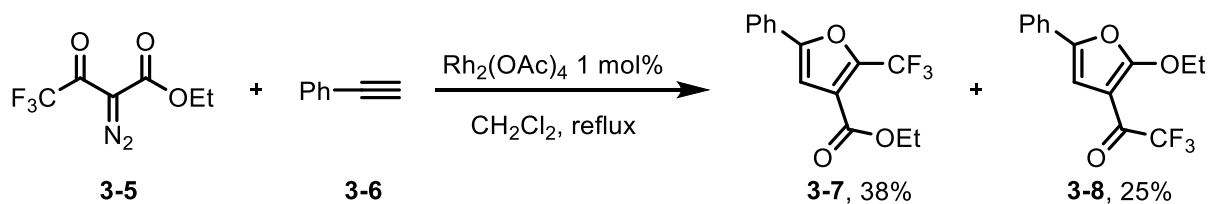
Scheme 3.4. Synthesis of trifluromethylated furans via a trifluoromethylacetyl diazo compound and terminal alkynes under metal catalysis conditions

To distinguish between the two furan isomers **3-7** and **3-8**, ^{19}F NMR analysis could be used. The ^{19}F NMR signal of trifluoromethyl group on the α-carbon of a furan ring is δ -60.9, whereas ^{19}F NMR signal of trifluoromethyl group on the carbonyl group is δ -75.5 (**Figure 3.3**).
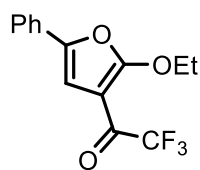
3-7, ^{19}F NMR (282 MHz,CDCl$_3$):   **3-8**, ^{19}F NMR (282 MHz,CDCl$_3$):
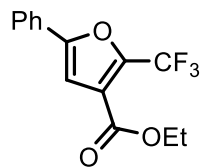
δ -75.5 (s, 3F)   δ −60.9(s, 3F)

Figure 3.3. ^{19}F NMR signals of trifluoromethyl containing furans

Iodonium ylides are also used for the synthesis of furans under transition metal catalysis.[138] Similar to diazo compounds, metallocarbene **3-12** is generated upon heating an iodonium ylide in the presence of a Cu^{2+} or Rh^{2+} catalyst. This intermediate then undergoes transmetallation with intermediate **3-13** that is generated by the decarboxylative reaction of **3-10** with silver oxide to produce intermediate **3-14** (**Scheme 3.5**). Then, direct insertion of an alkyne into the Rh-carbene produced intermediate **3-15**, which further reacted with Ag(I) to give **3-16** and Cp*RhCl$_2$. Finally, a protonation of **3-16** by acid or water produces **3-11** and silver metal. This procedure is used to form furan skeleton present in natural products and pharmaceutical molecules. A decarboxylation strategy allows for the construction of chemical bonds via extrusion of CO$_2$ from carboxylate salts or esters.[138]
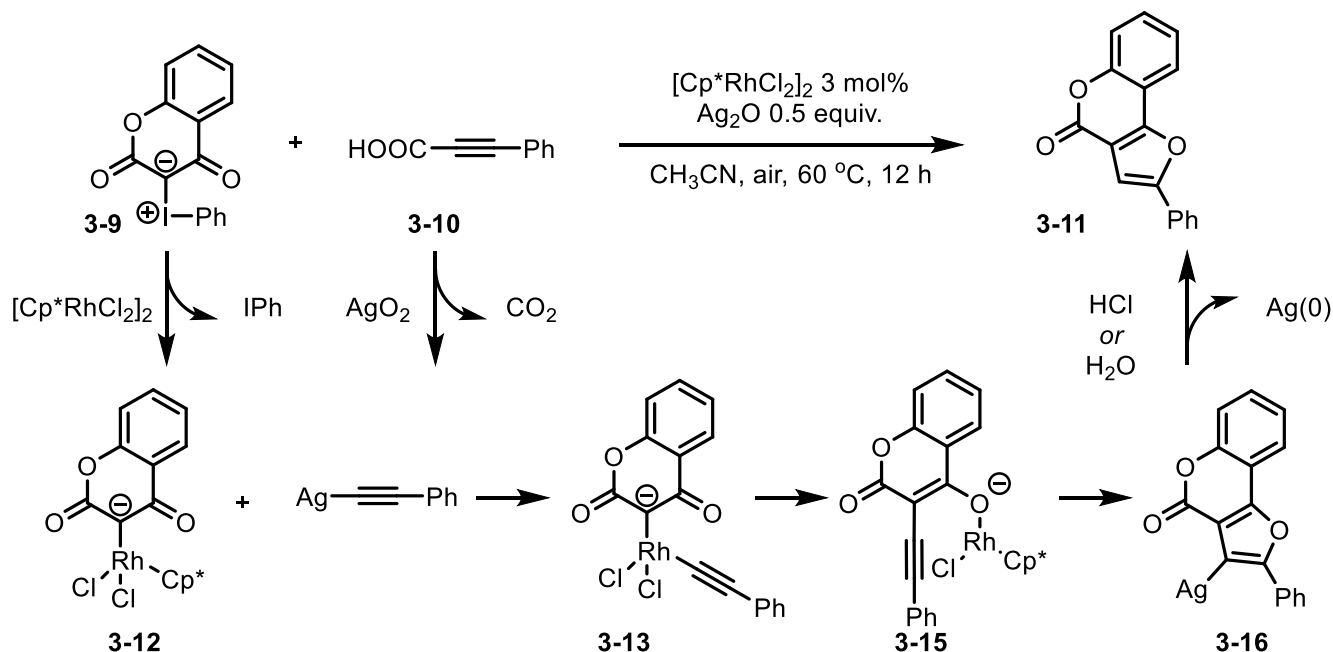
Scheme 3.5. Synthesis of furan by the reaction of iodonium ylides with alkynes under transition metal catalysis

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3.3   Activation of Iodonium Ylides with Blue Light

Iodonium ylides can serve as carbene precursors as their photoinitiated, thermal, or transition metal-catalyzed decomposition generates the corresponding carbenes or metal carbenoids, which subsequently leads to various transformations as mentioned in Chapter 1. Photoinitiated reactions of iodonium ylide compounds was first interduced by Hadjiarapoglou[139] and Spyroudis[140] around 1985 which is considered to be a more advantageous approach for activation due to the need to develop new environmentally friendly and safe synthetic practices. Irradiating iodonium ylides with a mercury lamp was proposed to generate a singlet carbene species, and the groups of Hadjiarapoglou,[141] Matveeva,[142] and Spyroudis[143] have reported examples of cyclopropanation and related cycloaddition reactions. A free carbene is generated from the cleavage of the C-IPh bond leading to free carbene-based reactions. One of the disadvantages of activating iodonium ylides by a mercury lamp is the unavoidable heat generated during the operation, leading to chemical selectivity complications and unwanted decomposition reactions. For instance, Hadjiarapoglou's work revealed that the irradiation of iodonium ylides with a mercury lamp generates enough heat to isomerize the cyclopropane intermediate formed into a dihydrofuran (**Scheme 3.6**).[141]
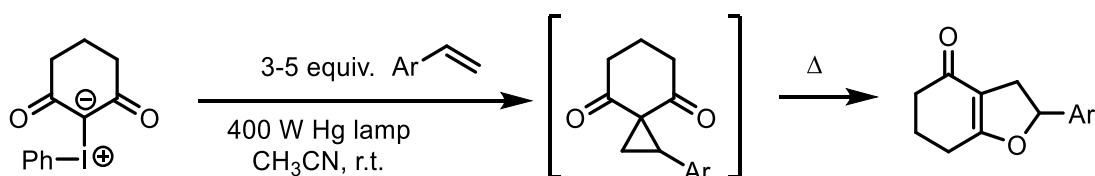
Scheme 3.6. Hg lamp irradiation of iodonium ylides gives dihydrofuran

Recently, a collaboration between the Murphy group and the Quideau group discovered that iodonium ylides absorb visible light in the violet-blue range (400-500 nm). This was an important discovery because unlike the other previous iodonium ylide photochemical reactions, LEDs are much more energy-efficient and can be used without significant heat generation, allowing for the selective production of reactive intermediates and the formation of heat-sensitive compounds.[144]

The emission spectrum for the blue LEDs used were measured using an Ocean Optics Spectrometer (Model: USB 4000). When overlaying the UV-Vis absorbance spectrum of iodonium ylide at 0.1 M in DCM with the emission spectrum of blue light (from LEDs), a

significant amount of overlap was observed (**Figure 3.4**). A series of dimedone-derived iodonium ylides with substituents on the phenyl ring was tested to determine if these alterations would affect the UV-Vis absorption spectra, but a minimal change was observed at 0.1 M. However, altering the structure of the dicarbonyl region of the ylide caused more significant changes in their absorption spectra. For example, the blue shift was observed when changing from the dimedone iodonium ylide, to the ketoester, to the diester (Meldrum's acid) iodonium ylide (**Figure 3.4**).
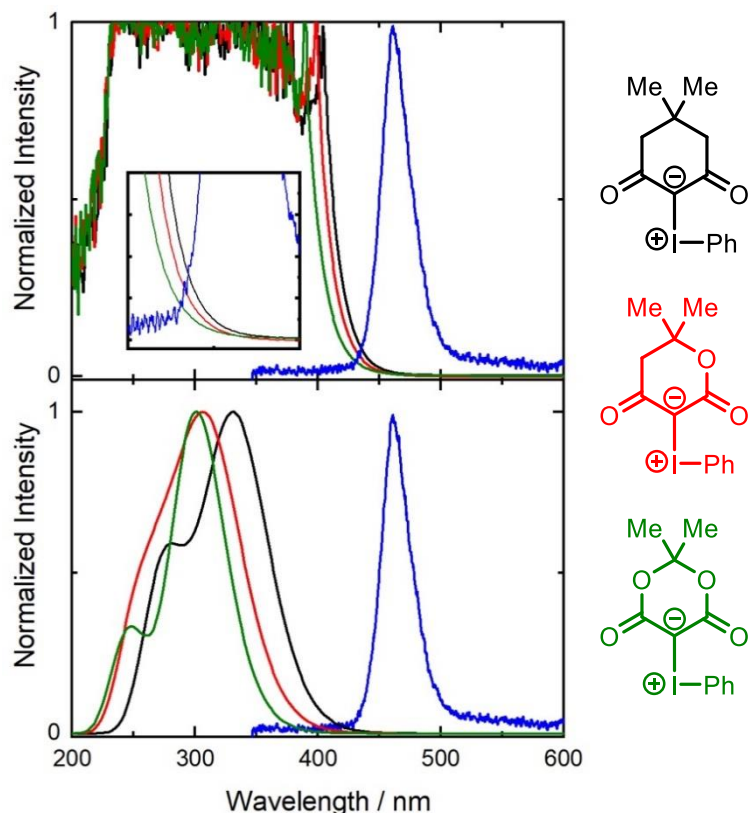
Figure 3.4. Iodonium ylides overlaid with the emission spectra of the blue LED[144]

Computational analyses are generally used to provide a representation of electron densities of molecules. One of the computational methods that are used to identify electron densities is density functional theory (DFT).[145] DFT was used to determine the electron densities of both the ground state and the excited state of a series of six iodonium ylides. These calculations showed that blue LEDs induce excitation of 0.29e of electron density (on average) from the HOMO to the LUMO state associated with the iodine center (**Figure 3.5**). Based on these findings, it has been concluded that iodonium ylides have the ability to undergo HOMO to LUMO activation when

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irradiating with blue light. Instead of undergoing heterolytic cleavage to give free carbenes, iodonium ylides afford 1,2-diradical species with unpaired electron density predominantly on the iodine and ylidic carbon.[144]
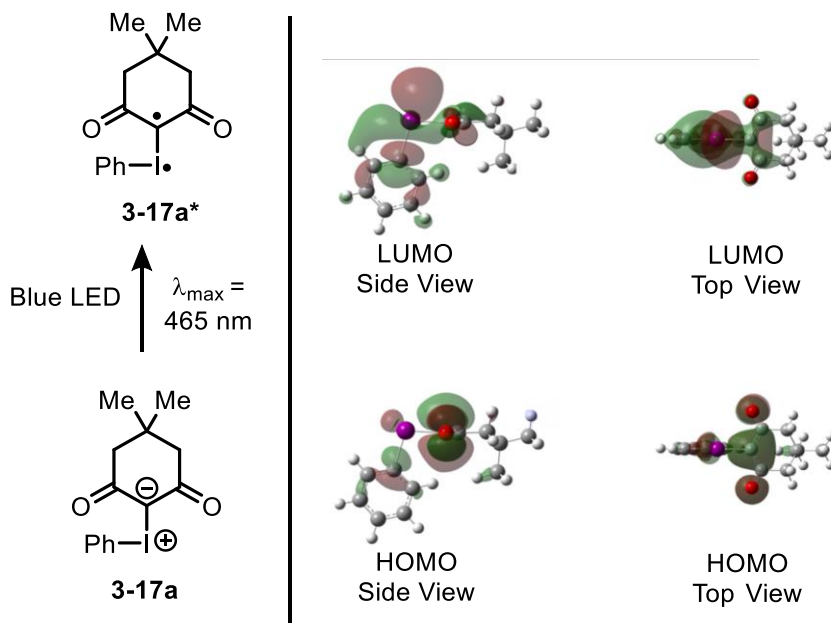
Figure 3.5. Calculated HOMO and LUMO diagrams of **3-17a**[144]

The intensity of the HOMO → LUMO band and its separation from other high energy electronic transitions was slightly different for each ylide. For compound **3-17a**, the HOMO to LUMO transition was predicted to be relatively intense, and well-separated from the other high energy electronic transitions (**Figure 3.6**).[144]
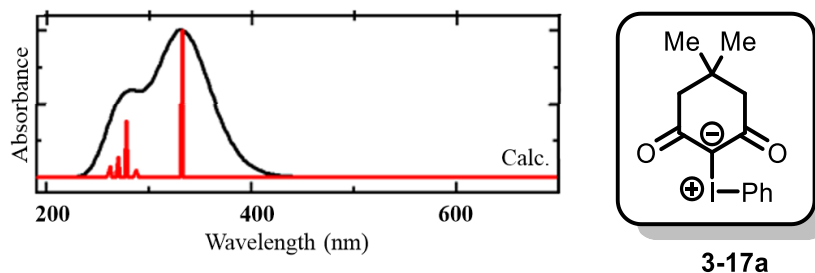
Figure 3.6. Predicted UV-Vis spectrum of **3-17a** at 0.03 mM[144]

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Blue light irradiation of dicarbonyl iodonium ylides have been successfully shown to function as an activation method with substrates such as alkenes to undergo cyclopropanation and this reaction proceeds in excellent yield.

Scheme 3.7. Cyclopropanation reaction of iodonium ylides and alkenes under blue light.

The blue-light-induced cyclopropanation reaction mechanism of iodonium ylides and alkenes can be explained by the involvement of a diradical species which forms *in situ* during the photochemical reaction (**Scheme 3.8**). The first step of the proposed mechanism is the excitation of iodonium ylide **3-17a** to form diradical intermediate **3-22** (Pathway 1). Then, the short-lived diradical intermediate reacts with an alkene forming four-membered ring intermediate **3-21**. It is also possible that the electron density around the alkene double bonds could coordinate to iodine center of the iodonium ylides perhaps to the σ-holes prior to the photochemical excitation (Pathway 2) to form complex **3-19**. Complex **3-19** could then potentially absorb a photon of blue light converting the ylide-alkene complex into four-membered ring intermediate **3-21**. Iodobenzene could then be eliminated in a favourable reduction of hypervalent iodine (III) to iodine (I) which in turn forms cyclopropane **3-20**.
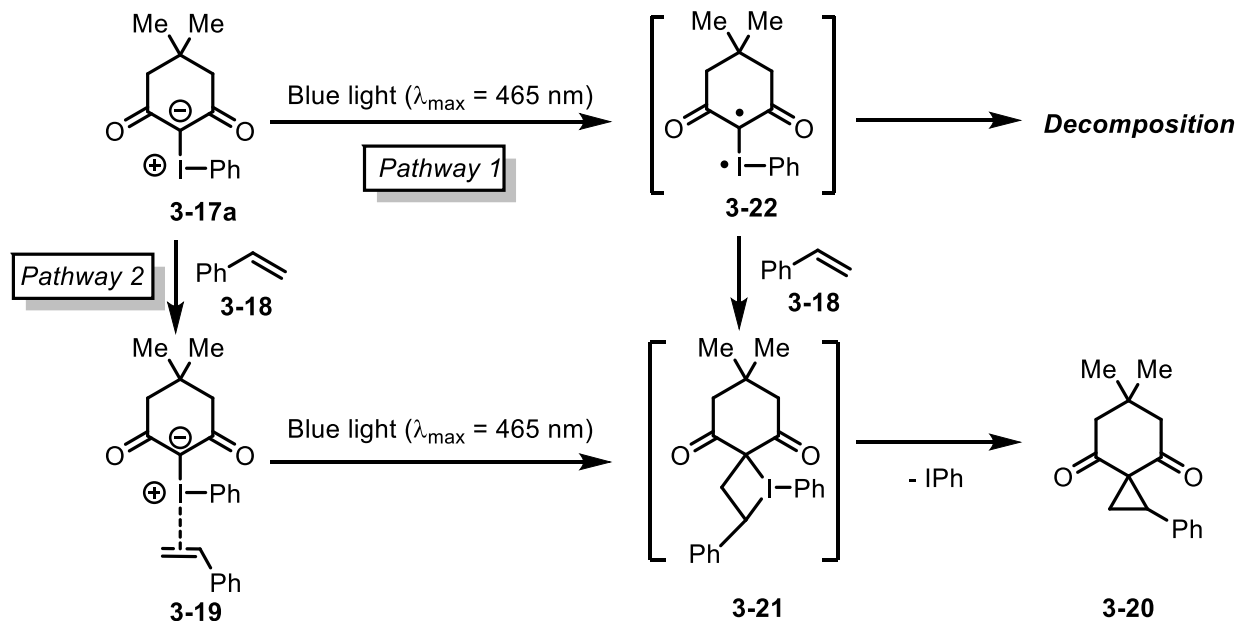
Scheme 3.8. Blue-light-induced cyclopropanation reaction mechanism

3.4   Proposed Research

This chapter will continue to explore the photo-activation of iodonium ylides with blue light. Specifically focusing on the synthesis of substituted furans by the reaction of iodonium ylides with alkynes in the presence of blue light.
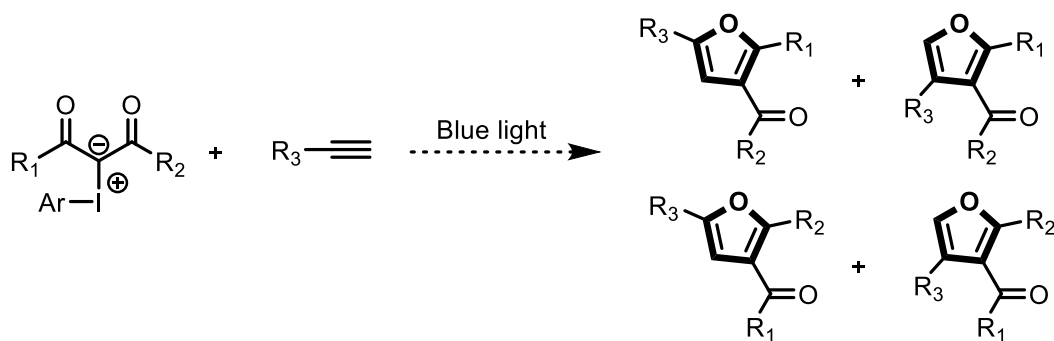
Scheme 3.9. Proposed synthesis of substituted furans

The photochemical reaction of acyclic iodonium ylides with alkynes could possibly lead to four different regioisomers in total (**Scheme 3.9**). The regioselectivity of the reaction will be studied and if possible, controlled to allow for efficient regioselective production of substitution

furans. The use of trifluoromethylacetyl iodonium ylide-based compounds may lead to the synthesis of CF$_3$-substituted furans which are very valuable in medicine. If successful, this work will introduce a new method for the synthesis of substituted furans in the hope of providing a simpler and more efficient way to synthesize furans and CF$_3$-substituted furans. This work may potentially be useful for the synthesis of natural products, drugs, and other valuable molecules.

3.5   Photoreactor Set-up

The photoreactor used in this project was designed according to previous studies done by the Murphy group member Tristan Chidley. These studies showed that the cyclopropanation reaction rate is variable depending on the distance between the vial used for the reaction and the LED light source.[144] The optimal distance was tested and determined to be 1 cm. The photoreactor used in this project was named the *hv*Box and was made using an LED strip and a 3D printed model such that each vial was situated directly above one single LED (**Figure 3.7**) at a 1 cm distance. The *hv*Box was designed to allow for running 18 different reactions simultaneously. Heat buildup was simply avoided using a fan to dissipate any heat generated. The blue LED strip was purchased from a local LED store in Waterloo, Ontario. It has a lifetime of approximately 50,000 hours, an input power of 0.9 W per each individual LED, and a DC voltage of 12 V. Most importantly, the light emission spectrum of the blue LED light was acquired using an Ocean Optics Spectrometre, and the λ_{max} was measured to be 449 nm.
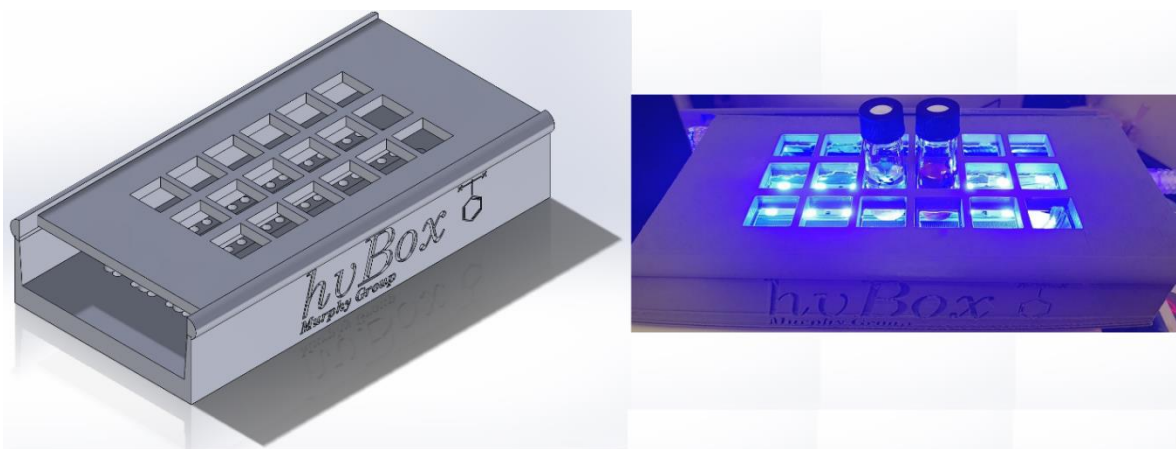
Figure 3.7. *hv*Box Photoreactor set-up

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3.6   Synthesis of Substrates

Most cyclic and acyclic β-dicarbonyl iodonium ylides used in this research are known compounds and were prepared in one step according to the established literature procedures by Koser[146] and Lick[112] from the corresponding β-dicarbonyl methylene compound (1 equiv.) and (diacetoxyiodo) benzene (1 equiv.). Deviations from the known procedures were made to synthesize the unknown iodonium ylides. Full procedures for the synthesis of these iodonium ylides can be found in the supporting information at the end of this chapter.

3.6.1   Properties of Acyclic Fluoroacetyl Iodonium Ylide Compounds

The UV-Vis absorbance spectra of iodonium ylides **3-23** and **3-24** at 0.1 M in DCM were overlaid with the emission spectrum of blue light and a significant amount of overlap was observed. When going from the methyl ketone iodonium ylide (**3-23**) to ethyl ester iodonium ylide (**3-24**) a blue shift and larger overlap was observed between the emission spectrum of blue light and the absorption spectrum of the ylides. This trend agrees with the blue shift observed when changing from dimedone, to the ketoester, to the diester (Meldrum's acid) iodonium ylide seen in **Figure 3.4**.
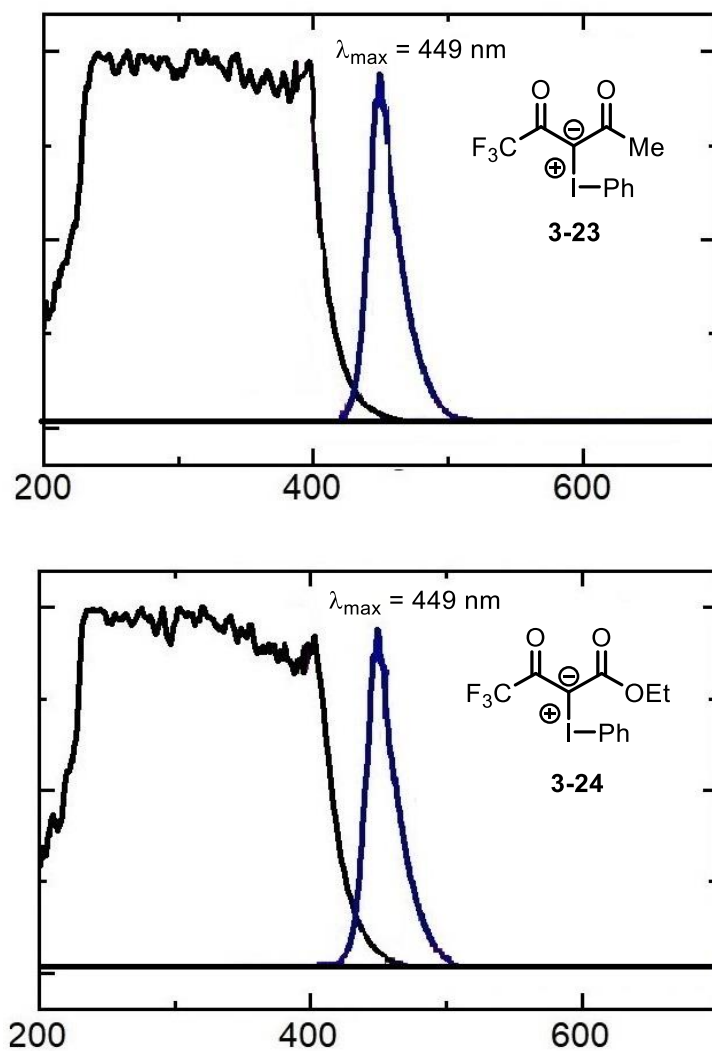
Figure 3.8. Absorption spectra of iodonium ylides overlaid with the emission spectra of the blue LED

3.7   Reaction Optimizations

This section will discuss the reaction optimization performed using different approaches with the intent of understanding the reaction mechanism and increasing the reaction yield using mild conditions. Each of the following sub-sections will introduce a concept, propose a hypothesis, and discuss the experiments that were performed.

3.7.1   Simple Optimizations

A series of controlled reactions of iodonium ylide **3-17a** (dimedone-derived iodonium ylide) and phenylacetylene **3-2** were completed to explore the nature of the reaction and optimize the yield. To begin, a mixture of iodonium ylide **3-17a** (1 equiv.) and phenylacetylene **3-2** (2 equiv.) was prepared as a 0.1 M solution in DCM and irradiated with blue LED (**Scheme 3.10**). Consumption of ylide **3-17a** was monitored by ^{1}H NMR analysis, and upon completion of the reaction, which occurred after 18 hours, 18% of furan **3-25** was isolated. The reaction of **3-17a** and **3-2** (**Scheme 3.10**) was repeated in the dark and the mixture was stirred for a total of four days. Both the NMR and TLC analysis showed no formation of furan at all, with a very small amount of ylide decomposition and no decomposition of alkyne was observed. Knowing that furan **3-25** forms from irradiating a mixture of dimedone-derived iodonium ylide **3-17a** and phenylacetylene **3-2** with blue light established this transformation as a light-dependent reaction. The percent yield of the furan was low (18%). The loss of mass and side reactions will be addressed and discussed in greater detail in later sections.
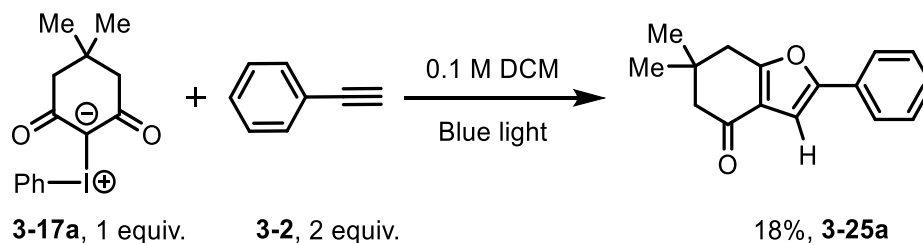
Scheme 3.10. Furan synthesis reaction between dimedone-derived iodonium ylide and phenylacetylene

The reaction between dimedone-derived iodonium ylide and phenylacetylene can theoretically form two regioisomers, isomer **A** and isomer **B** (**Figure 3.9**); however, as stated earlier, only isomer **A** was observed to form from the photochemical reaction of dimedone-derived iodonium ylide with phenylacetylene. ^{1}H NMR peaks of isomer **B** were not detected at all in the crude reaction mixture of this reaction. Both furan isomers are known compounds and they have been reported in literature.[147] Isomers **A** and **B** can be distinguished by ^{1}H NMR using the β and α hydrogens of isomers **A** and **B**, respectively, as seen **Figure 3.9**.
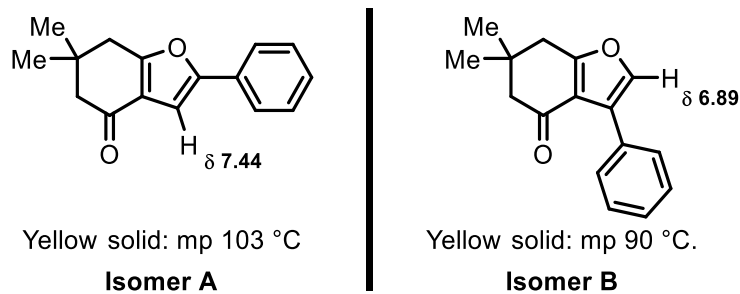
Figure 3.9. Substituted furans regioisomers

The regioselectivity of the light-induced reaction can be explained by the radical nature of the reaction and the reactivity of the starting materials. Due to the presence of π bonds in alkynes, the cloud of electrons surrounding the σ bond makes an alkyne an electron-rich molecule. They can therefore be considered nucleophilic in nature and can react with electrophiles if present in the reaction medium. Thus alkynes, like alkenes, undergo electrophilic addition reactions because of their weak π bonds. One could predict the same electrophilic reagents that add to alkenes also add to alkynes. Accordingly, we can therefore anticipate that coordination could occur between the positively charged iodine atom in an iodonium ylide with the π electron cloud in alkynes to form complex **3-26** as shown below in **Scheme 3.11**. Irradiation with blue light (400-500 nm) excites zwitterionic iodonium ylide **3-17a** to diradical intermediate **3-27** which then reacts with an alkyne to form either intermediate **3-28** or **3-30**. This is followed by homolytic cleavage of the carbon-iodine bond releasing iodobenzene. The last cyclization step leads to the formation of furan. Although in theory two regioisomers can be formed, an examination of the ^{1}H NMR of the crude reaction confirmed only one isomer, isomer **A**. The formation of one isomer **A** is the result of the stability of the radical intermediate. Intermediate **3-28** is more stable than intermediate **3-30**. Due to the unpaired electron properties of free radicals, they do not have a full octet, hence, they are electron deficient. They can be stabilized by resonance, hyperconjugation, and an adjacent EDG. The electron-deficient radical in intermediate **3-28** can be stabilized by the hyperconjugation provided by the adjacent phenyl group. Perhaps, unlike the formation of isomer **A**, there is a high energy barrier required to obtain isomer **B**.

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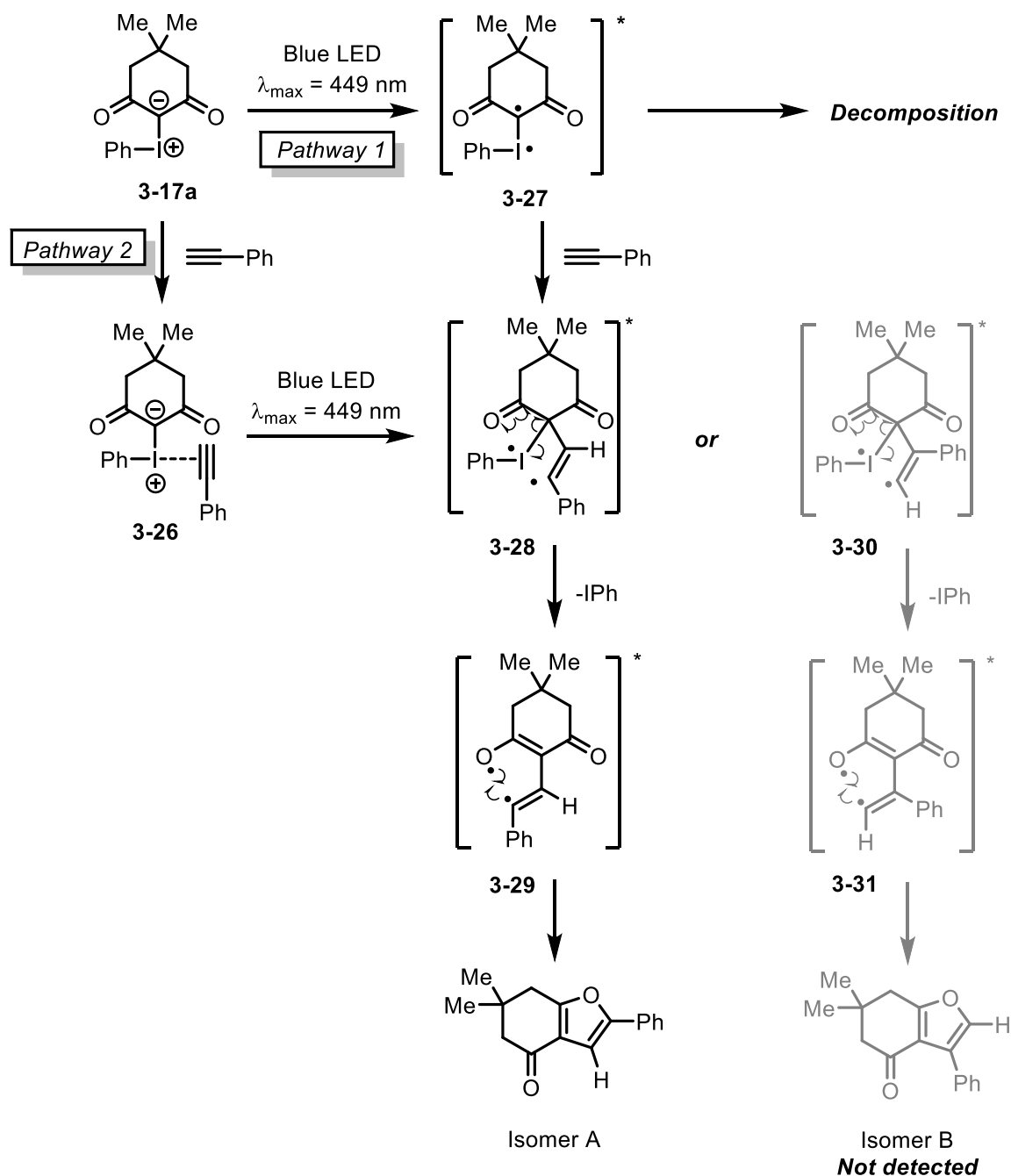
Scheme 3.11. Reaction mechanism pathways for furan synthesis

The yield of the reaction between an iodonium ylide and an alkyne (phenylacetylene) irradiated by blue light to form a furan is much lower than the yield of the reaction between an alkene (styrene) and the same iodonium ylide to form cyclopropane, which proceeds in nearly quantitative yields. Despite alkynes being less stable than alkenes, an alkyne is less reactive than

an alkene, since reactivity depends on $\Delta G^{\ddagger}$, which depends not only on the stability of the reactant but also on the stability of the transition state.[148] In regard to the reaction between an iodonium ylide and an alkyne irradiated by blue light, the transition state involves the formation of an alkenyl radical which is less stable than an alkyl radical in the parallel reaction between an alkene and an iodonium ylide. Radical stability decreases with increasing *s*-character of the orbital (**Figure 3.10**), because being closer to the nucleus, the electron affinity of the orbital will increase.[39]

$H_3C-\dot{C}H_2$

alkyl   aryl, alkenyl   alkynyl

Most stable   *Least stable*
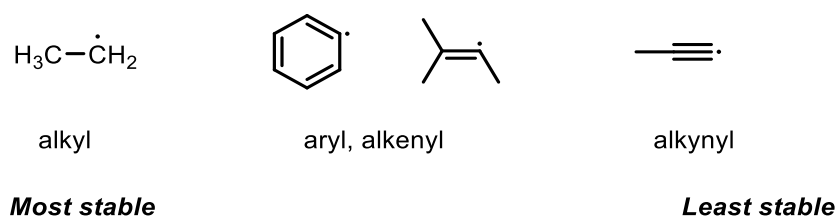
Figure 3.10. Radical stability of *sp*, *sp*^{2}, and *sp*^{3}

3.7.1.1   Solvent Screening

Solvents can affect solubility, stability and reaction rates. While almost all solvents absorb light in the UV-region,[149] they can also influence the absorbance spectra of solutes. The positions, intensities, and shapes of the absorption spectra can be modified by changing the polarity of the solvents. These changes are a consequence of different solvents having different types of physical intermolecular solute-solvent interactions such as ion-dipole, dipole-dipole, dipole-induced dipole, hydrogen bonding, etc. These differences in properties tends to alter the energy gap between the ground and excited state of the absorbing species.[150]

In general, radical reactions are greatly affected by the solvent used. Some solvent can stabilize the radical species, and the reaction intermediates. It is important to select a solvent for the proposed radical reaction of iodonium ylide and alkyne under blue light with considerable care if good product yields are to be achieved.

A solvent screening was performed and summarized in **Table 3.1** which indicates that the reaction can occur in different aprotic solvents but not in protic solvents. Dimedone-derived iodonium ylide is not fully soluble in THF, toluene, methanol, or ether; which could explain the

resulting poor reaction yields. Due to the high solubility of ylides in DCM and the resulting highest yield, DCM was selected to be used in the upcoming optimization experiments.

Table 3.1. Solvent screening for the reaction between a dimedone-derived iodonium ylide and phenylacetylene
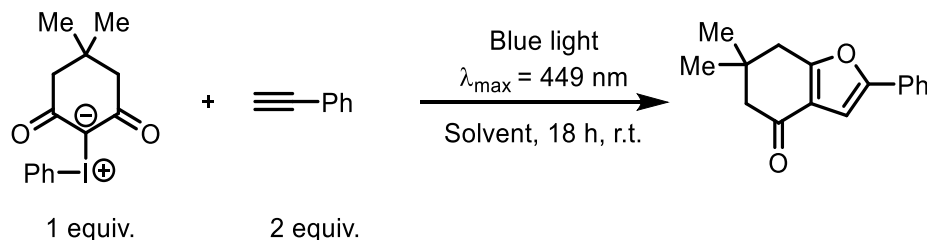
Entry	Solvent	Yield[a]
1	DCM	18%
2	DCE	16%
3	Acetonitrile	13%
4	THF	7%
5	Toluene	8%
6	Methanol	0%
7	Chloroform	14%
8	Ether	15%

[a]Yield was determined by ^{1}H NMR using 10 μL of HMDSO as an internal standard.

3.7.1.2   Testing the Effects of Different Reactant Concentrations

Increasing the concentration of a reactant is one of the main factors that can affect the rate of a reaction because a higher concentration of a reactant will lead to more collisions of that reactant with other reagents added in a specific time. When concentrations are already high, a limit is often reached where increasing the concentration has little effect on the rate of reaction. In multi-component reactions, increasing the concentration of one of the reactants may not affect the rate of reaction if other reactants are not present in sufficient amounts. Concentration is not the only determiner of the reaction rate, and the relationship is usually not simple or linear.[151]

Different reactants' concentrations were examined in the reaction of an iodonium ylide and an alkyne under blue light irradiation. The desire was to use alkyne in excess and the iodonium

ylide as a limiting reagent because alkynes are more available and can be made in high yields. However, the use of ylide in excess was also investigated. **.**

Table 3.2 summarizes the effect of different concentrations of reactants have on the reaction yield. The optimal equivalent ratio was chosen to be entry 2, where one equivalent of ylide is reacted with four equivalents of phenylacetylene offering 28% of the furan. Entry 3 confirms that a large excess of alkynes (10 equiv.) does not result in a significantly higher reaction yield. Even though excess amounts of ylides can in fact lead to moderate yields, 38%, as shown in entry 5, it was avoided to better the quality of the reaction and to reduce the amount of the waste generated (iodobenzene).

Table 3.2. Different reactants equivalents effects on the photochemical reaction between a dimedone-derived iodonium ylide and phenylacetylene

Entry	Equiv. of the ylide	Equiv. of alkyne	Yield[a]
1	1	2	18%
2	1	4	28%
3	1	10	30%
3	1.5	1	14%
4	2	1	20%
5	5	1	38%

[a]Yield was determined by ^{1}H NMR using 10 μL of HMDSO as an internal standard.

3.7.1.3 Side Reactions of the Model Substrates

Two main side reactions were observed in the photochemical reaction of the model substrates derivative iodonium **3-17a** and phenylacetylene. The first one is the isomerization of ylide **3-17a** into **3-31**, which is a known rearrangement that occurs upon the heating of some cyclic iodonium ylides in various solvents (**Scheme 3.12**).[152,153] The yield of this rearrangement depends on the temperature of the reaction mixture.
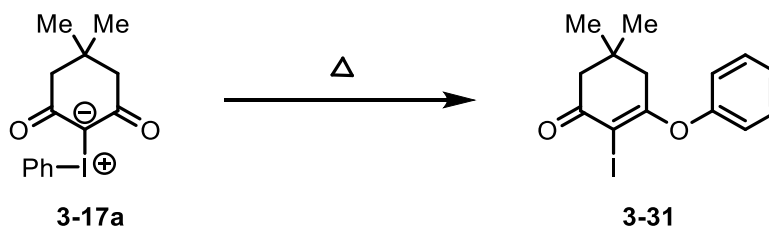
Scheme 3.12. The thermal rearrangement of cyclic iodonium ylide **3-17a**

When the temperature of the reaction between dimedone-derived iodonium ylide and alkynes under blue light irradiation is around 30 ℃, product **3-13** was formed in 14% yield and furan **3-25** was formed is 23%. The vial temperature was measured using a laser thermometer.
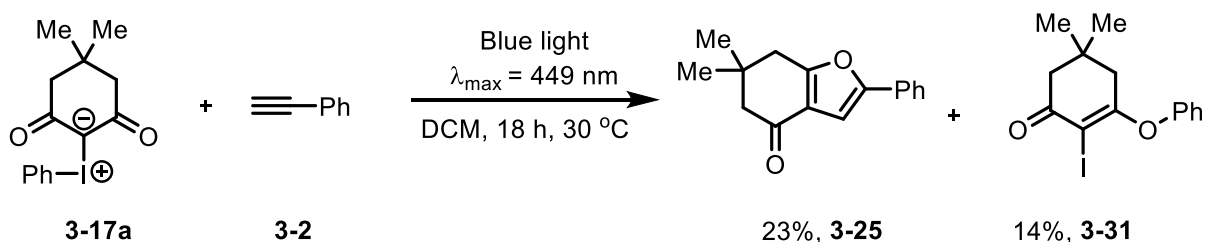
Scheme 3.13. Temperature effect on the reaction yield

To avoid the formation of this side product, holes were made in the photoreactor to allow for airflow, consequently, the temperature dropped to room temperature 25 ºC and only trace amount of **3-31** was observed by ^{1}H NMR analysis after 18 hours.

The second main side product was the formation of an acceptor cyclopropane by the dimerization of dimedone with alkyne and atmospheric oxygen. This reaction was first observed when running the reaction under air where a trace amount of a new product was observed, isolated, and characterized as **3-32**. This unexpected side product can potentially be put into use to access other useful structures (**Figure 3.11**).
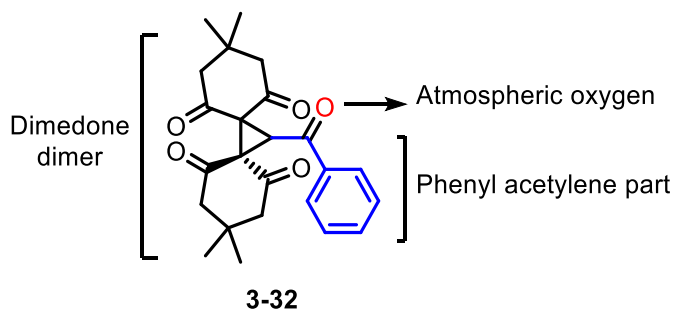
Figure 3.11. Side product generating from oxygen incorporation in the reaction between dimedone iodonium ylide with phenylacetylene

The reaction conditions were re-evaluated in the hope of finding a more robust set for the synthesis of this acceptor-acceptor-acceptor cyclopropane. **Table 3.3** summarizes the conditions investigated and the resulting outcomes. Oxygen was found to fully inhibit the synthesis of furan. Possibly because the oxygen in its singlet form which can be reached by the blue light energy interrupts the formation of furan synthesis and shifts the reaction to another pathway in which **3-32** is made. The use of different solvents was found to change the yield of the cyclopropane formed. Deuterated chloroform ($CDCl_3$) was found to be the best solvent for the reaction. $CDCl_3$ reacts photochemically with oxygen to form the highly toxic phosgene and DCl (deuterium chloride); this trace of acid may cause the increase of yield of **3-32**. To investigate this further, a reaction was performed where one drop of HCl in ether was added to the reaction mixture, after 18 h, **3-32** was generated in 70% yield suggesting that the formation of **3-32** increases in the presence of an acid (entry 5, **Table 3.3**).

Table 3.3. Optimization conditions of the **3-32** cyclopropane formation
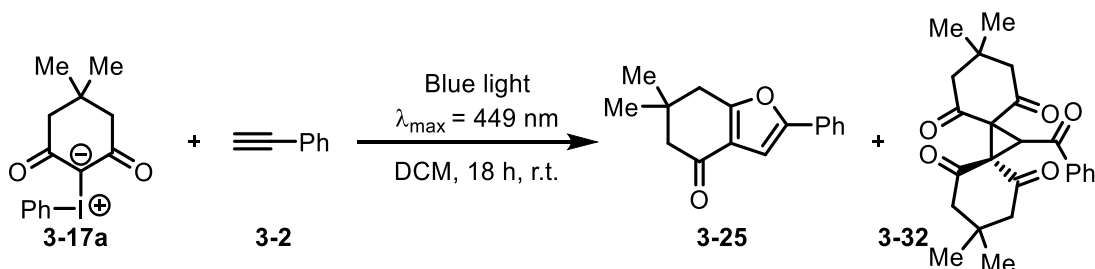
Entry	Atm.	Solvent	Equiv. of 3-17	Equiv. of 3-2	Yield[a] 3-25	Yield[a, c] 3-32
1	O_2	DCM	1	4	0%	20%
2	O_2	DCM	2	1	0%	11%
3	O_2	DCM	2.2	1	0%	12%
4	O_2	$CDCl_3$	1	4	0%	37%
5	O_2	DCM[b]	1	2	0%	35%
6	N_2	DCM	1	4	28%	0%

[a]Yield was determined by ^{1}H NMR using 10 µL of HMDSO as an internal standard.
[b]HCl in ether was added to DCM
[c]50% Theoretical yield

One of the major issues found in the photochemical reaction of the model substrates derived iodonium **3-17a** and phenylacetylene is the long reaction time that led to the decomposition of the iodonium ylide.

3.7.1.4   Alkyne Screening

Initial attempts to expand the alkyne scope revealed that the formation of substituted furans is possible with substituted and terminal alkynes. However, substituted alkynes gave the respective furans in very low yields. Further investigation showed that alkynes with strong EWG were unable to be converted to their respective furans. This can be explained by the stability of the radical intermediate as shown in **Scheme 3.11**.

Table 3.4. Alkyne screening in the reaction between a dimedone-derived iodonium ylide and alkynes
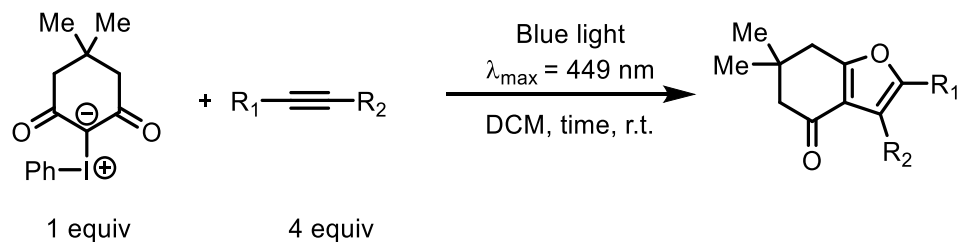
Entry	Time	Alkyne	Product C[a]	Yield[a]
1	18 h	≡—Ph		28%
2	24 h	Ph—≡—Ph		0%
4	4 h			0%
5	18 h			0%
6	5 h			0%
7	6 h			16%

[a]Yield was determined by ^{1}H NMR using 10 μL of HMDSO as an internal standard.

As shown in **Table 3.4**, phenylacetylene gave the highest yield among the different types of alkynes that were reacted with dimedone-derived iodonium ylide under blue light. Also, alkynes with a strong EWG did not react. To further test the effect of electronics effect on the reaction,

phenylacetylene derivatives containing an EWG or an EDG were synthesized to test if any difference in reactivity is observed. As seen in **Table 3.5**, electron-rich alkynes are more reactive which is consistent with the understanding of the reaction mechanism where the free radical intermediate can be stabilized by an EDG.
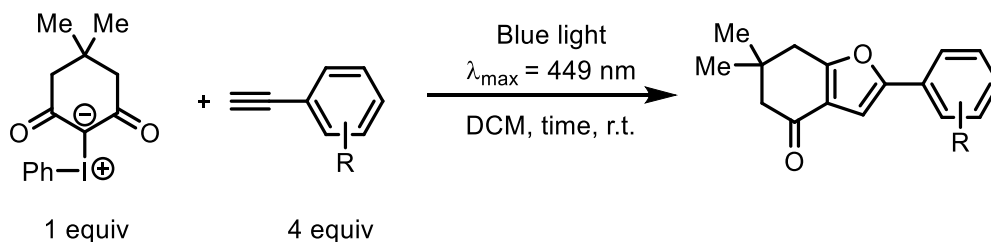
Table 3.5. Phenylacetylene derivatives screening

Entry	R	Time	R
1	4-H	18 h	4-H
2	4-OMe	8 h	4-OMe
3	2-NMe$_2$	8 h	2-NMe$_2$
4	4-NO$_2$	48 h	4-NO$_2$

3.7.1.5   Ylides Screening

Acyclic iodonium ylides are less stable and more challenging to synthesize compared to cyclic iodonium ylides. However, both classes are shown to be activated under blue light irradiation and are thought to go through a diradical intermediate.[144] Testing the reactivity of both of these types of ylides with alkynes under blue light irradiation is therefore essential to better understand the scope of the reaction. Hence, different ylides from both classes, cyclic and acyclic, were reacted under the optimized conditions which are one equivalent of the ylide reacting with four equivalents of phenylacetylene at a concentration of 0.1M in DCM (**Table 3.6**). Unfortunately, no furan was generated when using the cyclic ylide derived from Meldrum's acid. A potential reason is the decrease of the nucleophilicity of the carbonyl oxygen. Going from a ketone (in the case of dimedone-derived iodonium ylide) to an ester (Meldrum's acid) decreases the nucleophilicity of the carbonyl carbon which, in this case, is responsible to close the furan ring. It is also observed that acyclic iodonium ylides do not lead to the formation of furan. In previous sections, it was stated that one of the reaction limitations was the long reaction times resulting in the decomposition of the iodonium ylide used. Acyclic iodonium ylides are far less stable than

cyclic ones and the long reaction time causes decomposition of the ylide resulting in a very low yielding reaction. Acyclic iodonium ylides are known to dimerize, experiments showed that this occurs slowly upon storing at low temperature, rapidly upon heating or irradiation with blue light. After only 4 hours of blue light irradiation of the mixture of phenylacetylene with (bis(methoxycarbonyl)(phenyliodono)methanide) **3-34**, all the ylide dimerized and only a trace amount of the furan was observed. The use of dicarbonyl ketone ylide dibenzoylmethane phenyliodonium betaine **3-35** showed a higher yield of 18% when used in the reaction entry 4, compared to the bis(methoxycarbonyl)(phenyliodono)methanide, entry 5. Trifluoromethyl containing iodonium ylides **3-23** and **3-24**, were also investigated in the hopes of synthesizing the most valuable CF_3-containing furans and to test the regioselectivity of the reaction. One CF_3-containing furan **3-25h** isomer was obtained in a with a yield of 10% in the case of ylide **3-23** (entry 7, **Table 3.6**); and only a trace amount of furan was generated when using ylide **3-24** (entry 8, **Table 3.6**). Again, this shows that the yield decreases when going from a ketone to an ester.

Reaction scheme:

A + ≡—Ph → (Blue light, λ_max = 449 nm, DCM, time, r.t.) → Furan product **C** + Side product **D**
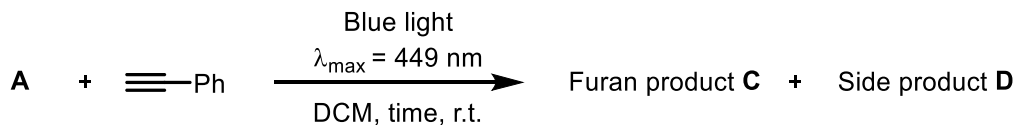
Table 3.6. Screening different cyclic and acyclic iodonium ylide for furan synthesis

Entry	Time	Ylide A	Product C[a]	Side products D[a]
1	18 h	**3-17a**	28%, **3-25d**	trace
2	24 h	**3-33**	0%, **3-25e**	-
4	4 h	**3-34**	0%, **3-25f**	88%
5	18 h	**3-35**	18%, **3-25g**	-
7	6 h	**3-23**	**3-25h**	-
8	6 h	**3-24**	**3-25i** / **3-25j** trace of both	-
6	5 h	**3-36**	0%, **3-25k**	26%

[a]Yield was determined by ^{1}H NMR using 10 μL of HMDSO as an internal standard.

Finally, in the hope of getting a single isomer from a non-symmetrical iodonium ylide, trifluoromethanesulfonyl iodonium ylide **3-36** was synthesized and tested in the reaction. Unexpectedly, SO$_2$CF$_3$ transfer to the alkyne occurred in 26% yield instead of the furan formation

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(entry 6, **Table 3.6**). The transfer of SO_2CF_3 using iodonium ylide **3-36** and other derivatives is not known in literature according to our knowledge. However, Shibata and co-workers have used ylide **3-36** as a novel electrophilic-type trifluoromethylthiolation reagent to introduce CF_3S- to a wide variety of nucleophiles affording CF_3S-substituted products catalyzed by copper. Generating SCF_3 occurs through the carbene pathway in a complex mechanism, the main steps are summarized in **Scheme 3.14**. Irradiating iodonium ylides with blue light leads to a diradical formation pathway, not carbene which could explain the transfer of SO_2CF_3 and not SCF_3. No further experiments were performed to better understand the mechanism and the scope of this novel reaction.
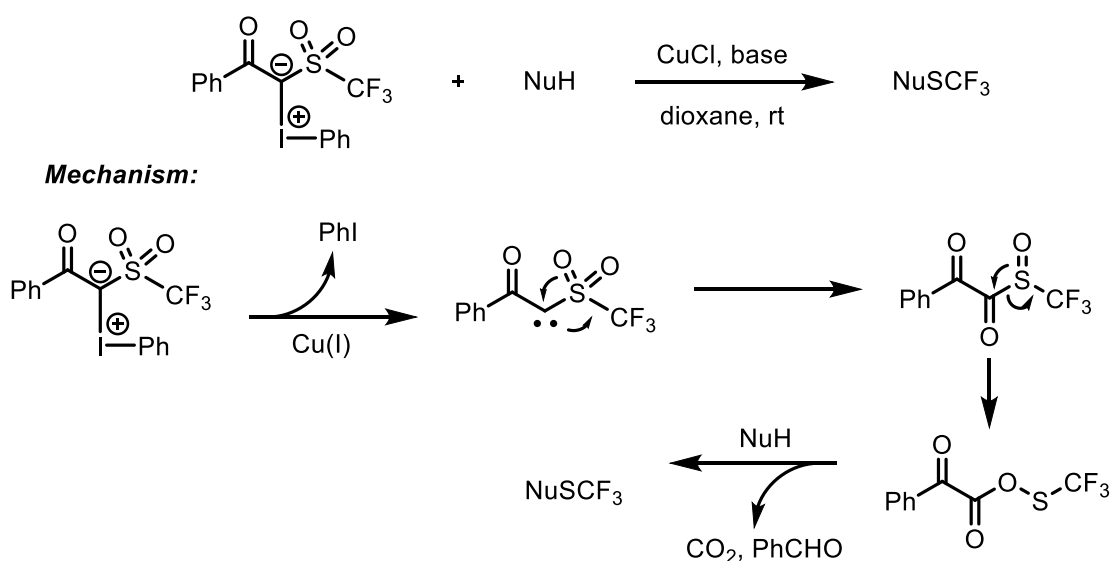
Scheme 3.14. Trifluoromethanesulfonyl iodonium ylide generates SCF_3

As seen in Section 3.7.1.3, dimedone-derived iodonium ylide yielded the best furan yield with minimum side reactions. Another investigation was conducted to see the effects of changing the iodoarene part of a dimedone-derived iodonium ylide. To minimize the rearrangement product, an EDG can be installed on the ylide making the *ipso*-substitution less likely to occur. The addition of an EWG was also studied as it could potentially increase the electrophilicity of the iodine, which could cause better docking between the iodine in an iodonium ylide and phenylacetylene. Both factors could help with increasing the yield of the furan produced.
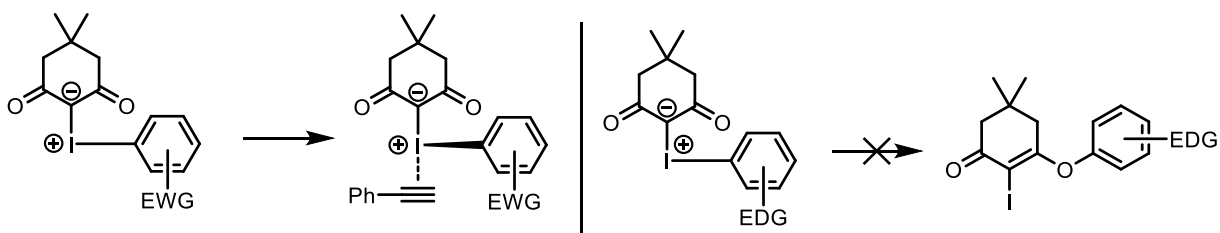
Figure 3.12. The effect of EWG and EDG in the iodoarene of iodonium ylide

The addition of an EDG or EWG did not increase the rate of the reaction or the reaction yield. In fact, adding an EWG destabilized the iodonium ylide, increasing the rate of decomposition which led to very poor yields (entries 3, 4, 5, and 6, **Table 3.7**). The addition of an EDG did not cause much of an effect on the yield (entry 3). When using a sterically crowded aryl iodide the reaction yield decreased significantly (entry 2, **Table 3.7**).

Table 3.7. Iodonium ylide's iodoarene derivatives screening in the reaction between a dimedone-derived iodonium ylide and phenylacetylene

Entry	Ylide (R=)	Yield[a]
1	4-H (**3-17a**)	28%
2	2,6-dimethoxy-4-methyl (**3-17b**)	10%
3	2-OMe (**3-17c**)	23%
4	4-CN (**3-17d**)	Trace
5	4-NO$_2$ (**3-17e**)	Trace
6	4-CF$_3$ (**3-17f**)	10%
7	2,3,4,5,6-pentafloro (**3-17g**)	Trace

[a]Yield was determined by ^{1}H NMR using 10 μL of HMDSO as an internal standard.

3.7.2 Lewis-Acids Catalyst Screening

The carbonyl group is one of the most ubiquitous functionalities of organic compounds. It is an extremely useful functional group to be manipulated by either Brønsted acids or Lewis acids to activate carbonyls in electrophilic substitution reactions, where the acids coordinate to the carbonyl oxygen to induce polarization in the molecule, effectively enhancing its reactivity by augmenting its electrophilicity. It is also important to shed light on the previous work by Ahles and coworkers where a bidentate Lewis acid was combined with a photoinduced ring-opening which formally inserts *o*-xylene moieties into enamine double bonds.[154]
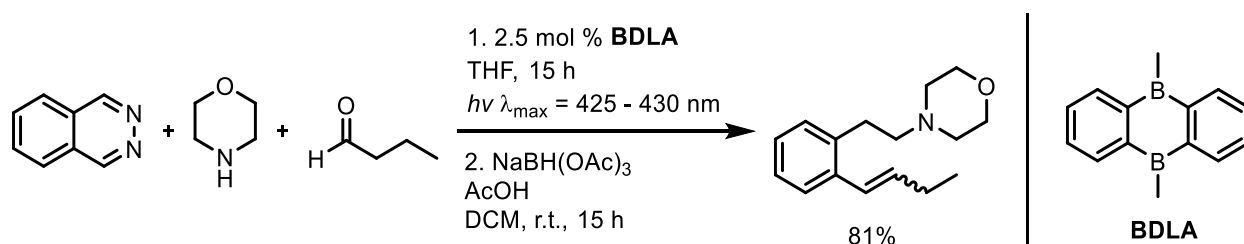
Scheme 3.15. A bidentate Lewis acid catalyzed domino inverse-electron-demand Diels−Alder

This is to state that the combination of ionic reactivity with photochemical reactions is not a foreign concept. There are many other examples of photochemical reactions in which a Lewis acid catalyst was needed. Dicarbonyl iodonium ylides have two carbonyl groups, raising the question of the effects of acids in the reactivity of iodonium ylides. Brønsted acids may protonate the carbonyl oxygen, which could dramatically increase the electrophilicity of the iodine center, attracting the alkyne to the site of reactivity prior to the photoactivation. However, the acidic proton may lead to unwanted side reactions. Lewis acids, bidentate and monodentate could be safer to use since they do not generate an acidic proton. They are also very well known to coordinate to carbonyl oxygens to increase the electrophilicity of the conjugated system connected to the carbonyl motif, in this case, the iodine center. This coordination encourages alkyne coordination to the reaction site prior to activating the ylide with blue light (**Figure 3.13**).
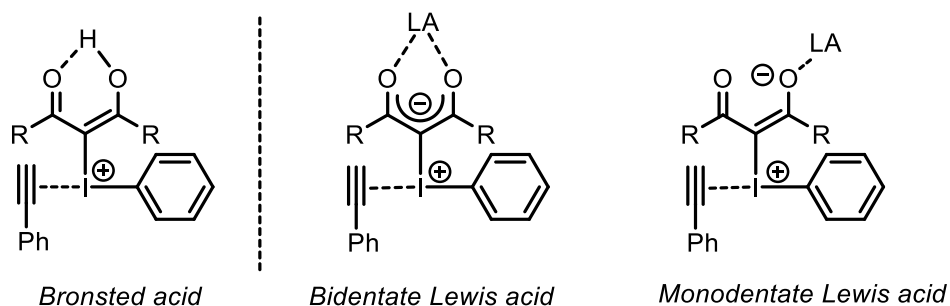
Figure 3.13. Possible coordination of Brønsted acids and Lewis acids to iodonium ylides

Thus, the effect of acids was studied in the case of the photo-induced reaction between iodonium ylides and alkynes. In this study, both Brønsted acids and Lewis acids are used with the intent of observing the reactivity changes and the change in the reaction yield. A summary of the results are found in **Table 3.8**.

Table 3.8. Lewis acid screening in the reaction between a dimedone-derived iodonium ylide and phenylacetylene
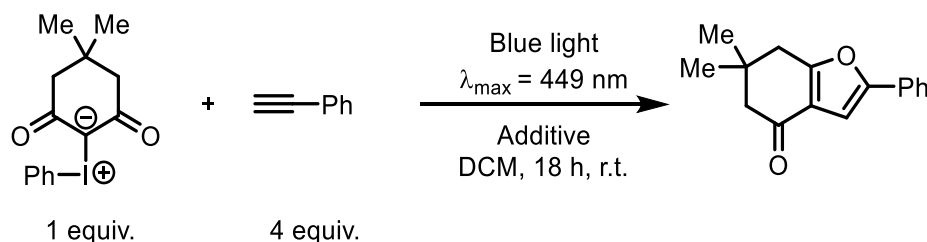
Entry	Additive	Additive equiv.	Solvent	Yield[a]
1	I_2	0.5	THF	9%
2	$BF_3 \cdot OEt_2$	0.5	DCM	30%
3	$MgCl_2$	0.5	THF	0%
4	$Sc(OTf)_3$	0.2	DCM	19%
5	$ZnCl_2$	0.5	THF	Trace
6	succinimide	0.5	DCM	27%
7	$AlCl_3$	0.5	THF	0%
8	$KClO_3$	0.5	THF	10%
9	TMSCl	0.5	DCM	Dimedone dimer 90%
10	Ph_2I^+ OTf[−]	20 mol %	DCM	24%
11	CH_3COOH	20%	DCM	25%
12	H_2SO_4	20%	DCM	0%

[a]Yield was determined by ^{1}H NMR using 10 μL of HMDSO as an internal standard.

The yield of the reaction did not improve by the use of acids. In fact, the use of metal Lewis acids (entries 3, 4, 5, 7, and 8, **Table 3.8**) led to the formation of a crude mixture that was not soluble in organic solvents such as DCM, $CDCl_3$, or MeOH or aqueous solvents such as water; and only trace amounts of the furan product was detected by NMR analysis when filtering out the insoluble solid. Brønsted acids did not improve the yield of the reaction (entries 11 and 12, **Table 3.8**).

3.7.3 Wavelength and Light Intensity

Iodonium ylides absorb light in the UV region and the visible light region. The use of the visible light segment (blue light) allows for a clean reaction where the ylide goes through a diradical intermediate instead of carbene which is the route taken when UV light is used. Shifting slightly from the blue light region to the violet light (λ_{max}= 395 nm) has some advantages. For example, the use of violet light in the reaction between Meldrum's acid iodonium ylide and styrene speeds the reaction from 20 hours to only 2 hours. The reaction yield decreases from 95% to 67%.[144] A Meldrum's acid dimer is observed in 30% yield when violet light is used. As stated earlier, the reaction between an iodonium ylide and an alkyne is slow, and the slow reaction time is potentially one of the causes of the ylide's decomposition. The use of a higher energy wavelength could speed the reaction time and it could also lead to other unwanted side products. The effect of using lower wavelength that possesses high energy was investigated to see the effects it may bring. The use of longer wavelengths that contains lower energy than blue light such as red and green light was also investigated to fully explore the sensitivity of the reaction to a different wavelength of light.

Table 3.9. Testing different visible light colours in the reaction between dimedone iodonium ylide and phenylacetylene
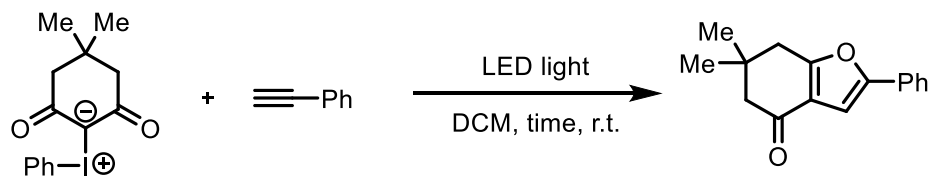
Entry	Colour	λ_{max}	Time (h)	Yield[a]
1	Red	630	72	0%
2	Green	510	72	0%
3	Blue	449	18	28%
4	Violet	395	4	14%
5	Violet	360	4	14%

[a]Yield was determined by ^{1}H NMR using 10 µL of HMDSO as an internal standard.

The use of lower energy wavelengths such as red and green light in the reaction between an alkyne and an iodonium ylide did not initiate the reaction and no furan was detected by NMR after 72 hours of irradiation. The use of high energy wavelengths such as violet light led to rapid decomposition of the iodonium ylide within 2 hours affording 14% furan. Therefore, blue light is the optimal energy source since it is not detrimental to the yield. At the same time, it provides the energy needed for the iodonium ylide to undergo a photochemical excitation leading to the formation of diradical intermediate.

3.7.4 Tuning the Reactivity by Blocking One σ-hole

As seen in Chapter 2, the iodine center of iodonium ylides has two σ-holes, which are two electrophilic sites that could coordinate to soft Lewis bases or nucleophiles. Having two sites of reactivity introduces some limitations like the instability of iodonium ylides and side reactions such as nucleophile dimerization. Gaining control of reactivity can be achieved by sterically or electronically blocking one of the two σ-holes thus selected reactivity could be markedly reduced or switched off. For example, in the reaction between thioamides and iodonium ylides, the introduction of a coordinating *ortho* substituent to the iodobenzene part of an iodonium ylide decreased side reactions by blocking one of the σ-holes resulting in a dramatic increase of the reaction yield as shown in **Scheme 3.16**. These results suggest the importance of the *ortho*

substitution on the aromatic ring of iodonium ylides for stability and inducing selective reactivity.[72]
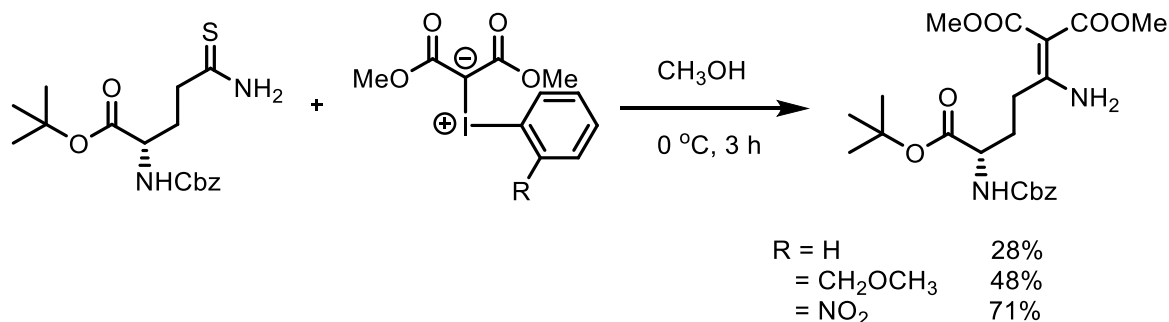
Scheme 3.16. Optimization of the reaction conditions with different σ-hole blockers

An *ortho* nitro-substituted iodonium ylide was found to be the best reagent to furnish the product. The crystal structure shows significant coordination between the *ortho* nitro group and the iodine center allowing only one σ-hole to react (**Figure 3.14**).[72]
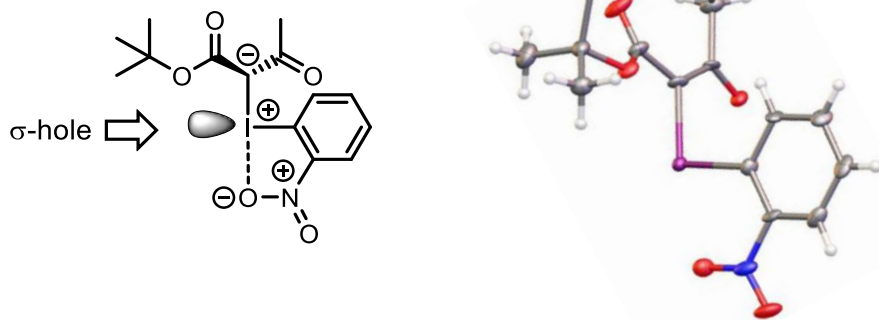
Figure 3.14. Crystal structure of *ortho* nitro-substituted iodonium ylide[72]

3.7.4.1   External σ-Hole Blocker

Before designing iodonium ylides that contain an aryl iodine group with an *ortho* group that acts as a σ-hole blocker, some experiments were performed to test the effects of Lewis bases that may act as σ-hole blockers. Since Lewis bases are electron-rich species that can donate

electron-pairs, they can coordinate to the partially positive charged σ-holes. The coordination between Lewis bases and hypervalent iodine σ-holes is known to occur with diaryliodonium salts and Togni derivatives.[155] For example, intramolecular halogen-bonding can be formed between an alcohol and the hypervalent iodine center as shown in **3-37** in **Figure 3.15**. Another example is the coordination between the nitrogen in acetonitrile and the iodine center in **3-38**. Also, pyridine acts as a σ-hole acceptor and was shown to coordinate to the iodine center in **3-39**.[155]

3-37   **3-38**   **3-39**
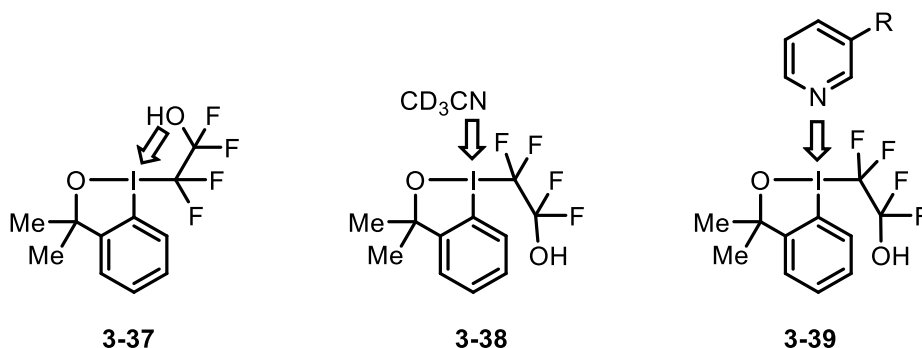
Figure 3.15. Examples of halogen bonding of iodonium ylides and nucleophiles

In the case of iodonium ylides, there are two σ-holes and there is yet to be a study about the differences in their Lewis acidic properties. Hence, the addition of Lewis bases wouldn't target a specific σ-hole and is only meant to stabilize the ylide to minimize side reactions. Common Lewis bases are ammonia, alkyl amines, and other conventional amines. Thus, amine derivatives were used besides other electron-rich Lewis bases that are known to not react with iodonium ylides under mild conditions (**Table 3.10**).

Table 3.10. Lewis bases screening of the reaction between an iodonium ylide and alkyne

1 equiv.   4 equiv.
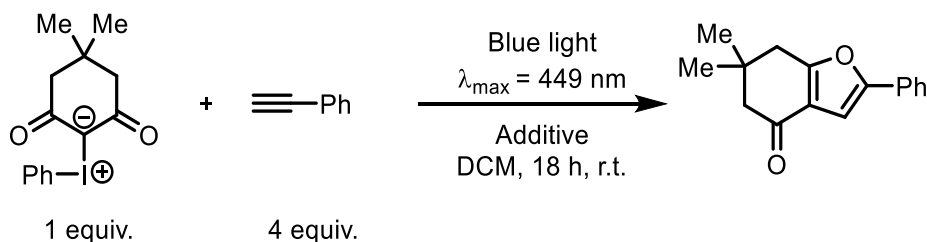
Entry	Lewis base	Equiv.	Yield (%)[a]
1	NEt$_3$	10%	23
2	2,6-Lutidine	10%	24
3	Pyridine	10%	27
4	PPh$_3$	10%	26
5	Diisopropylamine	10%	25
6	DMF	10%	24
7	DBU	5%	35
8	DBU	10%	14
9	DBU	50%	0

[a]Yield was determined by ^{1}H NMR using 10 μL of HMDSO as an internal standard.

The addition of Lewis bases did not significantly change the reaction yield. However, 5% of DBU increased the reaction yield of furan to 35%. Increasing DBU loading above 5% inhibits the reaction. The strong nucleophilicity of DBU could result in a stronger coordination to the σ-holes of iodonium ylides than that between the alkyne and the σ-holes of the ylide.

3.7.4.2   Synthesis and Reactivity of σ-Hole Blocker Iodonium Ylides

As seen previously, the photochemical reaction between an iodonium ylide and an alkyne suffers from many side reactions with identified and unidentified products. Thus, iodonium ylides containing a σ-hole blocker on the *ortho* position were synthesized to investigate if blocking one of the iodonium ylide's σ-holes would result in preventing side reactions and/or ylide decomposition, which will in turn increase the reaction yield.

Most of the σ-hole blocking ylides that were made for the purpose of preventing side reactions from occurring are not reported in the literature. Hence, they were made using altered known procedures in high yields under mild conditions. Detailed synthetic procedures are found in the supporting information of this chapter. Dimedone-derived iodonium ylide was the system

of choice to be examined with different σ-hole blocker groups on the aryl ring. Acyclic iodonium ylides were also made for a few examples that compare the reactivity between cyclic and acyclic iodonium ylides.

3-17h   3-17i   3-17j

3-17k   3-17l   3-40

3-41   3-42   3-43
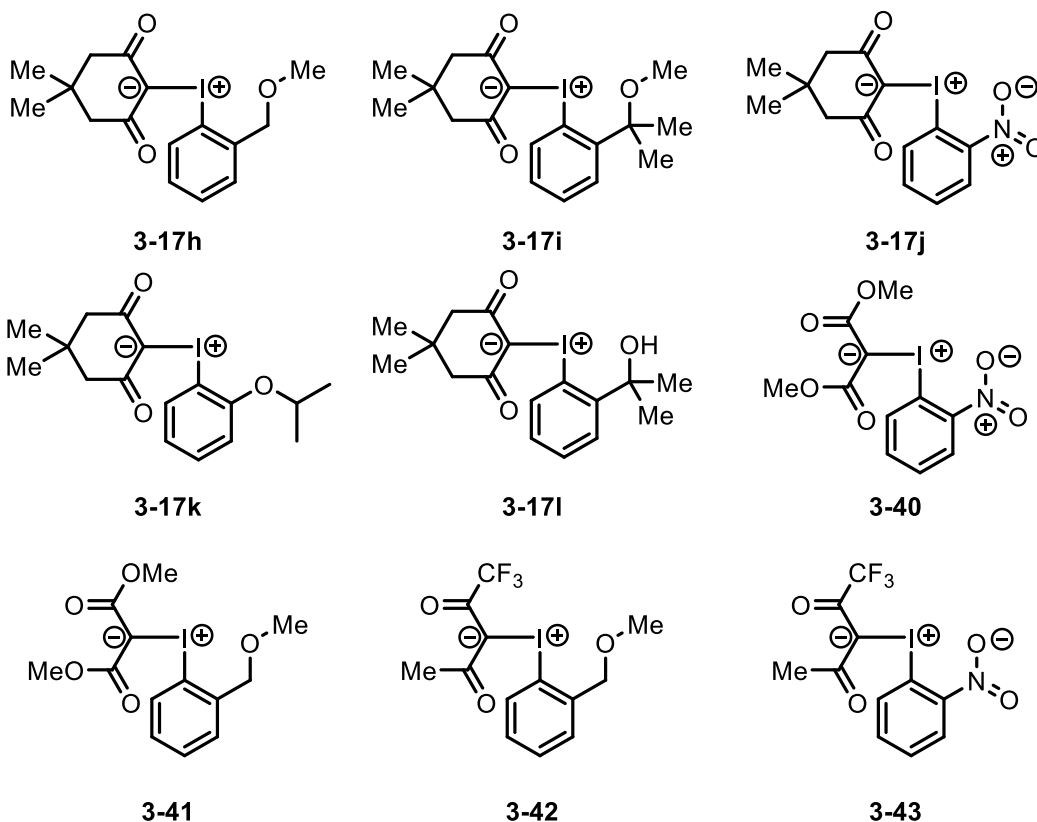
The synthesis of iodonium ylides with an *ortho* group is challenging in comparison to having groups on other positions on the iodoarene ring. An *ortho* group could be involved in steric or electronic interactions with the iodine center which may result in unpredictable outcomes. Another challenge of ylide synthesis is the oxidation of the aryl iodide that must be achieved then converted into the ylide. The most common synthetic route for ylide is going from the aryl diacetate to the iodonium ylide. The synthesis of diacetates from the corresponding aryl iodide is possible under many different conditions for example selectfluor,[156] sodium perborate,[157] acetic acid[158] and others. Most of these reactions requires the use of acids and long reaction times. Hence, there is no simple method for the synthesis of aryl diacetates that is needed to synthesize iodonium ylides.

To work with more challenging ylides, a new one-pot procedure for the synthesis of iodonium ylides was developed. This method utilizes the low solubility of hypervalent iodine reagents in hexane to precipitate the product as it is being formed. This method oxidizes the iodoarene using the first-ever method discovered for the synthesis of a hypervalent iodine reagent, which was bubbling Cl_2 in a solution of iodobenzene to synthesize (dichloro)iodobenzene. The most common solvents used for this reaction are dichloromethane or chloroform which solubilize the (dichloro)iodobenzene product. The (dichloro)iodoarenes product must be isolated and purified before proceeding to the next step. The altered procedure involves running this chlorination step in hexane.

Most aryl iodide are soluble in hexane or in a mixture of hexane and diethyl ether. (Dichloro)iodoarenes and almost all other hypervalent iodine reagents are not soluble in these solvents or in a mixture of them. Running the chlorination in hexane allows the product to precipitate as the reaction proceeds. The reaction is monitored by TLC, upon the completion of the reaction, hexane is decanted, and the dichloride is washed with hexane which is also decanted. At this stage, the (dichloro)iodobenzene is high in purity. A mixture of DCM and MeOH 10:1 is added and one equivalent of acetate salts such as sodium acetate or potassium acetate is added. Through a ligand exchange mechanism, the chloride ligands are replaced with acetates to form (diacetoxyiodo)arenes in around 5 minutes. The synthesis of the iodonium ylide is then achieved by adding 1 equivalent of the dicarbonyl compound such as dimedone with 1 equivalent of potassium carbonate as seen in **Scheme 3.17**.

1. Cl_2, hexane, 0 °C, 15 min

2. NaOAc, 10:1 DCM:MeOH, rt, 5 min
3. Dimedone 1 equiv, K_2CO_3 1 equiv, r.t., 20 min

65% over 3 steps
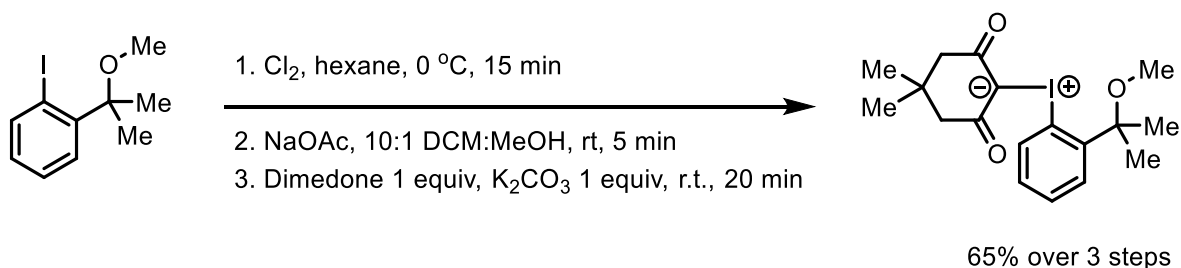
Scheme 3.17. One-pot synthesis of iodonium ylide under mild conditions

This new procedure allowed for the synthesis of a critical system for this research such as **3-17i**. It is also worth mentioning that this ylide was inaccessible by other known methods. The synthesis of (iodoarene)diacetate from the iodoarene **3-44** was not possible by other known

methods such as acetic anhydride, hydrogen peroxide, sodium perborate[159] or Selectfluor[TM] reagents.[160] In fact, running the chlorination reaction in chloroform or dichloromethane showed very inconsistent results. It was performed multiple times under the conditions outlined in **Scheme 3.18**. Dimedone dimer **3-45** was the only product obtained on a consistent basis and may have resulted from a trace amount of chlorine gas or HCl being present which causes dimerization of the ylide. When hexane was used as the solvent, a quick purification can be performed by decanting and then washing the crude product with fresh hexane. This minimizing the chances of dimerization of the ylide by removing residual chlorine gas or HCl when performing the synthesis in this one-pot method.
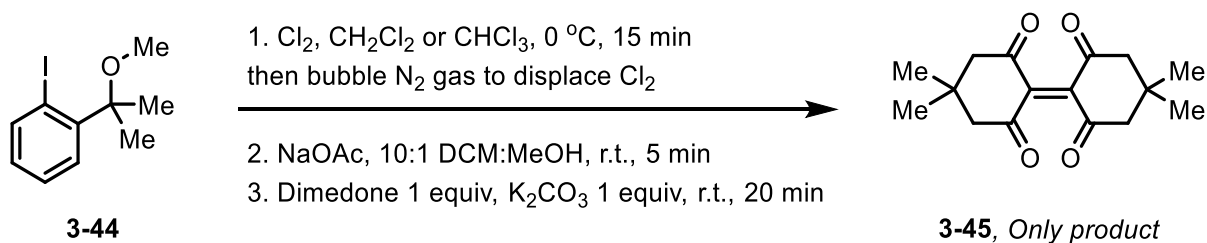
Scheme 3.18. Dimedone dimer formation when attempting the synthesis of one-pot procedure

The synthesis of some ylides containing an *ortho* group on the aryl iodide was not possible for some systems. For example, oxidation of the iodine center in aryl iodide **3-46** was not possible using known methods and the new one-pot procedure was developed as an additional method for oxidizing aryl iodides that are problematic using traditional procedures. The deprotection of the MOM group generally needs strong acidic conditions. But in this case, the MOM group was removed when using only slightly acidic conditions which are required for oxidation of the aryl iodide into a hypervalent iodine compound. The use of chlorine gas was also not successful as the starting material **3-46** rapidly decomposed into a black slurry paste.

Me
O
I
O

Selectfluor™
AcOH, MeCN

Cl₂ in Hexane

→ *Decomposition of SM*

3-46
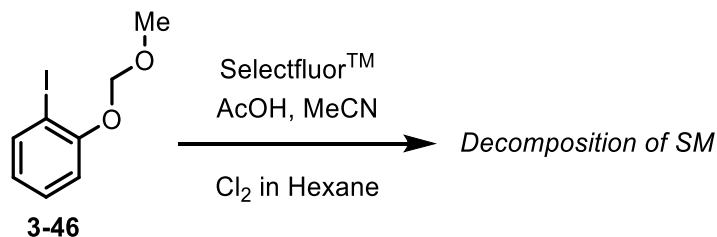
Scheme 3.19. Decomposition of 1-MOM-2-iodobenzene

Hypervalent iodine compounds containing an *ortho*-SO₂^{t}Bu group are known, including the iodosoarene derivative discovered by the Protasiewicz group.[161] Unlike other iodosoarene compounds, it is known to be highly soluble in most organic solvents. Thus, the synthesis of the ylide derivative was a matter of interest. However, when reacting diacetate **3-47** with dimedone under mild conditions the aryl iodide **3-48** was obtained and there was no trace of the iodonium ylide (**Scheme 3.20**).

Me Me

AcO—I—OAc
SO₂^{t}Bu

O   O

DCM, 0 °C, 3 h
K₂CO₃

I
SO₂^{t}Bu

3-47   **3-48**
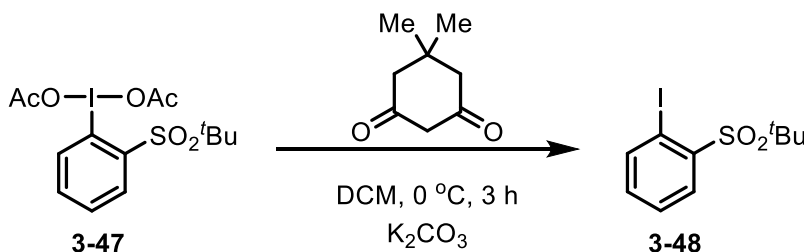
Scheme 3.20. Failed synthesis of a dimedone-derived iodonium ylide with *ortho*-SO₂^{t}Bu

^{1}H NMR analysis of some of the newly synthesized iodonium ylides showed interesting findings where the chemical shifts of the iodoarene in the ylides are more shielded than their non-hypervalent species. This contradicts the well-established trend in which the hydrogens on the iodoarene part in hypervalent iodine species are always slightly more downfield compared to the non-hypervalent iodoarene as shown in **Figure 3.16**. It is also worth noticing that this effect is not seen in the diacetate **3-50**. The addition of a group onto the iodoarene that is capable of blocking a σ-hole, such as *ortho*-(methoxymethyl), causes the *ortho* hydrogen in the iodonium ylide **3-17h** to be more shielded than the non-hypervalent iodoarene, 1-iodo-2-(methoxymethyl)benzene (**3-49**). This may suggest that the oxygen atom in the methoxy group has significant intramolecular coordination to the positively charged iodine atom in **3-17h**. The electronic coordination to the

iodine center decreases the positive charge of the iodine causing the electron-withdrawing effect on the aryl iodide to decrease.
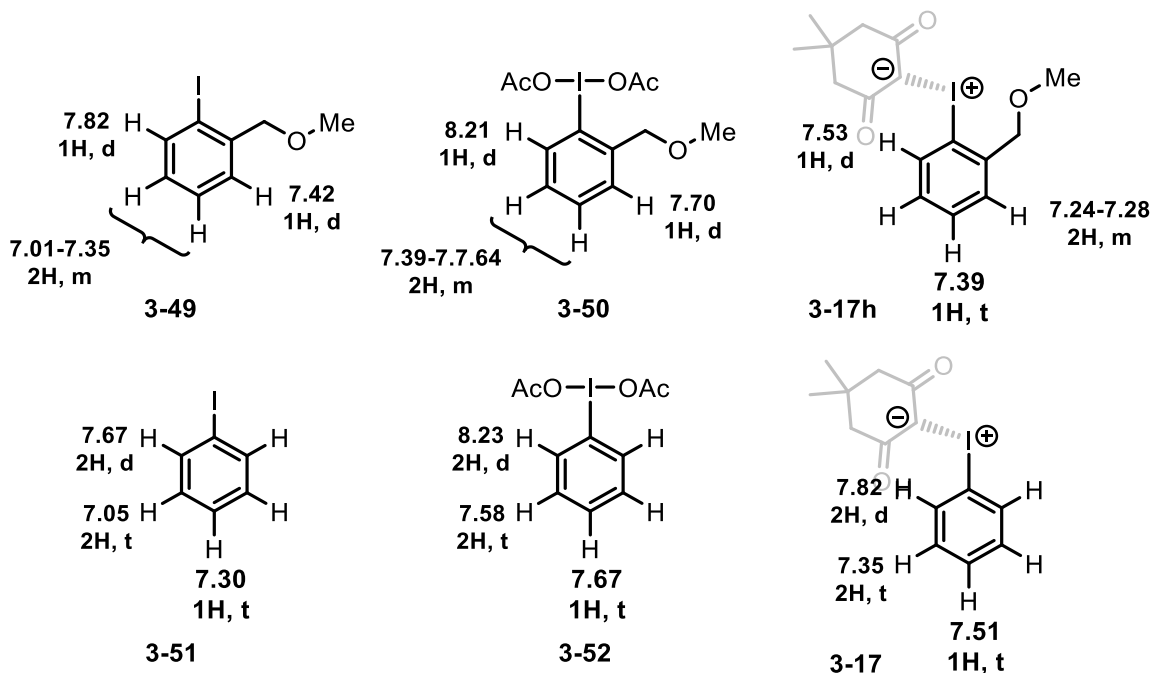
Figure 3.16. ^{1}H NMR analysis of dimedone-derived iodonium ylides

Ylide **3-17i** showed similar shielding patterns when analysing ^{1}H NMR results. Another interesting observation in regard to the ylides that contain various groups in the *ortho* position, is that they have much higher solubility compared to dimedone iodonium ylide derived from iodobenzene. For example, iodonium ylide **3.17h** is slightly soluble in diethyl ether which is not the case with **3-17a**.

3.7.4.3   Testing the Reactivity of Iodonium Ylides Containing a σ-Hole Blocker

After accomplishing the synthesis of a series of ylides with various groups in the *ortho* position which have the potential to act as σ-hole blockers, they were reacted with phenylacetylene under the optimized conditions to analyze the yield of furan produced (**Table 3.11**).

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Table 3.11. Testing the yield change when reacting iodonium ylides with *ortho* groups on the aryl iodide with phenylacetylene under blue light irradiation

Entry	*Ortho* group	Yield of furan
1	-NO$_2$ (**3-17j**)	19%[a]
2	CH$_2$OMe (**3-17h**)	40%[b]
3	C(Me)$_2$OMe (**3-17i**)	60%[b]
4	C(Me)$_2$OH (**3-17l**)	No reaction
5	OiPr (**3-17k**)	24%[a]

[a]Yield was determined by ^{1}H NMR using 10 μL of HMDSO as an internal standard.
[b]Isolated yield

The reaction yield significantly increases in entries 2 and 3, suggesting that the addition of a σ−hole blocker to the iodonium ylide may have helped the reaction. Another experiment was performed to investigate the stability of the new ylides. Ylides **3-17h** and **3-17i** were stirred in DCM under blue light irradiation for two days. Ylide **3-17i** show no significant decomposition whereas ylide **3-17h** showed slight decomposition. The addition of the *ortho* groups on both ylides **3-17h** and **3-17i** acted as a stabilizing factor to minimize side reactions, thus, increasing the reaction yield. These two best ylides were used for the synthesis of other furan rings (**Table 3.12**).

Table 3.12. Furan synthesis using dimedone-derived iodonium ylides containing σ-hole blockers
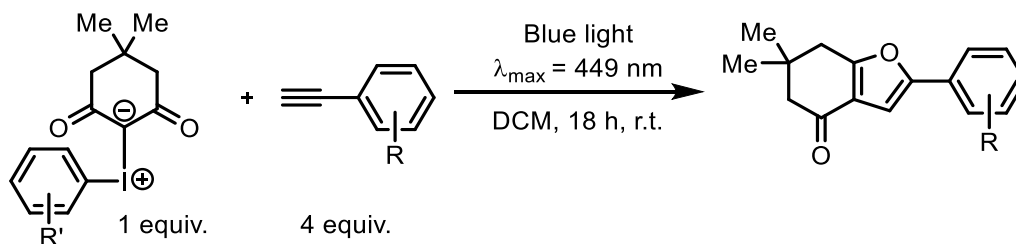
Entry	R	R' = CH$_2$OMe (**3-17h**)	R' = CMe$_2$OMe (**3-17i**)
1	H	40%[b]	60%[b] (**3-25**)
2	4-*t*Bu	55%[b]	70%[b] (**3-25c**)
3	4-OMe	60%[b]	30%[a] (**3-25a**)
4	2-NMe$_2$	65%[b]	0%[b] (**3-25b**)
5	4-NO$_2$	0%[a]	0%[a]

[a]Yield was determined by ^{1}H NMR using 10 μL of HMDSO as an internal standard.
[b]Isolated yield

Each of the ylides **3-17h** and **3-17i** showed a unique trend. In the case of **3-17h** the reaction yield increases with more electron-rich phenylacetylene derivatives. For **3-17i**, the reaction yield decreases when adding heteroatoms (entries 3 and 4, **Table 3.12**), the phenylacetylene derivatives and the starting materials are fully recovered without decomposition. The addition of heteroatoms could have added another stabilizing factor that inhibited the reaction from proceeding. The reaction failed to produce any furan when working with electron-poor phenylacetylene derivatives (4-NO$_2$). Perhaps the strong electron-withdrawing ability of the 4-NO$_2$ group causes problems in the formation of radical-based intermediates which are just too unstable to exist and therefore the reaction does not occur.

The reaction between acyclic iodonium ylides and phenylacetylene is extremely low yielding and only trace of furan is detected by ^{1}H NMR analysis. However, when a σ-hole blocker is added, the yield increased to 12% with *ortho*-NO$_2$, and 30% with *ortho*-CH$_2$OMe (**Table 3.13**).

Table 3.13. Furan synthesis of acyclic iodonium ylides containing σ-hole blockers
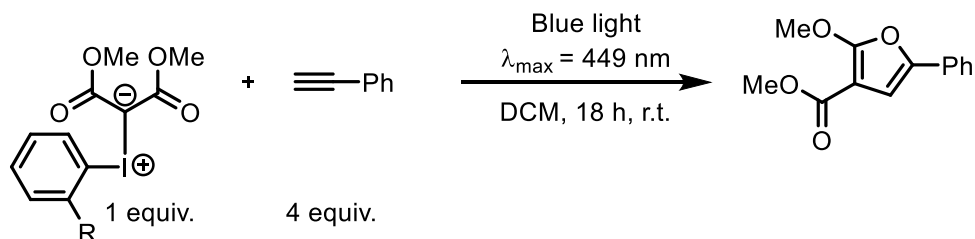
Entry	R	Yield of furan[a]
1	H (**3-34**)	Trace
2	NO_2 (**3-40**)	12%
3	CH_2OMe (**3-41**)	30%

[a]Yield was determined by ^1H NMR using 10 μL of HMDSO as an internal standard.

3.8   Conclusion

In conclusion, the blue-light-induced photochemical reaction between iodonium ylides and alkynes resulted in the formation of furans. Blue LED irradiation of iodonium ylides gives diradical intermediates which are then capable of reacting with alkynes for the formation of furans. The reaction of iodonium ylides with terminal alkynes under blue light irradiation is regioselective to form products A (**Scheme 3.21**), following the pathway of the most stable radical intermediate.
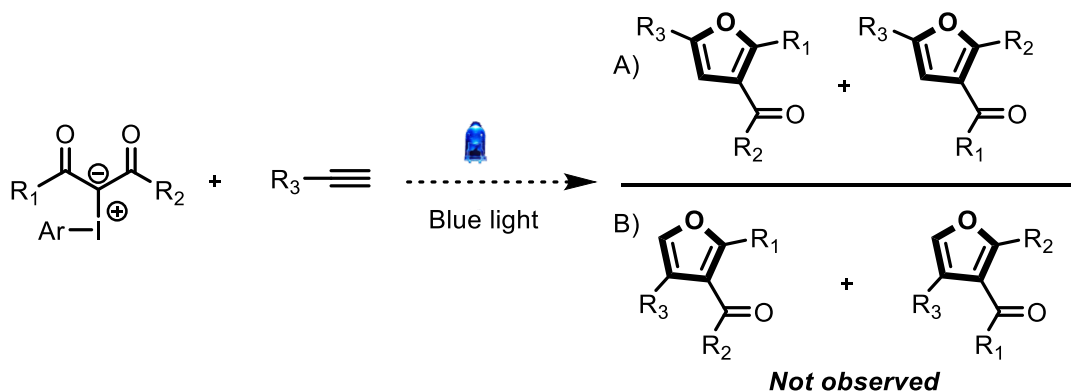
Scheme 3.21 Blue light photochemical synthesis of furans

Products B (**Scheme 3.21**) were not observed in any of the reactions performed. The reaction yields varied between systems from 12-28% yield. The highest reaction yield was

observed from the reaction between dimedone iodonium ylide and phenylacetylene; thus, they were chosen to be the model substrates. Different approaches to optimize the yield of furan using the model substrates were utilized. The reactions conditions were screened, and the optimal conditions of the blue-light-induced reaction were discovered to be one equiv. of the ylide and four equiv. of the alkyne in 0.1 M DCM under N_2 atmosphere at room temperature. The reaction is sensitive to oxygen, in the presence of oxygen atmosphere, a new side reaction was observed (**3-32**). Heat also induced ylide rearrangement forming another side product through a known thermal-induced transformation. Lewis acid additives decreased the reaction yield and some Lewis bases increased the reaction yield, such as DBU, which increased the yield of the model reaction to 35%. The use of lower wavelengths of light caused higher decomposition and lower yield, whereas the use of higher wavelength such as green and red light did not initiate the reaction.

The use of phenylacetylene derivatives showed results that are consistent with the theory behind a radical stabilization-based mechanism. Having an EDG such as *para*-OMe or *ortho*-NMe$_2$ on the alkyne increased the reaction yield significantly from 28% yield when using phenylacetylene to 50% with *para*-OMe substitution and 60% with *ortho*-NMe$_2$. The presence of an EDG on the alkyne increases the stability of the radical intermediate, which in turn leads to higher yields of the furan. On the other hand, the use of phenylacetylene derivatives with an EWG such as *para*-NO$_2$, decreased the reaction yield to 0%. This is also predictable given that the radical intermediate is extremely unstable with electron deficient alkynes.

Then, in the aim of increasing the stability of the dimedone-derived iodonium ylides and decreasing side reactions, new dimedone-derived iodonium ylides were synthesized in which the aryl group contain an *ortho* group intended to block one of the iodonium ylide's σ-hole. Some of these ylides such as **3-17h** and **3-17l** showed a dramatic increase in furan yield when reacting with phenylacetylene, 40% and 60% respectively. Unfortunately, when reacting these ylides with alkynes that were composed of a phenylacetylene derivative containing a heteroatom in an *ortho* or *para* position under the optimized conditions, low ylides were observed with **3-17h**, and no reaction was detected with **3-17i**. Acyclic iodonium ylides containing a σ-hole blocker (which is always located in an *ortho* position) also showed some increase in the furan yield. The reaction between acyclic iodonium ylide bis(methoxycarbonyl)(phenyliodono) methanide **3-34** with phenylacetylene under the optimized conditions lead to a trace amount of furan. When installing an *ortho*-CH$_2$OMe group onto an acyclic iodonium ylide, such as **3-41**, the yield of the reaction

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increased to 30%. Therefore, after attempting many different strategies for increasing the yield of furan, much success has come in the form of knowledge gained of how iodonium ylides react and can be controlled to give desired products under mild conditions while simultaneously limiting the amount of side products generated. Although the yields of furan can be considered low from some of the reactions presented, a great deal of information was gained which may be helpful when applied to other reactions that are sure to soon be discovered in the near future in our group and others.

3.9   Supporting Information

All reactions were carried out in flame-dried glassware under a dry nitrogen atmosphere, unless otherwise noted. Solvents were either obtained from a JC Meyer solvent purification system or purified according to the Purification of Laboratory Chemicals handbook. All reagents were purchased from Sigma-Aldrich and used without further purification. ^{1}H NMR spectra were recorded on Bruker instruments at 300 MHz, and were referenced to residual ^{1}H shift in CDCl$_3$ (7.24 ppm). ^{13}C NMR were recorded at 75 or 125 MHz, and CDCl$_3$ (77.0 ppm) was used as the internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, br s = broad singlet. Reactions were monitored by thin-layer chromatography (TLC) on commercial silica pre-coated plates with a particle size of 60 Å and viewed by UV lamp (254 nm) or by ^{1}H NMR. Flash chromatography was performed using 60Å (230-400 mesh) silica gel. InfraRed (IR) data was recorded using an ATR-FTIR (Attenuated Total Reflection Fourier Transform InfraRed) instrument. The following abbreviations were used to explain the IR peak intensities: (s) = strong, (m) = medium, (w) = weak. Positive ion electrospray ionization (ESI) was performed with a Thermo Scientific Q-Exactive hybrid mass spectrometer. Accurate mass determinations were performed at a mass resolution of 70,000. For ESI, samples were infused at 10 μL/min in 1:1 CH$_3$OH/H$_2$O + 0.1% formic acid or CH$_3$OH/H$_2$O + 0.1% formic acid or or CH$_3$OH/H$_2$O + 0.1% LiOAc.

3.9.1   General Procedure for Synthesis of Iodonium Ylides (GP1)

Cyclic β-dicarbonyl iodonium ylides are known compounds and were prepared in one step from the corresponding β-dicarbonyl methylene compound (1 equiv.), and (diacetoxyiodo)benzene (1 equiv.) following procedures found in the literature by Koser[146] and Lick.[112] The iodonium ylides were purified as follows: the crude reaction mixture was dissolved in a minimal amount of CH$_2$Cl$_2$ (5 mL), then this solution was added to Et$_2$O (50 mL) in a flask that was stirred and cooled in an ice bath. After stirring for 10 min, the suspension was filtered, and the solids were dried in air or under vacuum until a constant weight was obtained.

3.9.2 General Procedure for Synthesis of Trifluoromethyl-Containing Iodonium Ylides (GP2)

In a round bottom flask containing CF$_3$-β-dicarbonyl (1 equiv.) in EtOH (0.17 M) at 0 °C, sodium methoxide solution 25 wt. % in methanol (1 equiv.) was added. The solution was stirred for 5 min at the same temperature. Then (diacetoxyiodo)benzene (1 equiv.) was added in portions. Stirred for 30 min at 0 °C. Then the reaction was quenched with ice-cold water and the ylide was extracted with CH$_2$Cl$_2$ (20 mL x 3 times). The obtained organic solution was placed in an ice bath and dried with MgSO$_4$. MgSO$_4$ was filtered and the organic solvent was placed under reduced pressure using rotary evaporator. The crude reaction mixture was dissolved in a minimal amount of CH$_2$Cl$_2$ (5 mL), then this solution was added to Et$_2$O (50 mL) in a flask that was stirred and cooled in an ice bath. After stirring for 10 min, the suspension was filtered, and the solids were dried in air or under vacuum until a constant weight was obtained.
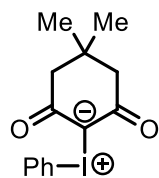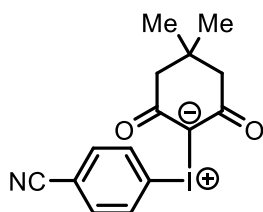
2-Phenyliodonio-5,5-dimethyl-1,3-dioxocyclohexanemethylide (3-17a, dimedone iodonium ylide): Iodonium ylide **3-17a** was prepared according to GP1 from 5,5-dimethyl-1,3-cyclohexanedione (2.80 g, 20 mmol, 1 equiv.) and (diacetoxyiodo)benzene (6.4 g, 20 mmol, 1 equiv.) in CH$_2$Cl$_2$ (50 mL) for 3 h at room temperature. Purification by trituration (CH$_2$Cl$_2$:Et$_2$O 1:10) led to the title compound isolated as a white solid (5.14 g, 80% yield). The characterization data matches what has already been reported in the literature.[144] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.82 (d, *J* = 7.9 Hz, 2 H), 7.51 (t, *J* = 7.8 Hz, 1 H), 7.35 (t, *J* = 7.6 Hz, 2 H), 2.50 (s, 4 H), 1.05 (s, 6 H).
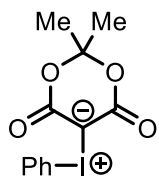
Meldrum's acid iodonium ylide 3-33: Iodonium ylide **3-33** was prepared according to GP1 from 2,2-dimethyl-1,3-dioxane-4,6-dione (0.288 g, 2.0 mmol, 1 equiv.) and (diacetoxyiodo)benzene (0.644 g, 2.0 mmol, 1 equiv.) in CH$_2$Cl$_2$ (15 mL) for 1.5 h at room temperature. Purification by trituration (CH$_2$Cl$_2$:Et$_2$O 1:10) led to the title compound isolated as a white solid (0.540 g, 77% yield). The characterization data matches what has already been reported in the literature.[144] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.88 (d, *J* = 7.5 Hz, 2 H), 7.59 (t, *J* = 7.4 Hz, 1 H), 7.43 (t, *J* = 7.8 Hz, 2 H), 1.71 (s, 6 H).
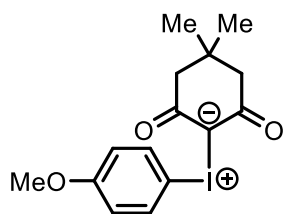
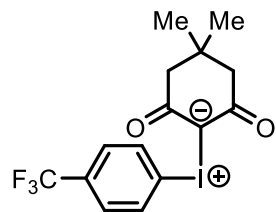(4-Methoxyphenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium (**3-17c**) Iodonium ylide **3-17c** was prepared according to GP1 from 5,5-dimethyl-1,3-cyclohexanedione (0.140 g, 1.0 mmol, 1 equiv.) and 4-methoxy-(diacetoxyiodo)benzene (0.352 g, 1.0 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) for 2 h at room temperature. Purification by trituration (CH2Cl2:Et2O 1:10) led to the title compound isolated as a white solid (0.364 g, 91% yield). The characterization data matches what has already been reported in the literature.[162] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.80 (d, J = 9.0 Hz, 2 H), 6.84 (d, J = 9.0 Hz, 2 H), 3.80 (s, 3 H), 2.47 (s, 4 H), 1.03 (s, 6 H).

(4-Cyanophenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium: (**3-17d**) Iodonium ylide **3-17d** was prepared according to GP1 from 5,5-dimethyl-1,**3-**cyclohexanedione (0.280 g, 2.0 mmol, 1 equiv.) and 4-cyano-(diacetoxyiodo)benzene (0.694 g, 2.0 mmol, 1 equiv.) in CH_2Cl_2 (20 mL) for 3.5 h at room temperature. Purification by trituration (CH2Cl2:Et2O 1:10) led to the title compound isolated as a white solid (0.420 g, 59% yield). The characterization data matches what has already been reported in the literature.[144] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.92 (d, J = 8.4 Hz, 2 H), 7.63 (d, J = 8.4 Hz, 2 H), 2.53 (s, 4 H), 1.08 (s, 6 H).
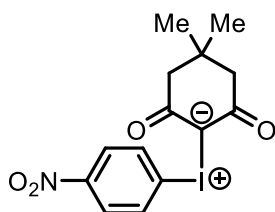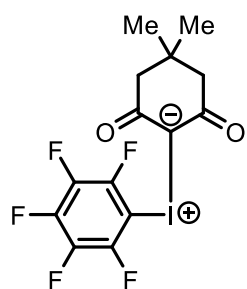
(4-Nitrophenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium (**3-17e**): Iodonium ylide **3-17e** was prepared according to GP1 from 5,5-dimethyl-1,3-cyclohexanedione (0.280 g, 2.0 mmol, 1 equiv.) and 4-nitro-(diacetoxyiodo)benzene (0.734 g, 2.0 mmol, 1 equiv.) in CH_2Cl_2 (30 mL) for 2 h at room temperature. Purification by trituration (CH2Cl2:Et2O 1:10) led to the title compound isolated as a white solid (0.393 g, 53% yield). The characterization data matches what has already been reported in the literature.[144] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 8.19 (d, J = 8.7 Hz, 2 H), 7.99 (d, J = 8.7 Hz, 2 H), 2.53 (s, 4 H), 1.08 (s, 6 H).
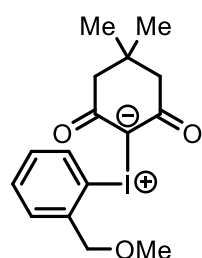
Me Me

(4-Trifluoromethylphenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium (**3-17f**): Iodonium ylide **3-17f** was prepared according to GP1 from 5,5-dimethyl-1,**3**-cyclohexanedione (0.100 g, 0.7 mmol, 1 equiv.) and 1-iodo-4-(trifluoromethyl)benzene (0.273 g, 0.7 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) for 2 h at room temperature. Purification by trituration (CH_2Cl_2:Et_2O 1:10) led to the title compound isolated as a white solid (0.219 g, 74% yield). The characterization data matches what has already been reported in the literature.[144] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.94 (d, J = 8.8 Hz, 2 H), 7.61 (d, J = 8.8 Hz, 2 H), 2.52 (s, 4 H), 1.07 (s, 6 H). **^{19}F NMR** (282 MHz, CDCl$_3$): δ -63.5.

Me Me

(2,3,4,5,6-Pentafluorophenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium **3-17g:** Iodonium ylide **3-17g** was prepared from 5,5-dimethyl-1,3-cyclohexanedione (0.280 g, 2.0 mmol, 1 equiv.) and [Hydroxy(tosyloxy)iodo](2,3,4,5,6-pentafluorophenyl) (0.964 g, 2.0 mmol, 1 equiv.) in CH_2Cl_2 (30 mL) for 1 h at room temperature. The mixture was then evaporated and a solution of 10% K_2CO_3 was added and stirred for 30 min at room temperature. Product was then extracted with CH_2Cl_2 and dried with magnesium sulfates. Then purification by trituration (CH_2Cl_2:Et_2O 1:10) led to the title compound isolated as a white solid (0.605 g, 70% yield). The characterization data matches what has already been reported in the literature.[163] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 1.05 (s, 6 H), 2.46 (s, 4 H).

Me Me

2-((2-(Methoxymethyl)phenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium **3-17h:** Iodonium ylide **3-17h** was prepared according to GP1 from 5,5-dimethyl-1,3-cyclohexanedione (0.280 g, 2.0 mmol, 1 equiv.) and 2-methoxymethyl-(diacetoxyiodo)benzene (0.732 g, 2.0 mmol, 1 equiv.) in CH_2Cl_2 (30 mL) for 2 h at room temperature. Purification by trituration (CH_2Cl_2:Et_2O 1:10) led to the title compound isolated as a white solid (0.617 g, 80% yield). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.51 (d, J = 8.5 Hz, 1 H), 7.43 (t, J = 8.7 Hz, 1 H), 7.25-7.29 (m, 2 H), 4.66 (s, 2 H), 3.45 (s, 3 H), 2.55 (s, 4 H), 1.13 (s, 6 H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 191.0, 146.7, 129.8, 129.5, 128.0, 127.5, 108.3, 91.7, 73.5, 50.4, 32.0, 30.3, 28.5. **IR** (**ATR**): 2950.6 (w), 1621.0 (w), 1549.9 (s), 1461.3 (w), 1340.0 (m), 1275.1 (m) cm^{-1}. **HRMS** (**ESI**): Calculated for $C_{16}H_{20}IO_3$ (M+H)$^+$ 387.0451, found 387.0447.
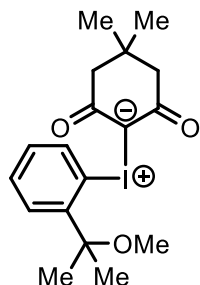
(2-(2-Methoxypropan)phenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium 3-17i: In dry round bottom flask charged with a stir bar, 1-iodo-2-(2-methoxypropan-2-yl)benzene (1.38 g, 5.0 mmol, 1 equiv.) was dissolved in 40 mL of hexane at 0 °C. In a separate 3 neck round bottom flask, potassium permanganate was placed. Addition funnel (25 mL) charged with 10 mL of concentrated HCl (12 M) was placed on one of the necks, a stopper was used to close one of the necks (this to aid with addition of more $KMnO_4$ if needed), and the third neck had an adapter connected to a PFA plastic tube that discharge Cl_2 gas into the round bottom flask containing 1-iodo-2-(2-methoxypropan-2-yl)benzene in hexane as seem in **Figure 3.17**. Cl_2 gas was bubbled until the disappearance of starting materials monitored by TLC and the precipitation of a yellow powder. The hexane is then decanted, and 40 mL of hexane is added and decanted again. Then, 30 mL of DCM is added at 0 °C to dissolve the yellow powder. Then, a solution of potassium acetate (0.982 g, 10.0 mmol, 2 equiv.) in 4 mL of MeOH is added in one portion. After 15 minutes, 5,5-dimethyl-1,3-cyclohexanedione (0.700 g, 5.0 mmol, 1 equiv.) is added. After 15 minutes, the reaction was quenched with cold water and the ylide was extracted with DCM and dried with sodium sulphate. Then the solution was concentrated and purification by trituration (CH_2Cl_2:Et_2O 1:10) led to the title compound isolated as a white solid (1.300 g, 65% yield). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.33-7.44 (m, 3 H), 7.21-7.26 (t, J = 7.4 Hz, 1 H), 3.31 (s, 3 H), 2.58 (s, 4 H), 1.69 (s, 6 H), 1.18 (s, 6 H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 190.4, 143.9, 130.3, 130.2, 129.0, 128.4, 108.8, 91.1, 78.6, 50.6, 50.2, 32.0, 28.5, 26.1. **IR (ATR)**: 2949.6 (w), 1552.0 (s), 1342.1 (m), 1297.1 (m), 1053.8 (m), 765.0 (m) cm^{-1}. **HRMS (ESI)**: Calculated for: C$_{18}$H$_{24}$IO$_3$ (M+H)$^+$ 415.0765, found 415.0761.

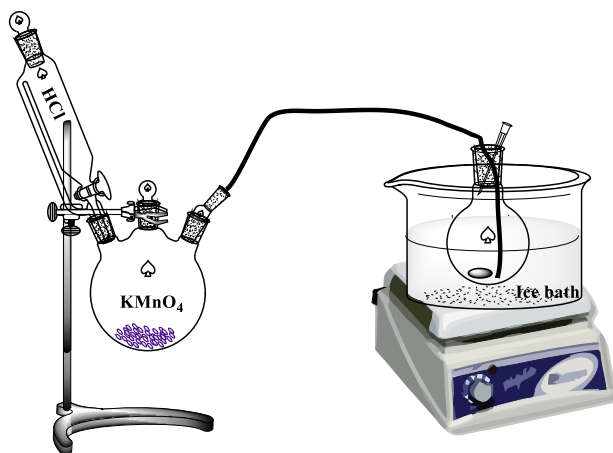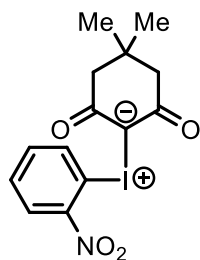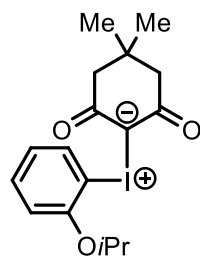**Figure 3.17.** Apparatus used for the synthesis of **2-17i**

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(2-Nitrophenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium **(3-17j)**: Iodonium ylide **3-17j** was prepared according to GP1 from 5,5-dimethyl-1,3-cyclohexanedione (0.280 g, 2.0 mmol, 1 equiv.) and 2-nitro-(diacetoxyiodo)benzene (0.734 g, 2.0 mmol, 1 equiv.) in CH_2Cl_2 (30 mL) for 1 h at room temperature. Purification by trituration (CH_2Cl_2:Et_2O 1:10) led to the title compound isolated as a yellow solid (0.619 g, 80% yield). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 8.48 (d, J = 8.7 Hz, 1 H), 7.73-7.75 (m, 2 H), 7.49 (m, 1 H), 2.62 (s, 4 H), 1.20 (s, 6 H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 190.6, 145.4, 136.9, 131.5, 129.7, 127.6, 104.5, 90.3, 50.7, 32.0, 28.5. **IR (ATR)**: 3093.8 (w), 2945.9 (w), 1529.6 (s), 1517.4 (s), 1326.3 (s), 1295.4 (m) cm^{-1}. **HRMS (ESI)**: Calculated for C$_{14}$H$_{15}$INO$_4$ (M+H)$^+$ 388.0040, found 388.0036.
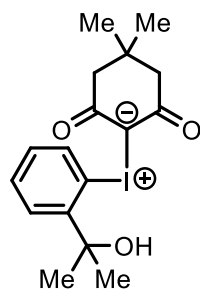
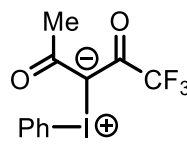(2-Isopropoxyphenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium **(3-17k)**: Iodonium ylide **3-17k** was prepared according to GP1 from 5,5-dimethyl-1,3-cyclohexanedione (0.280 g, 2.0 mmol, 1 equiv.) and 2-Isopropoxy-(diacetoxyiodo)benzene (0.640 g, 2.0 mmol, 1 equiv.) in CH_2Cl_2 (30 mL) for 2 h at room temperature. Purification by trituration (CH_2Cl_2:Et_2O 1:10) led to the title compound isolated as a white solid (0.393 g, 53% yield). The characterization data matches what has already been reported in the literature. [164] **^{1}H NMR** (500 MHz, CDCl$_3$): δ 7.37 (t, J = 8.0 Hz, 1 H), 7.15 (d, J = 8.0 Hz, 1 H), 6.90-6.96 (m, 2 H), 4.68-4.71 (m, 1 H), 2.58 (s, 4 H), 1.43 (d, J = 6.0 Hz, 6 H), 1.16 (s, 6 H).
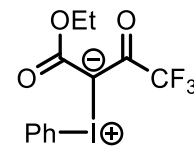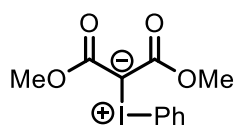
(2-(2-hydroxypropan-2-yl)phenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium **(3-17l)**: Iodonium ylide **3-17l** was prepared according to GP1 from 5,5-dimethyl-1,3-cyclohexanedione (0.280 g, 2.0 mmol, 1 equiv.) and 1,3-dihydro-1-hydroxy-3,3-dimethyl-1,2-benziodoxole (0.556 g, 2.0 mmol, 1 equiv.) in CH_2Cl_2 (30 mL) for 3 h at 40 ℃. Purification by trituration (CH_2Cl_2:Et_2O 1:10) led to the title compound isolated as a white solid (0.696 g, 87% yield).**^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.25-7.35 (m, 1 H), 7.18-7.20 (m, 2 H), 7.07-7.13 (m, 1 H), 6.38 (br. S, 1 H), 2.51 (s, 4 H), 1.64 (s, 6 H), 1.15 (s, 6 H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 191.0, 146.7, 129.8, 129.5, 128.0, 127.5, 108.3, 91.7, 73.5, 50.4, 32.0, 30.3, 28.5. **IR (ATR)**:

2931.9 (w), 1548.2 (s), 1464.8 (s), 1338.2 (s), 1296.4 (m), 763.4 (s) cm^{-1}. **HRMS** (**ESI**): Calculated for $C_{17}H_{22}IO_3$ (M+H)$^+$ 401.0606, found 401.0608.

1,1,1-Trifluoro-3-(phenyl- λ^3-iodaneylidene)pentane-2,4-dione (**3-23**): Iodonium ylide **3-23** was prepared according to GP2 from 1,1,1-trifluoropentane-2,4-dione (0.606 mL, 5.0 mmol, 1 equiv.), sodium methoxide solution 25 wt. % in methanol (0.72 mL, 1 equiv.), and (diacetoxyiodo)benzene (1.6 g, 5.0 mmol, 1 equiv.) in EtOH (30 mL) at 0 °C. Purification by trituration (CH$_2$Cl$_2$:Et$_2$O 1:10) led to the title compound isolated as a white solid (1.34 g, 75% yield). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.89 (d, J = 7.8 Hz, 2 H), 7.61 (t, J = 7.8, 1 H), 7.43 (t, J = 7.8, 1 H), 2.63 (s, 3 H). **^{19}F NMR** (282 MHz, CDCl$_3$): -68.0. **^{13}C NMR** (75 MHz, CDCl$_3$): *The ylide decomposes before a complete spectrum can be acquired. Increasing sample concentration was not possible due to poor solubility.* **IR** (**ATR**): 3056.9 (w), 1614.7 (m), 1556.6 (s), 1445.5 (w), 1131.4 (s) cm^{-1}. **HRMS** (**ESI**): Calculated for $C_{11}H_9F_3IO_2$ (M+H)$^+$ 356.9593, found 356.9594.

Ethyl 4,4,4-trifluoro-3-oxo-2-(phenyl- λ^3-iodaneylidene)butanoate (**3-24**): Iodonium ylide **3-24** was prepared according to GP2 from ethyl 4,4,4-trifluoro-3-oxobutanoate (0.724 mL, 5.0 mmol, 1 equiv.), sodium methoxide solution 25 wt. % in methanol (0.72 mL, 1 equiv.), and (diacetoxyiodo)benzene (1.6 g, 5.0 mmol, 1 equiv.) in EtOH (30 mL) at 0 °C. Purification by trituration (CH$_2$Cl$_2$:Et$_2$O 1:10) led to the title compound isolated as a white solid (1.51 g, 78% yield). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.90 (d, J = 7.8 Hz, 2 H), 7.62 (t, J = 7.8 Hz, 1 H), 7.46 (t, J = 7.8 Hz, 2 H), 4.21 (q, J = 7.8 Hz, 2 H), 1.29 (t, J = 7.8 Hz, 3 H). **^{19}F NMR** (282 MHz, CDCl$_3$): δ -69.1. **^{13}C NMR** (75 MHz, CDCl$_3$): *The ylide decomposes before a complete spectrum can be acquired. Increasing sample concentration was not possible due to poor solubility.* **IR** (**ATR**): 3102.9 (w), 1657.9 (m), 1556.2 (s), 1252.1 (m), 1159.1 (s), 1039.9 (s) cm^{-1}. **HRMS** (**ESI**): Calculated for $C_{12}H_{11}F_3IO_3$ (M+H)$^+$ 386.9692, found 386.970.
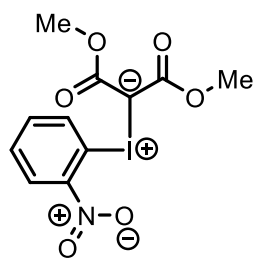
Dimethyl 2-(phenyl- λ^3-iodaneylidene)malonate (**3-34**): Iodonium ylide **3-34** was prepared according to Charette's literature procedure[113] from dimethyl malonate (0.693 mL, 6.0 mmol, 1 equiv.), KOH (2.0 g, 36 mmol, 6 equiv.)

and (diacetoxyiodo)benzene (2.13 g, 6.0 mmol, 1 equiv.) in CH$_3$CN (20 mL) for 2 h at 0 °C. Purification by trituration (CH$_2$Cl$_2$:Et$_2$O 1:10) led to the title compound isolated as a white solid (1.51 g, 75% yield). The characterization data matches what has already been reported in the literature.[144] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.72 (d, J = 8.3 Hz, 2 H), 7.52 (t, J = 7.5 Hz, 1 H), 7.40 (t, J = 7.6 Hz, 2 H), 3.73 (s, 6 H).
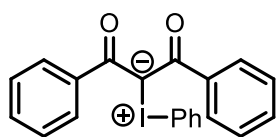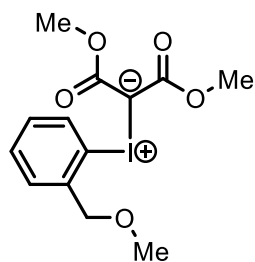
1,3-Diphenyl-2-(phenyl- λ^3-iodaneylidene)propane-1,3-dione (**3-25**): Iodonium ylide **3-25** was prepared according to Charette's literature procedure[113] from 1,3-diphenylpropane-1,3-dione (1.12 g, 5.0 mmol, 1 equiv.), KOH (1.68 g, 30 mmol, 6 equiv.) and (diacetoxyiodo)benzene (1.60 g, 5.0 mmol, 1 equiv.) in MeOH (15 mL) for 2 h at 0 °C. Purification by trituration (CH$_2$Cl$_2$:Et$_2$O 1:10) led to the title compound isolated as a yellow solid (1.49 g, 70% yield). The characterization data matches what has already been reported in the literature.[112] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 8.04-8.06 (m, 2 H), 7.55-7.59 (m, 2 H), 7.41-7.34 (m, 2 H), 7.23-7.26 (m, 4 H), 7.08-7.13 (m, 1 H), 6.92-7.96 (m, 4 H).

Dimethyl 2-((2-nitrophenyl)- λ^3-iodaneylidene)malonate (**3-40**): Iodonium ylide **3-40** was prepared according to Charette's literature procedure[113] from dimethyl malonate (0.693 mL, 6.0 mmol, 1 equiv.), KOH (2.0 g, 36 mmol, 6 equiv.) and 2-nitro-(diacetoxyiodo)ben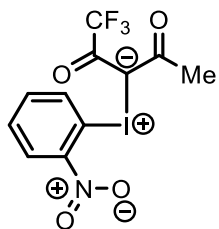zene (2.20 g, 6.0 mmol, 1 equiv.) CH$_3$CN (20 mL) for 2 h at 0 °C. Purification by trituration (CH$_2$Cl$_2$:Et$_2$O 1:10) led to the title compound isolated as a Yellow amorphous solid; (1.51 g, 76% yield). The characterization data matches what has already been reported in the literature.[112] **^{1}H NMR** (300 MHz, CDCl$_3$): δ (dd, J = 8.1 Hz, 1.2 Hz, 1 H), 7.86 (td, J = 7.5 Hz, 1.4 Hz, 1 H), 7.75 (t, J = 7.5 Hz, 2 H), 3.74 (s, 6 H).

Dimethyl 2-((2-(methoxymethyl)phenyl)- λ^3-iodaneylidene)malonate (**3-41**): Iodonium ylide **3-41** was prepared according to Charette's literature procedure[113] from dimethyl malonate (0.693 mL, 6.0 mmol, 1 equiv.), KOH (2.0 g, 36 mmol, 6 equiv.) and 2-methoxymethyl-(diacetoxyiodo)benzene (2.20 g, 6.0 mmol, 1 equiv.)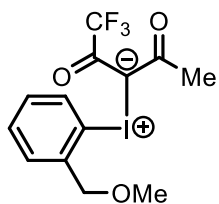 in CH$_3$CN (20 mL) for 2 h at 0 °C. Purification by trituration (CH$_2$Cl$_2$:Et$_2$O 1:10) led to the title compound isolated as a white solid (1.51 g, 77%

yield). The characterization data matches what has already been reported in the literature.[155] **¹H NMR** (300 MHz, CDCl₃): δ 7.64 (d, J = 8.7 Hz, 1 H), 7.38-7.45 (m, 2 H), 7.25-7.29 (m, 1 H), 4.66 (s, 2 H), 3.76 (s, 3 H), 3.47 (s, 3 H).

1,1,1-Trifluoro-3-((2-nitrophenyl)- λ^3-iodaneylidene)pentane-2,4-dione (**3-42**): Iodonium ylide **3-42** was prepared according to GP2 from 1,1,1-trifluoropentane-2,4-dione (0.606 mL, 5.0 mmol, 1 equiv.), sodium methoxide solution 25 wt. % in methanol (0.72 mL, 1 equiv.), and 2-nitro-(diacetoxyiodo)benzene (1.84 g, 5.0 mmol, 1 equiv.) in EtOH (30 mL) at 0 °C. Purification by trituration (CH₂Cl₂:Et₂O 1:10) led to the title compound isolated as a white solid (1.72g, 80% yield). **¹H NMR** (300 MHz, CDCl₃): δ 8.52 (dd, J = 1.8 Hz, 8.7 Hz, 1 H), 7.79-7.85 (m, 2 H), 7.48 (m, 1 H), 2.77 (s, 3 H). **¹⁹F NMR** (282 MHz, CDCl₃): -68.8. **¹³C NMR** (75 MHz, CDCl₃): *The ylide decomposes before a complete spectrum can be acquired. Increasing sample concentration was not possible due to poor solubility.* **IR** (**ATR**): 1701.4 (s), 1522.2 (m), 1325.1 (s), 1186.5 (w), 1084.0 (m), 726.9 (m) cm⁻¹. **HRMS** (**ESI**): Calculated for C₁₁H₈F₃INO₄ (M+H)⁺ 401.9432, found 401.9432.

1,1,1-Trifluoro-3-((2-(methoxymethyl)phenyl)- λ^3-iodaneylidene)pentane-2,4-dione (**3-43**): Iodonium ylide **3-43** was prepared according to GP2 from 1,1,1-trifluoropentane-2,4-dione (0.606 mL, 5.0 mmol, 1 equiv.), sodium methoxide solution 25 wt. % in methanol (0.72 mL, 1 equiv.), and 2-methoxymethyl-(diacetoxyiodo)benzene (1.83 g, 5.0 mmol, 1 equiv.) in EtOH (30 mL) at 0 °C. Purification by trituration (CH₂Cl₂:Et₂O 1:10) led to the title compound isolated as a white solid (1.72g, 76% yield). **¹H NMR** (300 MHz, CDCl3): δ 7.46 (m, 2 H), 7.30-7.38 (m, 2 H), 4.70 (s, 2 H), 3.50 (s, 3 H), 2.71 (s, 3 H). **¹³C NMR** (75 MHz, CDCl₃): *The ylide decomposes before a complete spectrum can be acquired. Increasing sample concentration was not possible due to poor solubility.* **¹⁹F NMR** (282 MHz, CDCl₃): δ -68.5. **IR** (**ATR**): 2959.8 (w), 1700.9 (s), 1536.1 (s), 1478.3 (w), 1292.8 (m), 1175.3 (m) cm⁻¹. **HRMS** (**ESI**): Calculated for C₁₃H₁₃F₃IO₃ (M+H)⁺ 400.9857, found 400.9852.

Ph
O⎓⊖SO₂CF₃
Ph—I⊕
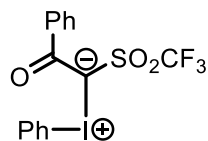
1-Phenyl-2-(phenyl- λ^3-iodaneylidene)-2-((trifluoromethyl)sulfonyl)ethan-1-one (**3-36**): Iodonium ylide **3-36** was prepared according to GP1 from 1-phenyl-2-((trifluoromethyl)sulfonyl)ethanone (1.26 g, 5.0 mmol, 1 equiv.) and (diacetoxyiodo)benzene (1.62 g, 5 mmol, 1 equiv.) in CH₂Cl₂ (30 mL) for 3 h at room temperature. Purification by trituration (CH₂Cl₂:Et₂O 1:10) led to the title compound isolated as a white solid (5.14 g, 80% yield). The characterization data matches what has already been reported in the literature.[165] **¹H NMR** (300 MHz, CD₃)₂CO) δ 8.15 (d, J = 8.1 Hz, 2 H), 7.71 (t, J = 7.8 Hz, 1 H), 7.59 (d, J = 7.8 Hz, 2 H), 7.41-7.29 (m, 5 H); **¹⁹F NMR** (282 MHz, (CD₃)₂CO) δ -77.6 (s, 3F).

3.9.3 General Procedure for Synthesis of Furans (GP3)

In a dry 1 dram (4.0 mL) vial was added iodonium ylide (0.1 mmol, 1 equiv.) and CH₂Cl₂ (1.0 ml, 0.1 M), and this loaded into the photoreactor and stirred at room temperature for 2 min, giving either a clear solution or a slurry. Phenylacetylene (0.044 mL, 0.4 mmol, 4 equiv.) was added in one portion and after stirring for 1 min, the blue LED was turned on. The reaction mixture was stirred at room temperature until the reaction was observed to be complete by TLC or NMR analysis. The mixture was then evaporated to dryness and purified by column chromatography, eluting with mixtures of ethyl acetate and hexanes. For determining the yields using ¹H NMR, 10 μL of an internal standard, hexamethyldisiloxane (HMDSO) was added to the reaction mixture prior to ¹H NMR spectroscopic analysis. Direct comparison of the integrated HMDSO signal with a signal from the desired furan product allowed for the calculation of the reaction yields.
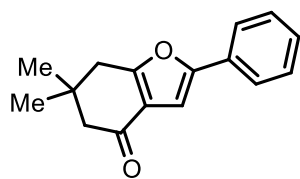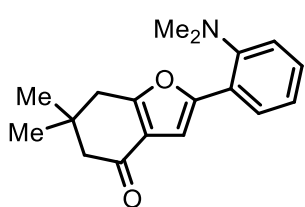
6,6-Dimethyl-2-phenyl-6,7-dihydrobenzofuran-4(5*H*)-one (**3-25**): Furan **3-25** was synthesized according to GP3 using iodonium ylide **3-17l** (0.042 g, 0.10 mmol, 1 equiv.), phenylacetylene (0.044 mL, 0.40 mmol, 4 equiv.), CH₂Cl₂ (1.0 mL). The reaction was stirred for 18 h at 25 °C until the ylide was consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a yellow solid (0.015 g, 60% yield). R_f = 0.70 (hexanes:EtOAc 3:1). The characterization data matches what has already been reported in the literature.[166] **¹H NMR** (300 MHz, CDCl₃) δ 7.66-7.70 (m, 2 H), 7.40-7.45 (m, 2 H), 7.32-7.35 (m, 1 H), 6.91 (s, 1 H), 2.85 (s, 2 H), 2.43 (s, 1 H), 1.20 (s, 6 H).
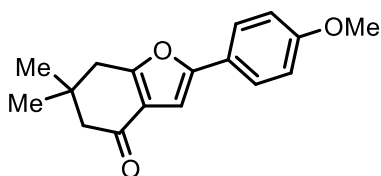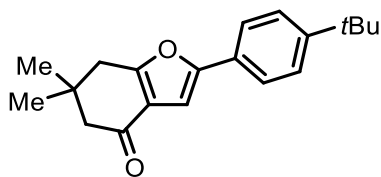
2-(4-Methoxyphenyl)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5H)-one (**3-25a**): Furan **3-25a** was synthesized to GP3 using iodonium ylide **3-17** (0.042 g, 0.10 mmol, 1 equiv.), 4-ethynylanisole (0.048 mL, 0.40 mmol, 4 equiv.), CH$_2$Cl$_2$ (1.0 mL). The reaction was stirred for 8 h at 25 °C until the ylide was consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a brown oil (0.014 g, 50% yield). R$_f$ = 0.65 (hexanes:EtOAc 3:1). The characterization data matches what has already been reported in the literature.[167] **^{1}H NMR** (300 MHz, CDCl$_3$): δ 6.93-7.58 (AA'XX', 4 H), 6.93 (d, J = 8.9 Hz, 2 H), 6.74 (s, 1 H), 3.84 (s, 3 H), 2.81 (s, 2 H), 2.40 (s, 2 H), 1.17 (s, 6 H).

2-(2-(Dimethylamino)phenyl)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5H)-one (**3-25b**): Furan **3-25b** was synthesized according to GP3 using iodonium ylide **3-17** (0.042 g, 0.10 mmol, 1 equiv.), 2-ethynyl-N,N-dimethylaniline (0.058 mL, 0.40 m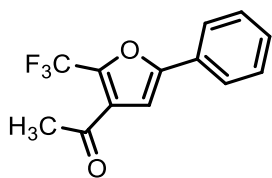mol, 4 equiv.), CH$_2$Cl$_2$ (1.0 mL). The reaction was stirred for 8 h at 25 °C until the ylide was consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a white solid (0.017 g, 60% yield). R$_f$ = 0.55 (hexanes:EtOAc 3:1). **^{1}H NMR** (300 MHz, CDCl$_3$): δ 7.77-7.80 (d, J = 9.00 Hz, 1 H), 7.31 (s, 1 H), 7.25 (s, 1 H), 7.16-7.18 (m, 1 H), 7.06-7.11 (m, 1 H), 2.84 (s, 2 H), 2.71 (s, 6 H), 2.44 (s, 2 H), 1.20 (s, 6 H). **^{13}C NMR** (75 MHz, CDCl$_3$): δ 195.2, 165.9, 153.7, 152.0, 129.6, 128.0, 124.7, 123.6, 122.8, 120.5, 105.6, 53.1, 45.0, 38.5, 36.3, 29.7. **IR** (**ATR**): 3264.6 (w), 2955.4 (w), 1634.0 (m), 1605.0 (m), 1513.1 (s), 1345.4 (m) cm^{-1}. **HRMS** (**ESI**): Calculated for C$_{18}$H$_{20}$NO$_2$ (M+H)$^+$ 284.1645, found 284.1645.

2-(4-(Tert-butyl)phenyl)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5H)-one (**3-25c**): Furan **3-25c** was synthesized according to GP3 using iodonium ylide **3-17** (0.042 g, 0.10 mmol, 1 equiv.), 4-ethynylanisole (0.048 mL, 0.40 mmol, 4 equiv.), CH$_2$Cl$_2$ (1.0 mL). The reaction was stirred for 8 h at 25 °C until the ylide was consumed as indicated by NMR.

Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a yellow oil (0.014 g, 50% yield). Rf = 0.65 (hexanes:EtOAc 3:1). **¹H NMR** (300 MHz, CDCl₃): δ 7.43-7.62 (AA'BB', 4 H), 6.86 (s, 1H), 2.85 (s, 2 H), 2.43 (s, 2 H), 1.36 (s, 9 H), 1.19 (s, 6 H). **¹³C NMR** (75 MHz, CDCl₃): δ 194.0, 165.6, 154.8, 151.3, 127.1, 125.7, 123.7, 121.7, 100.1, 52.0, 37.5, 35.3, 34.7, 31.2, 28.7. **IR** (**ATR**): 2957.8 (s), 1666.7 (s), 1603.7 (m), 1448.5 (m), 1223.2 (m), 829.5 (s) cm⁻¹. **HRMS** (**ESI**): Calculated for C₂₀ H₂₅O₂ (M+H)⁺ 297.1862, found 297.1849.

1-(5-Phenyl-2-(trifluoromethyl)furan-3-yl)ethan-1-one **(3-25f)**: **3-25f** was synthesized according to GP3 using iodonium ylide **3-23** (0.142 g, 0.40 mmol, 1 equiv.), phenylacetylene (1.76 mL, 1.6 mmol, 4 equiv.), CH₂Cl₂ (1.0 mL). The reaction was stirred for 6 h at 25 °C until the ylide was consumed as indicated by NMR. Purification by flash chromatography through a column of silica gel (hexanes:EtOAc 3:1) led to the title compound isolated as a yellow solid (0.010 g, 10% yield). Rf = 0.62 (hexanes:EtOAc 3:1). **¹H NMR** (300 MHz, CDCl₃): δ 7.73 (d, *J* = 6.9 Hz), 7.41-7.50 (m, 3 H), 7.02 (s, 1 H), 2.59 (s, 3 H). **¹⁹F NMR** (600 MHz, CDCl₃): δ -69.6. **¹³C NMR** (600 MHz, CDCl₃, H and F decoupling): δ 191.7, 155.0, 143.9, 129.5, 129.0, 128.3, 127.8, 126.0, 124.6, 106.2, 29.7. **IR** (**ATR**): 2985.2 (w), 1764.8 (s), 1605.5 (m), 1590.0 (m), 1337.6 (m), 1052.7 (m) cm⁻¹. **HRMS** (**ESI**): Calculated for C₁₃H₉F₃O₂Li (M+Li)⁺ 261.0706, found 261.0709.

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Appendices

Appendix A – NMR spectra for Chapter 2

Figure 3.18. ^{1}H NMR (300 MHz, CDCl3) of diethyl 2-(benzoyloxy)malonate **(2-29a)**

1.305
1.329
1.353

4.291
4.298
4.315
4.322
4.338
4.346
4.361
4.369

5.758

7.444
7.469
7.495
7.584
7.609

8.105
8.125
8.150
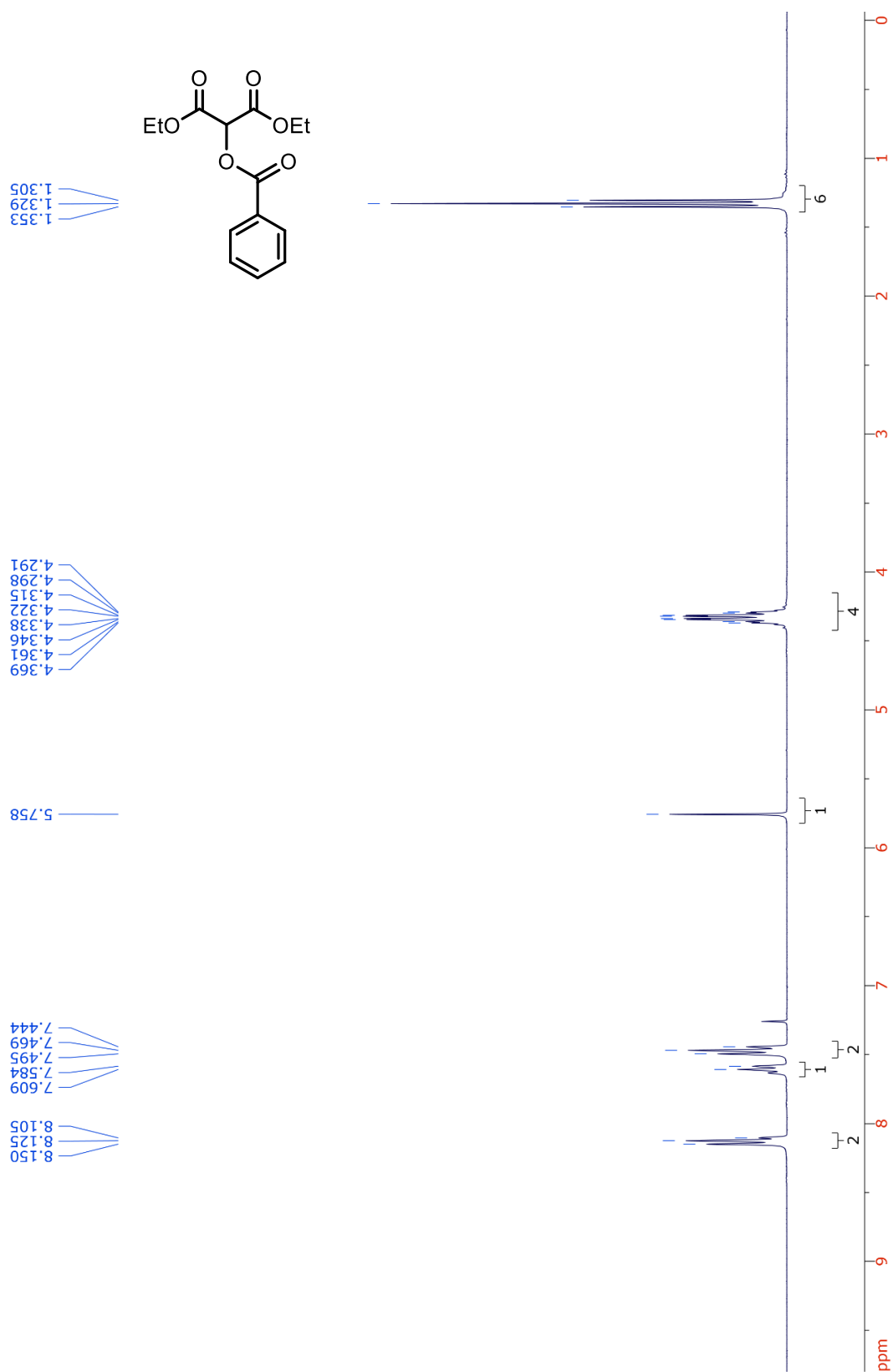
Figure 3.19. ^{1}H NMR (300 MHz, CDCl$_3$) of diethyl 2-((4-nitrobenzoyl)oxy)malonate **(2-29b)**

163
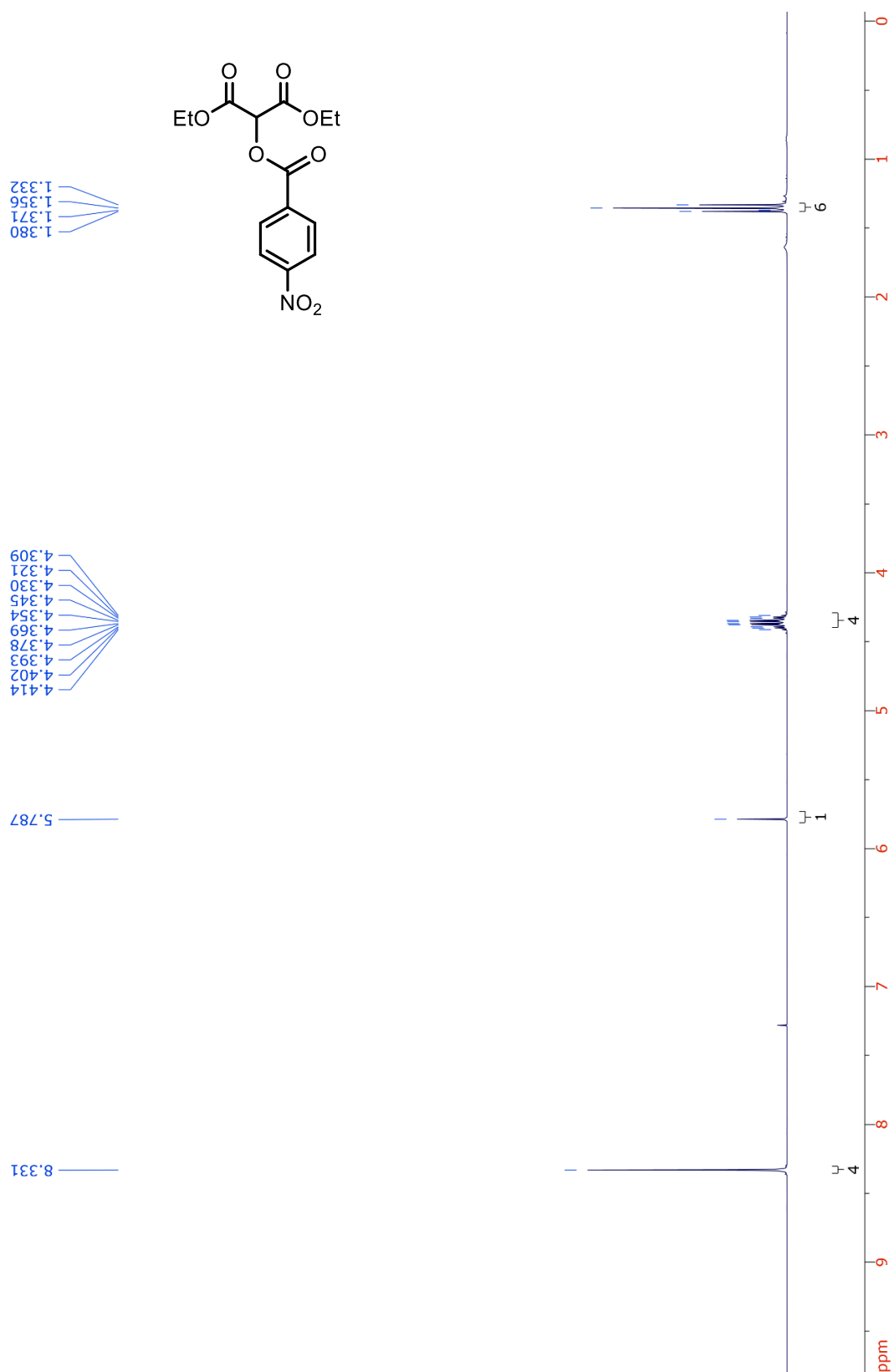
Figure 3.20. ^{1}H NMR (300 MHz, CDCl$_3$) of diethyl 2-(benzoyloxy)malonate (**2-29c**)
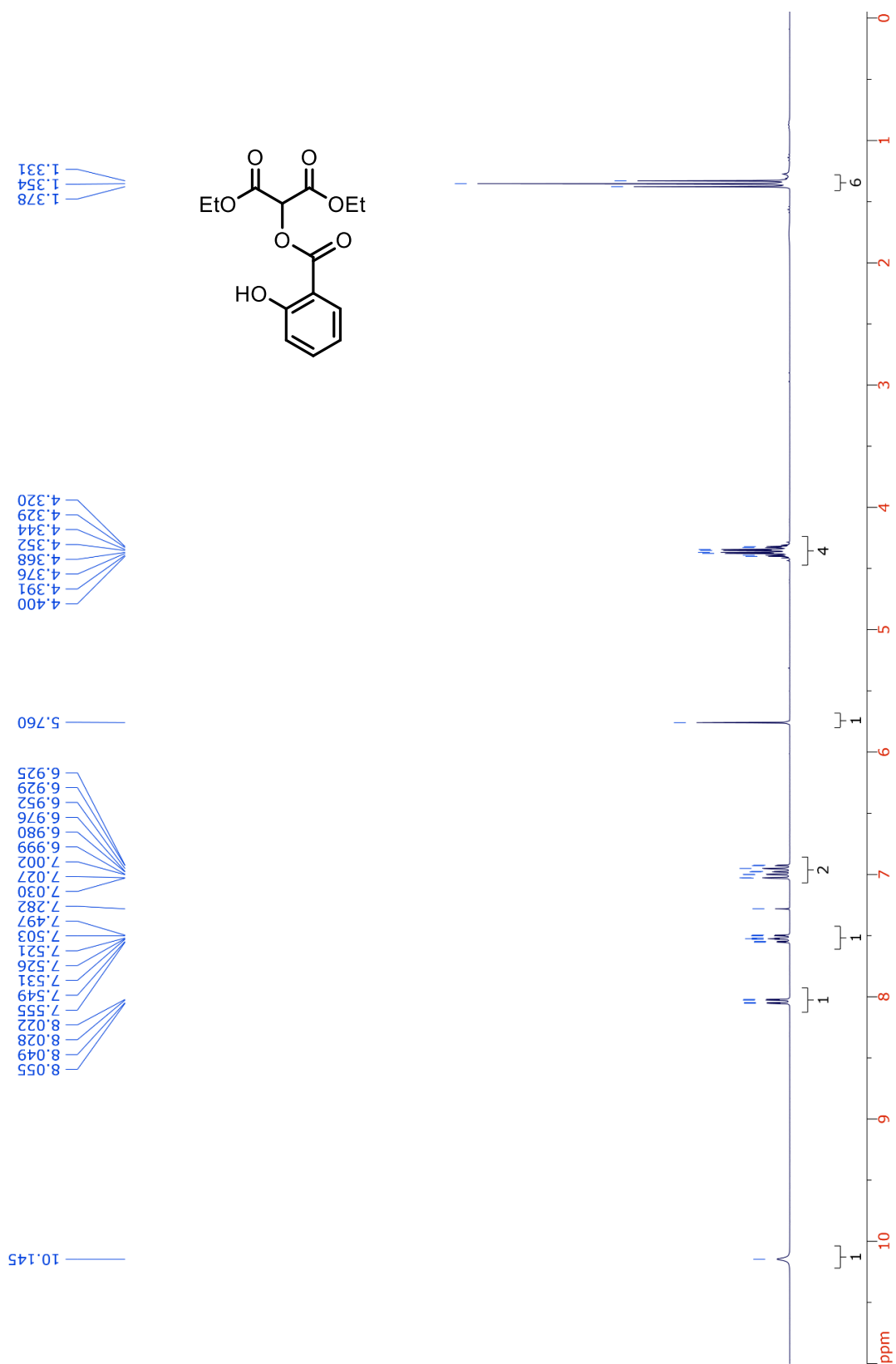
Figure 3.21. ^{1}H NMR (300 MHz, CDCl$_3$) of diethyl 2-((4-methoxybenzoyl)oxy)malonate (**2-29d**)
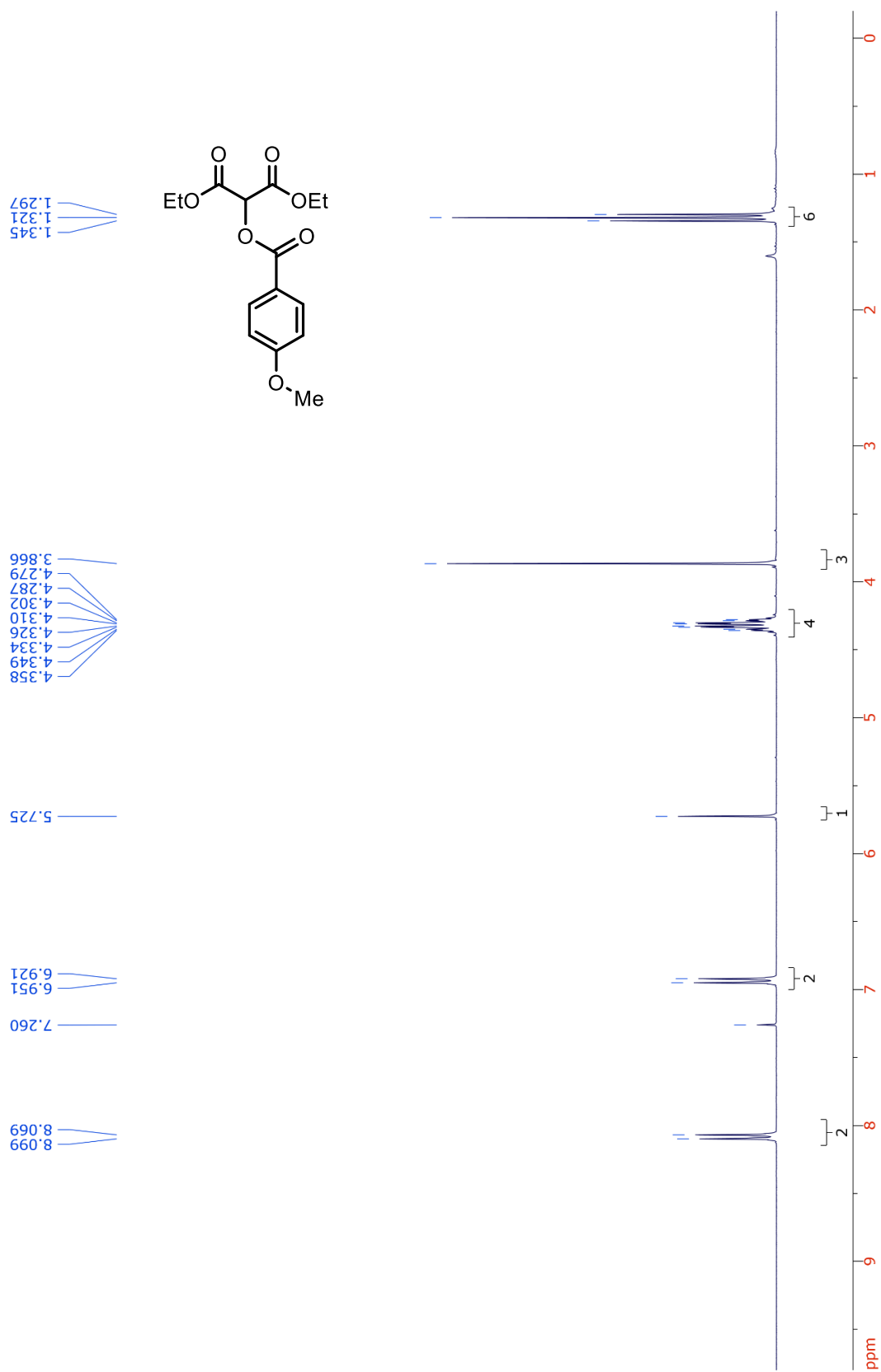
Figure 3.22. ^{1}H NMR (300 MHz, CDCl$_3$) of diethyl 2-((4-bromobenzoyl)oxy)malonate (**2-29e**)
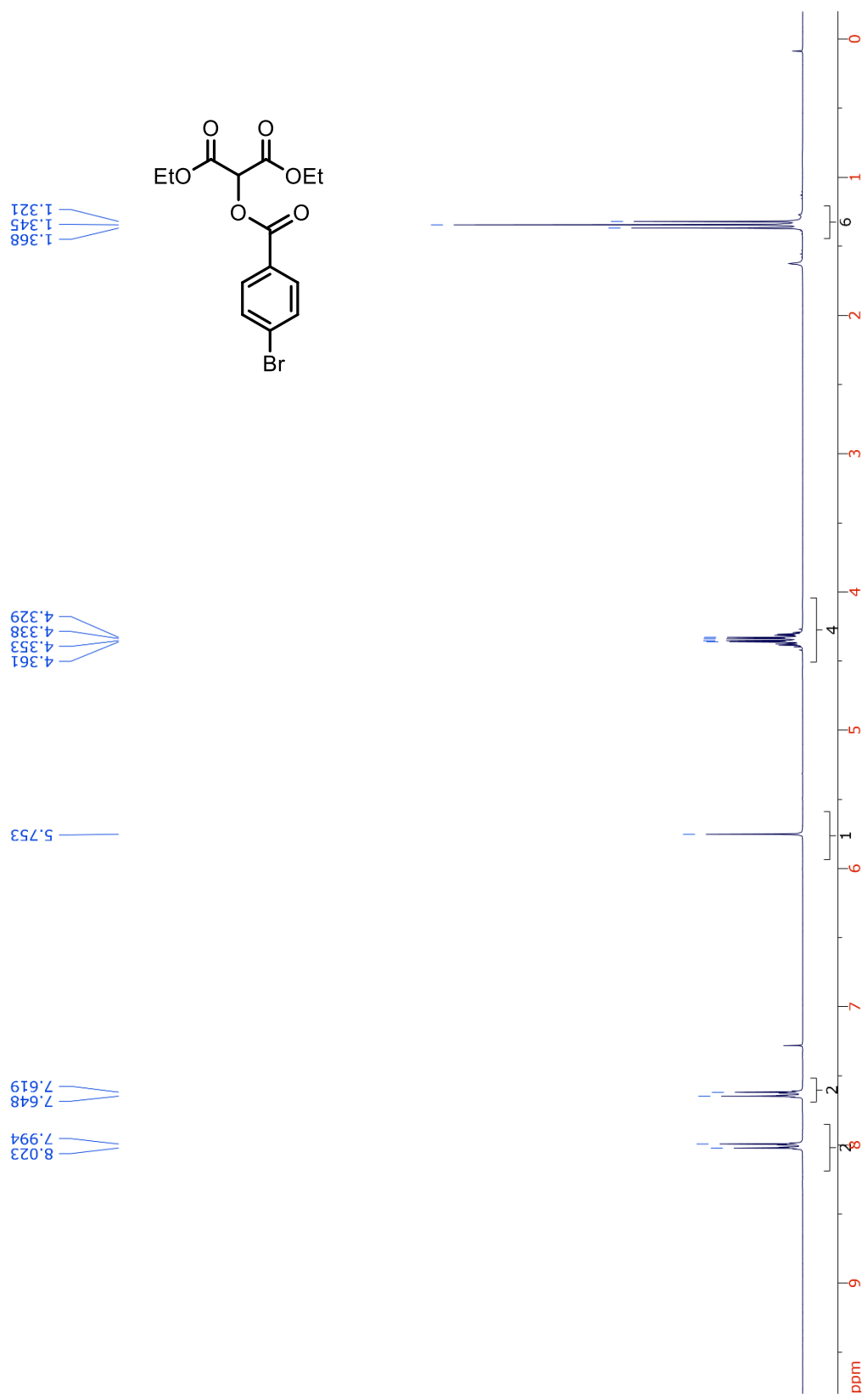
Figure 3.23. ^{13}C NMR (75 MHz, CDCl$_3$) of diethyl 2-((4-bromobenzoyl)oxy)malonate (**2-29e**)
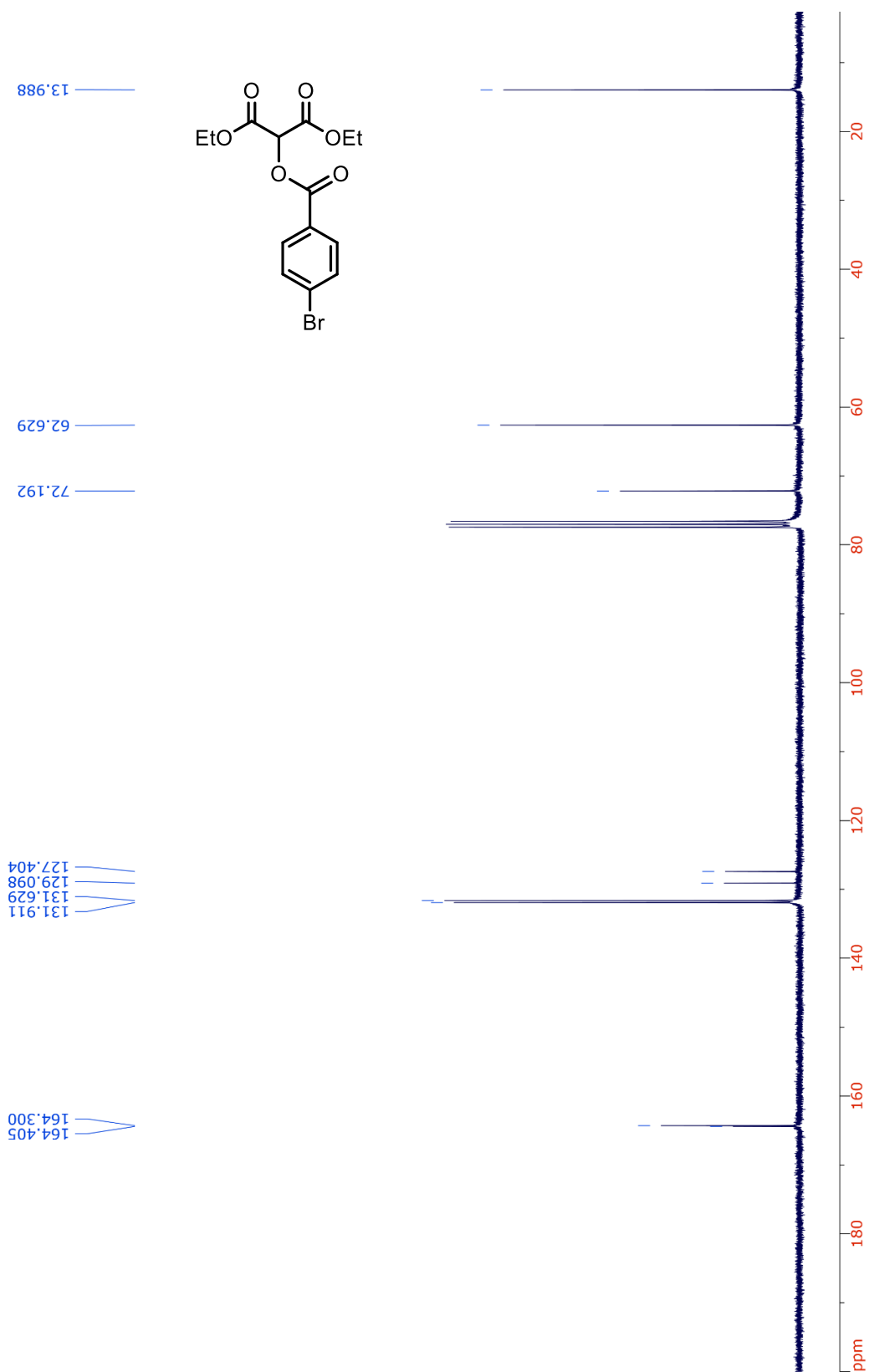
Figure 3.24. ^{1}H NMR (300 MHz, CDCl$_3$) of dimethyl 2-(benzoyloxy)malonate (**2-29f**)

168
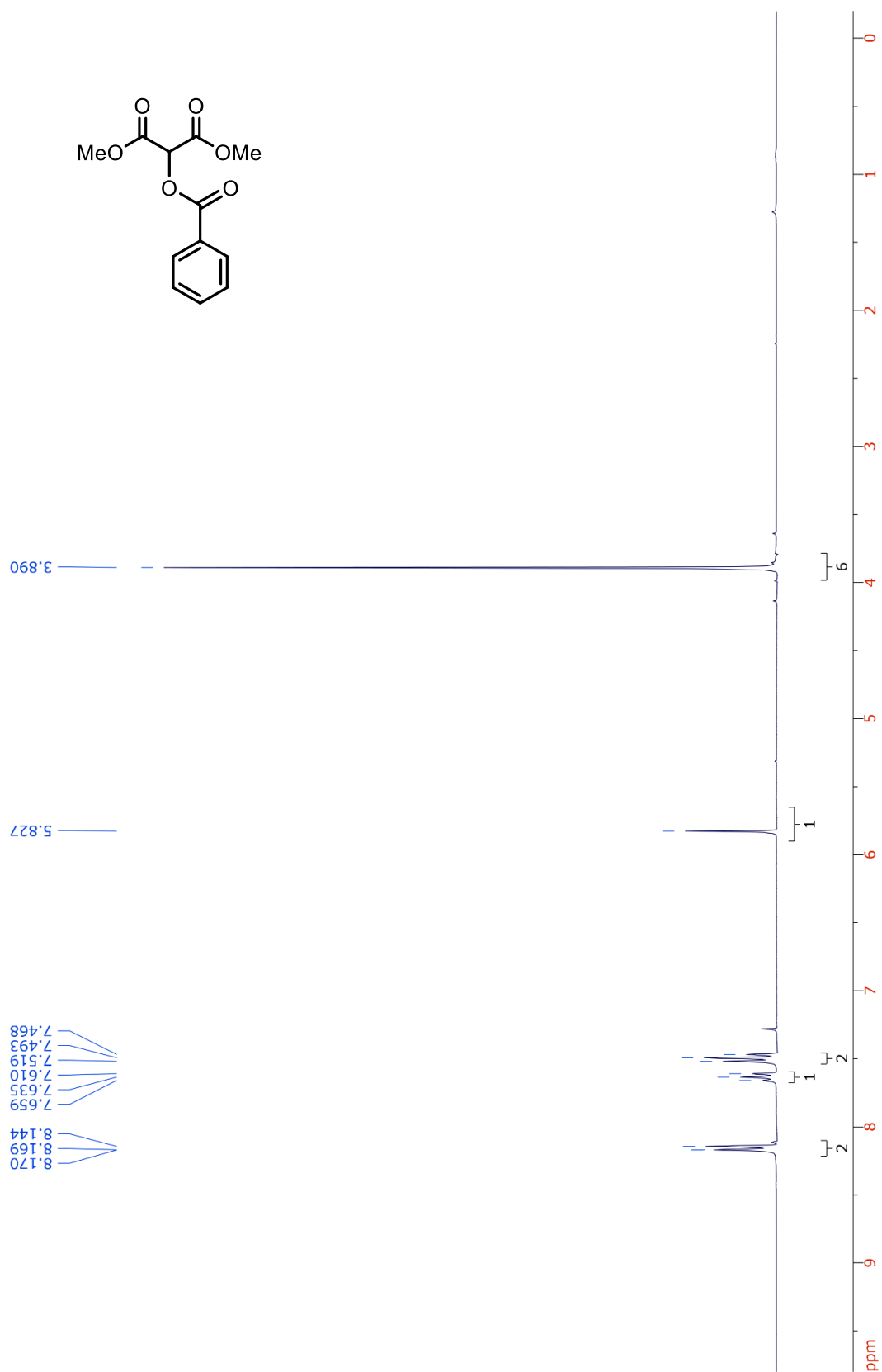
Figure 3.25. ^{1}H NMR (300 MHz, CDCl$_3$) of 1-methoxy-1,3-dioxobutan-2-yl benzoate (**2-29g**)
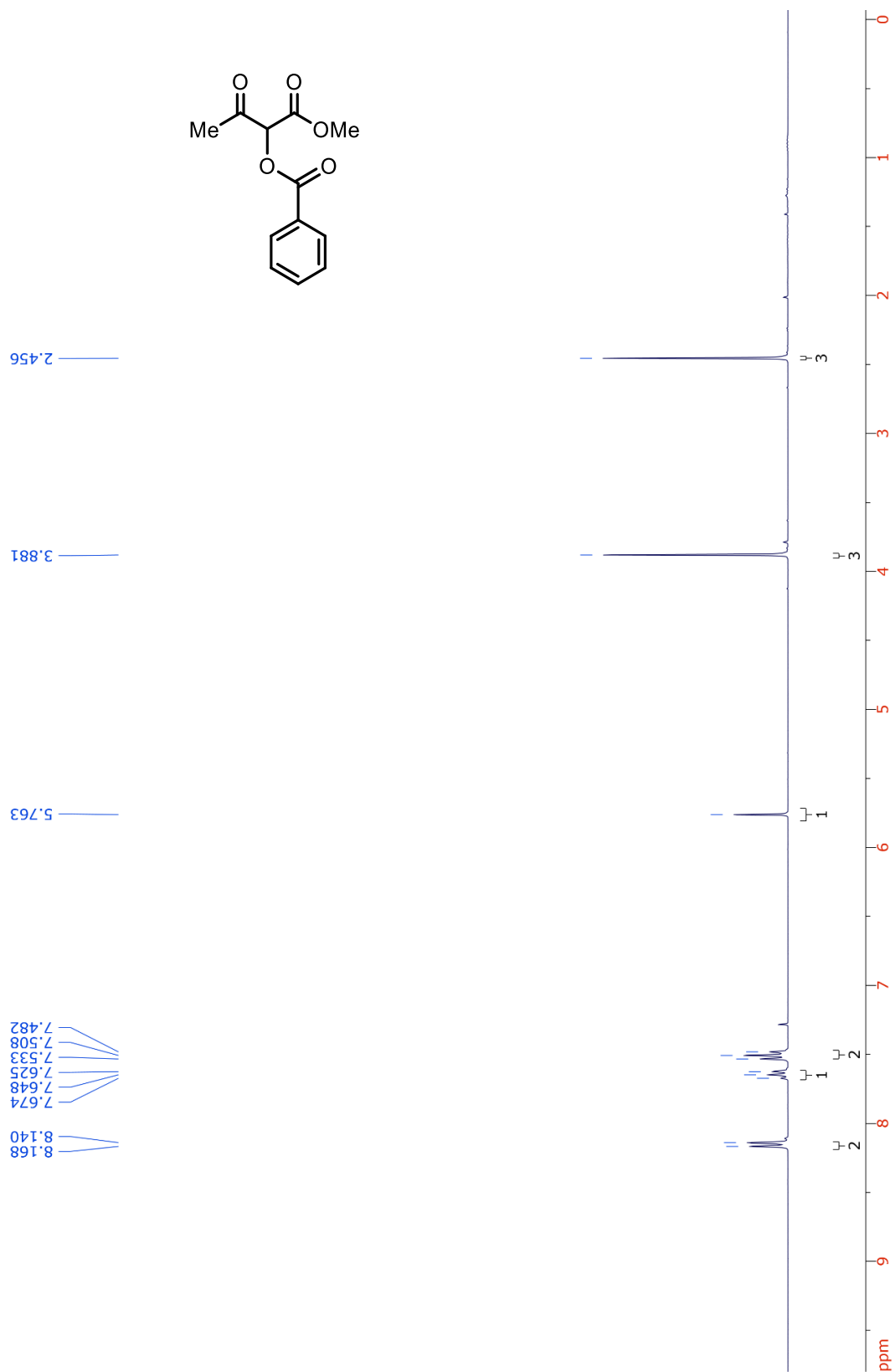
Figure 3.26. ^{13}C NMR (75 MHz, CDCl$_3$) of 1-methoxy-1,3-dioxobutan-2-yl benzoate (**2-29g**)
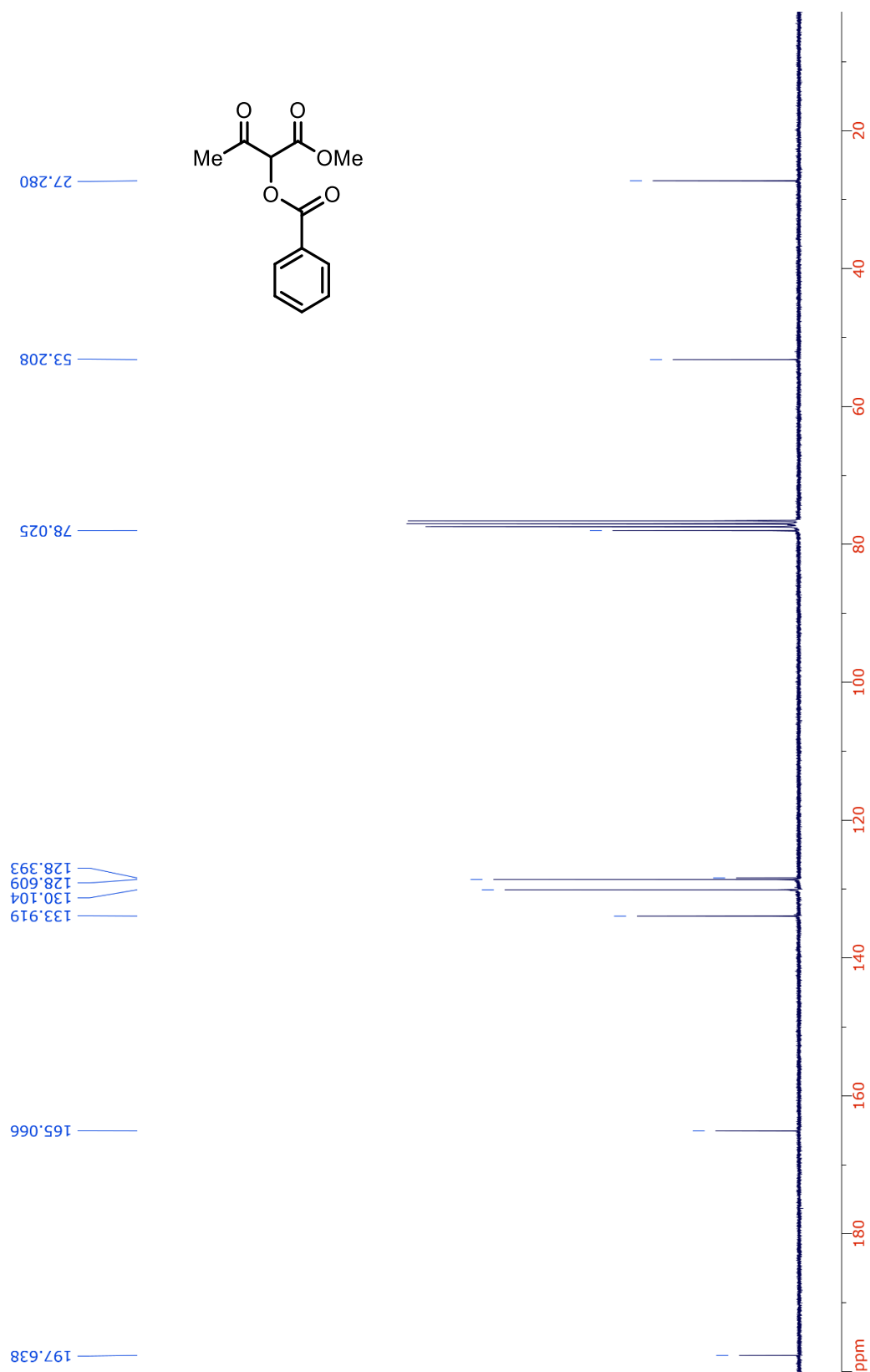
Figure 3.27. ^{1}H NMR (300 MHz, CDCl$_3$) of 2,4-dioxopentan-3-yl benzoate (**2-29h**)
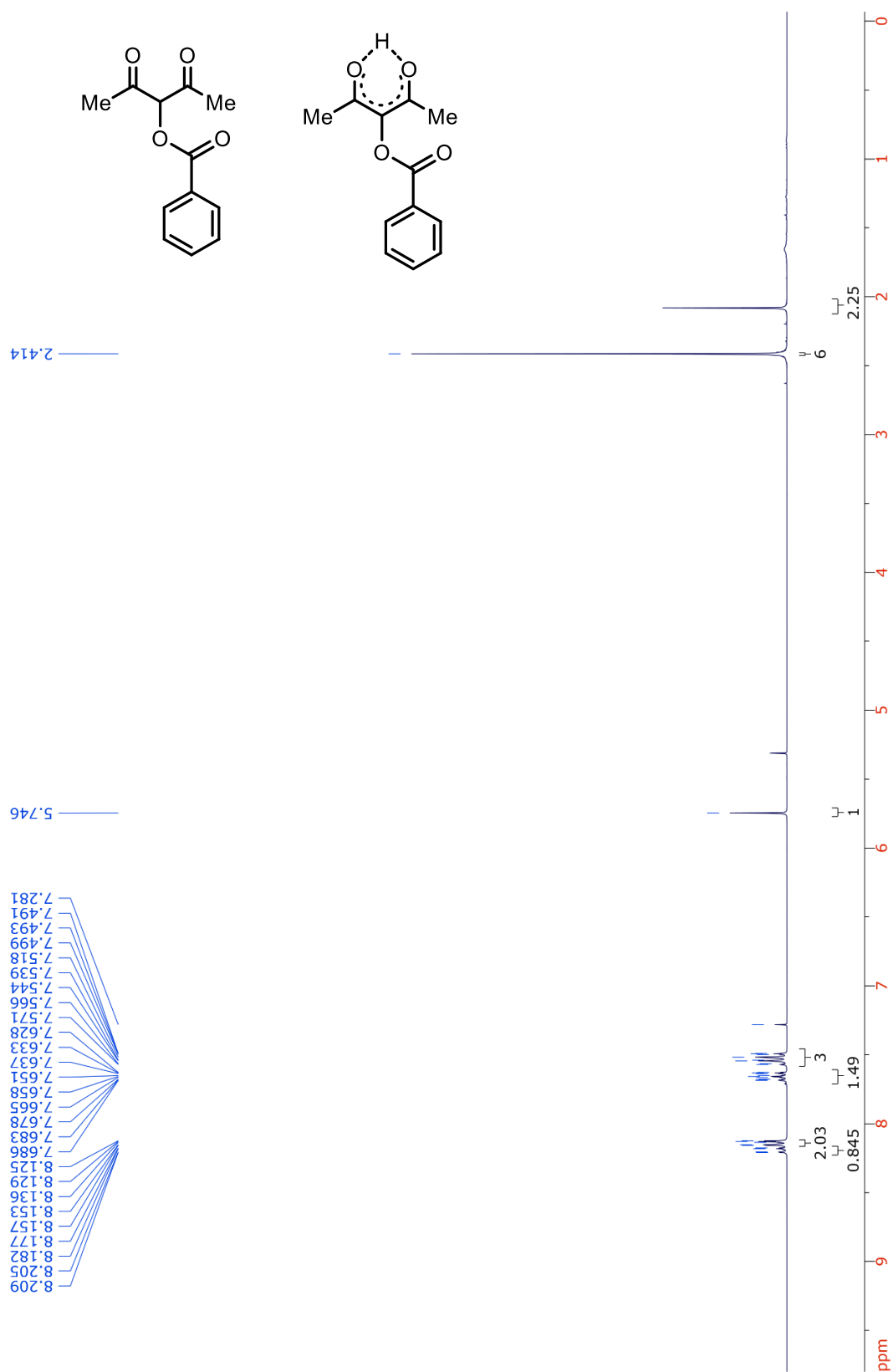
Figure 3.28. ^{1}H NMR (300 MHz, CDCl$_3$) of 1,3-dioxo-1,3-diphenylpropan-2-yl benzoate (**2-29i**)

172
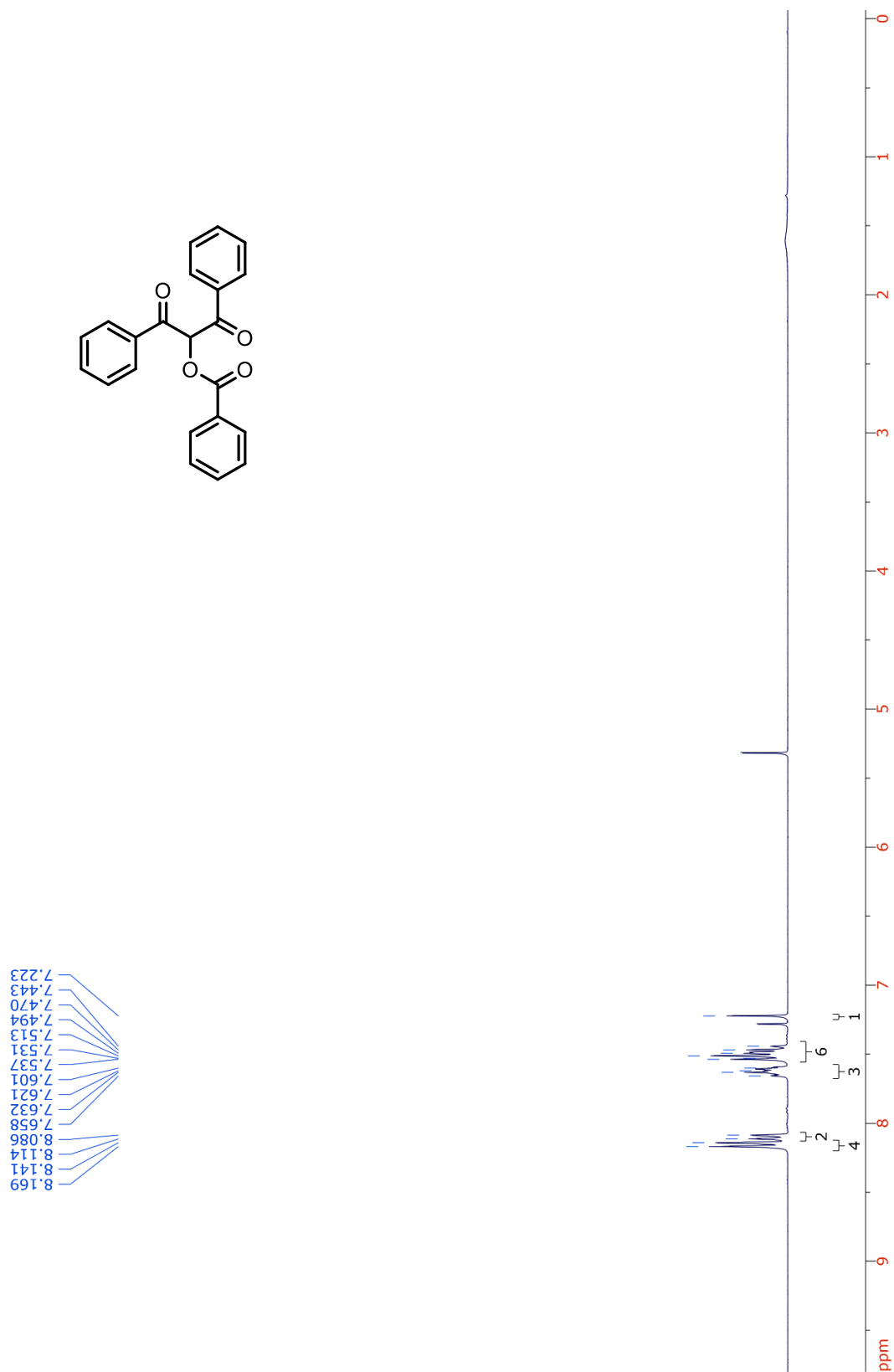
Figure 3.29. ^{13}C NMR (75 MHz, CDCl$_3$) of 1-(benzhydryloxy)-1,3-dioxo-3-phenylpropan-2-yl benzoate (**2-29j**)

Figure 3.30. ^{1}H NMR (300 MHz, CDCl$_3$) of 1-(benzhydryloxy)-1,3-dioxo-3-phenylpropan-2-yl benzoate (**2-29j**)

6.700
6.975
7.129
7.141
7.154
7.159
7.198
7.199
7.228
7.241
7.249
7.283
7.301
7.319
7.340
7.360
7.448
7.473
7.498
7.522
7.598
7.623
7.648
7.673
8.061
8.086
8.124
8.148
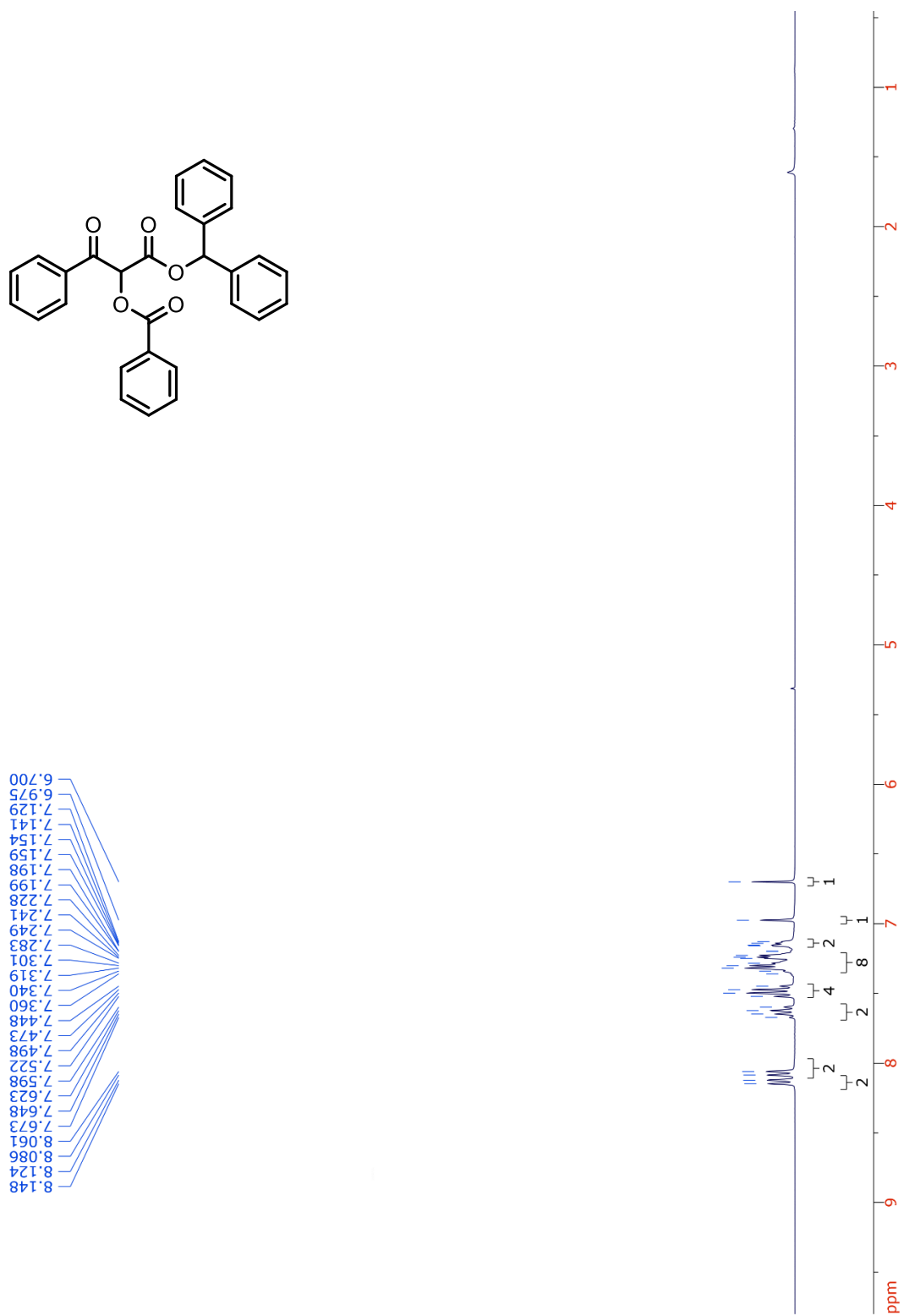
Figure 3.31. ^{13}C NMR (75 MHz, CDCl$_3$) of 1-(benzhydryloxy)-1,3-dioxo-3-phenylpropan-2-yl benzoate (**2-29j**)
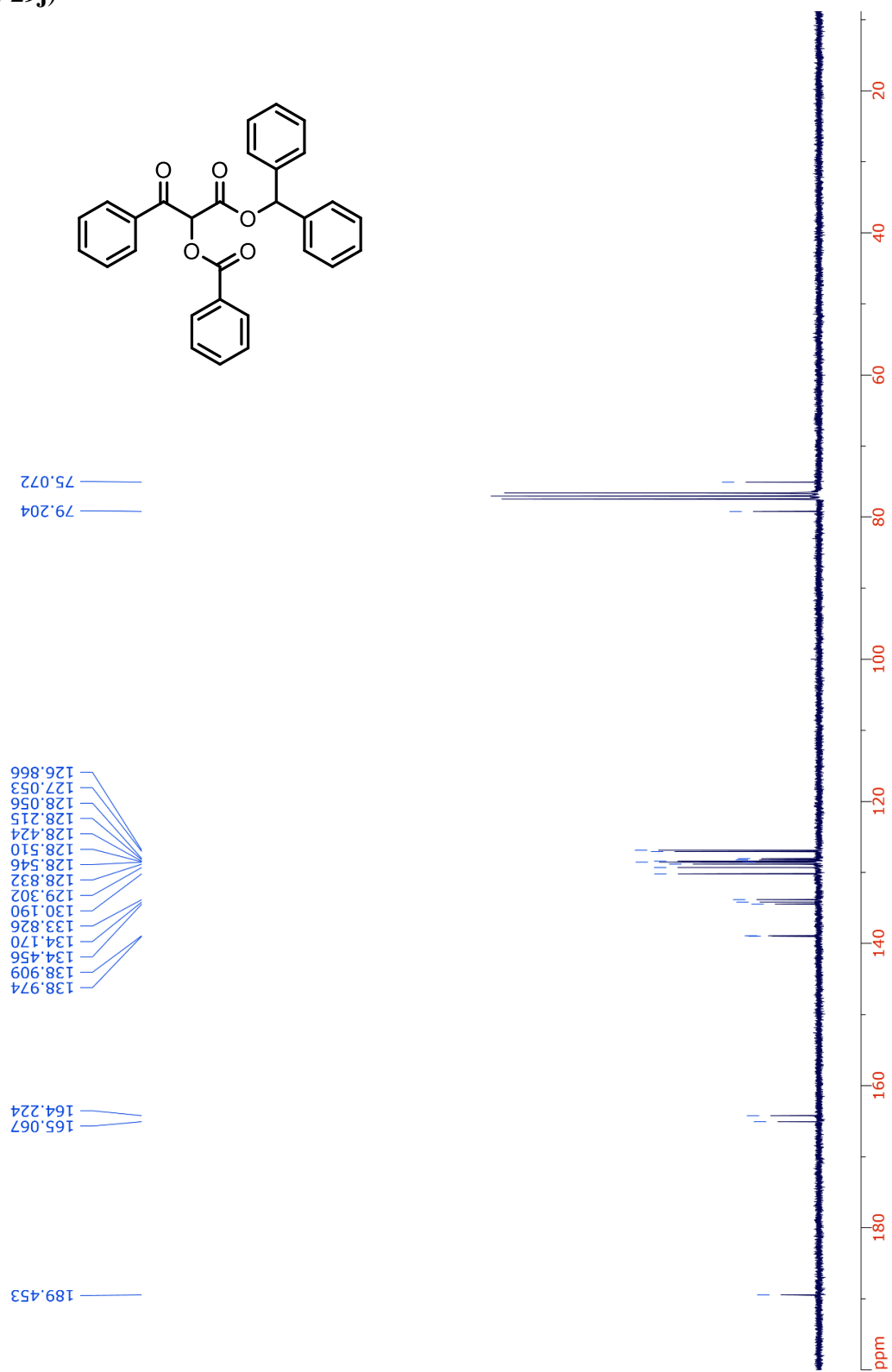
Figure 3.32. ^{1}H NMR (300 MHz, CDCl$_3$) of methyl 2-acetoxy-3-oxo-3-(p-tolyl)propanoate (**2-29k**)
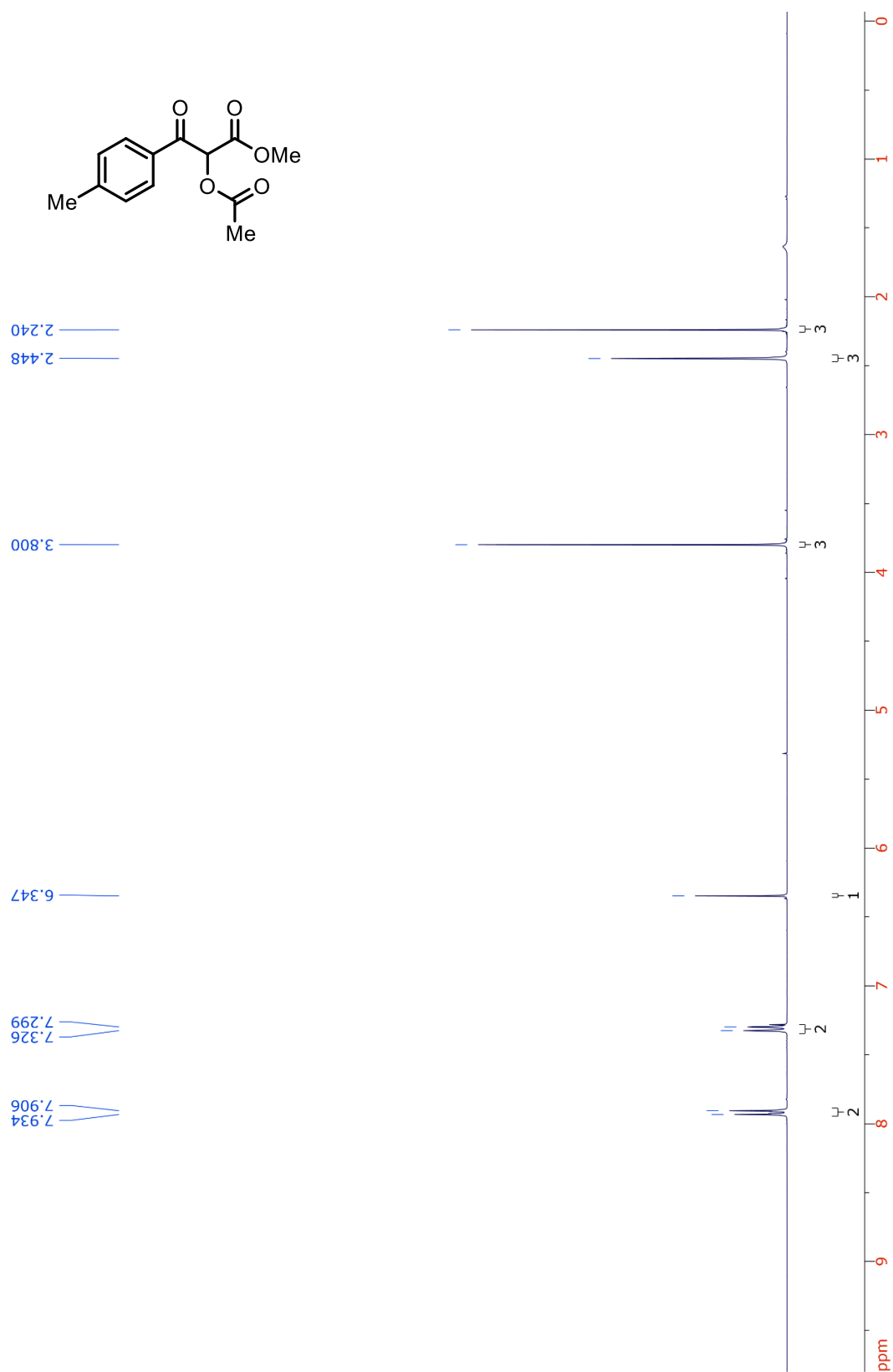
Figure 3.33. ^{13}C NMR (75 MHz, CDCl$_3$) of methyl 2-acetoxy-3-oxo-3-(p-tolyl)propanoate (**2-29k**)
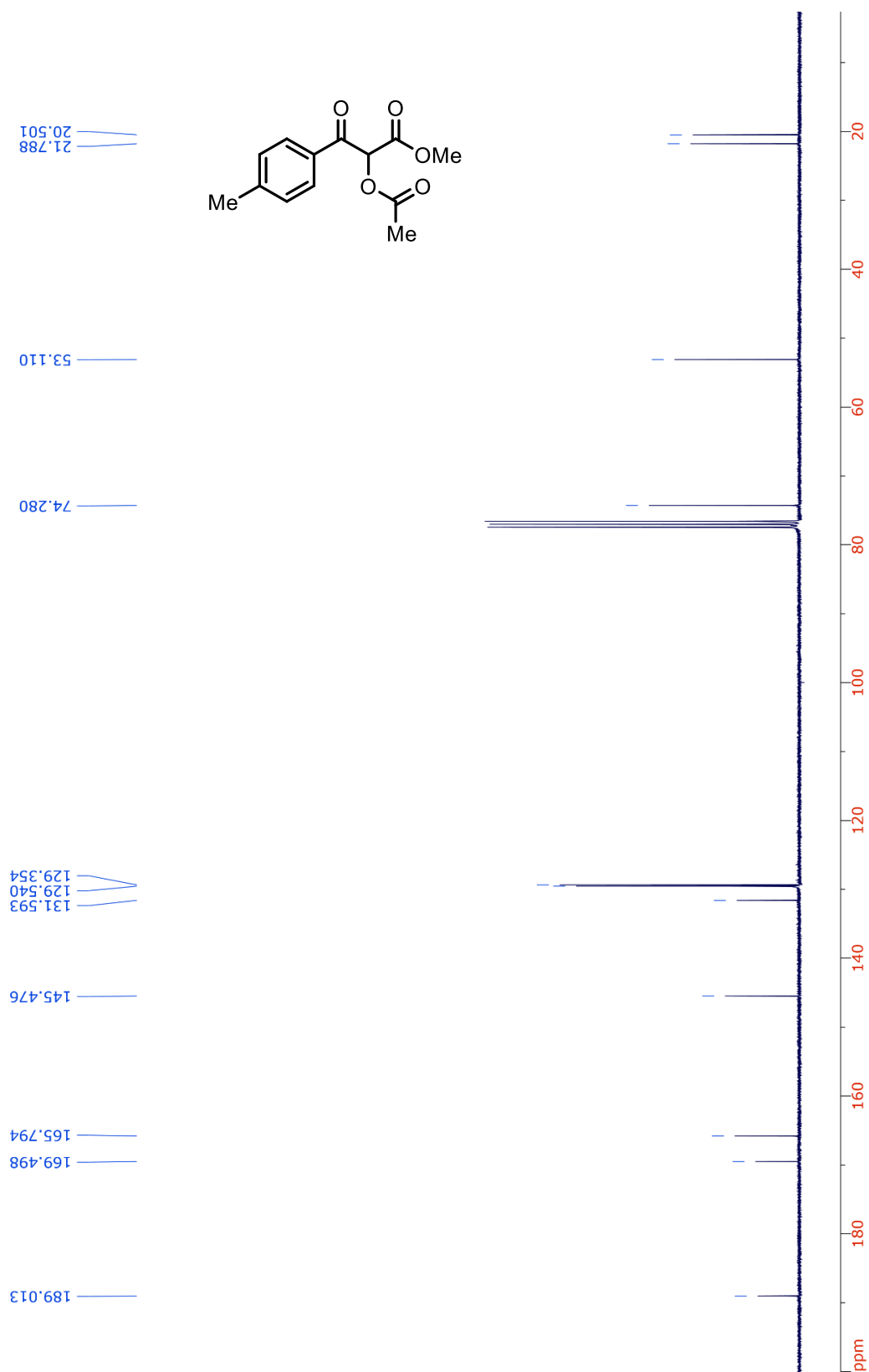
Figure 3.34. ^{1}H NMR (300 MHz, CDCl$_3$) of 1-benzyl 2-(1,3-diethoxy-1,3-dioxopropan-2-yl) pyrrolidine-1,2-dicarboxylate (**2-29l**)
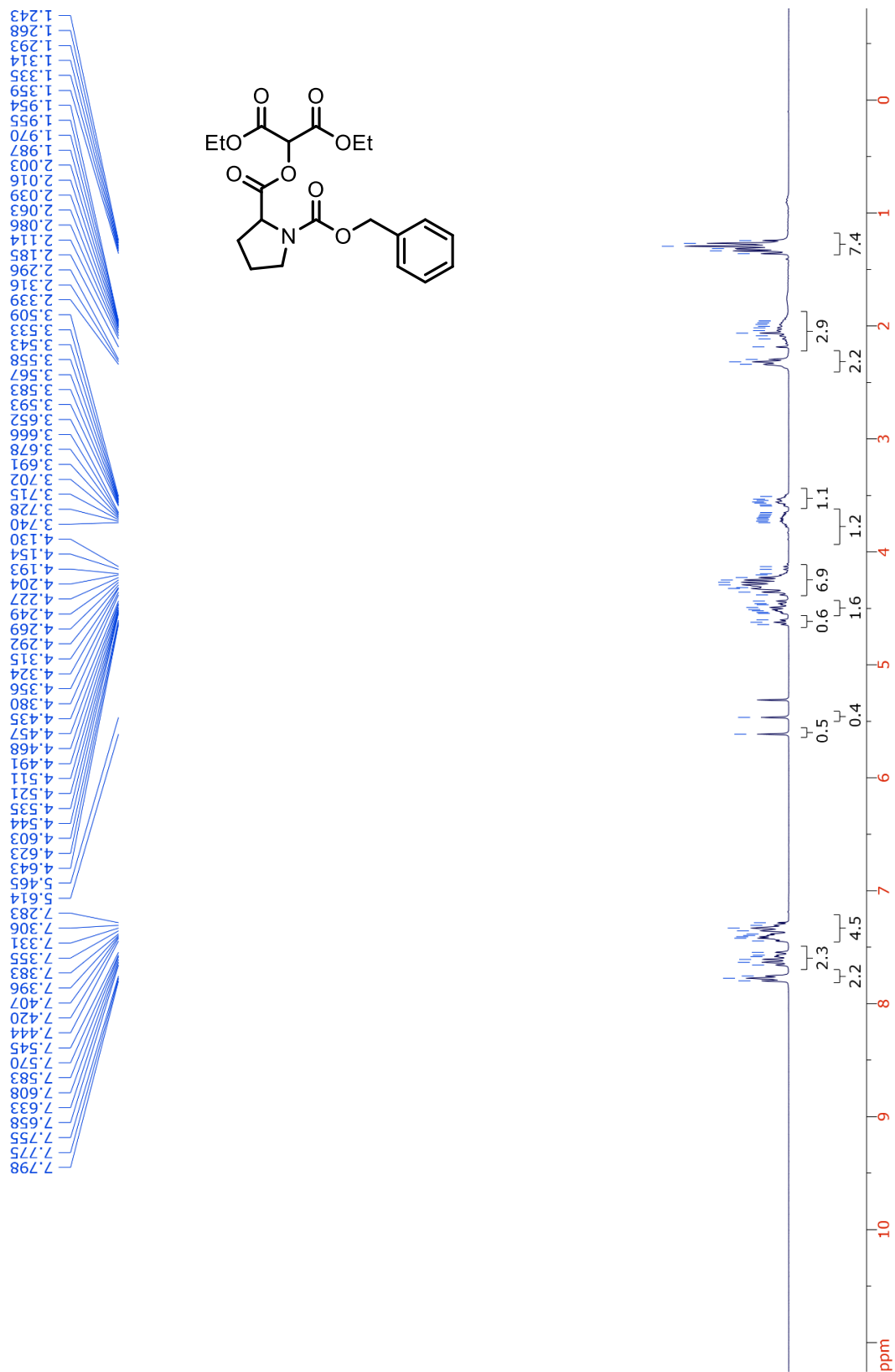
Figure 3.35. ^{13}C NMR (75 MHz, CDCl$_3$) of 1-benzyl 2-(1,3-diethoxy-1,3-dioxopropan-2-yl) pyrrolidine-1,2-dicarboxylate (**2-29l**)
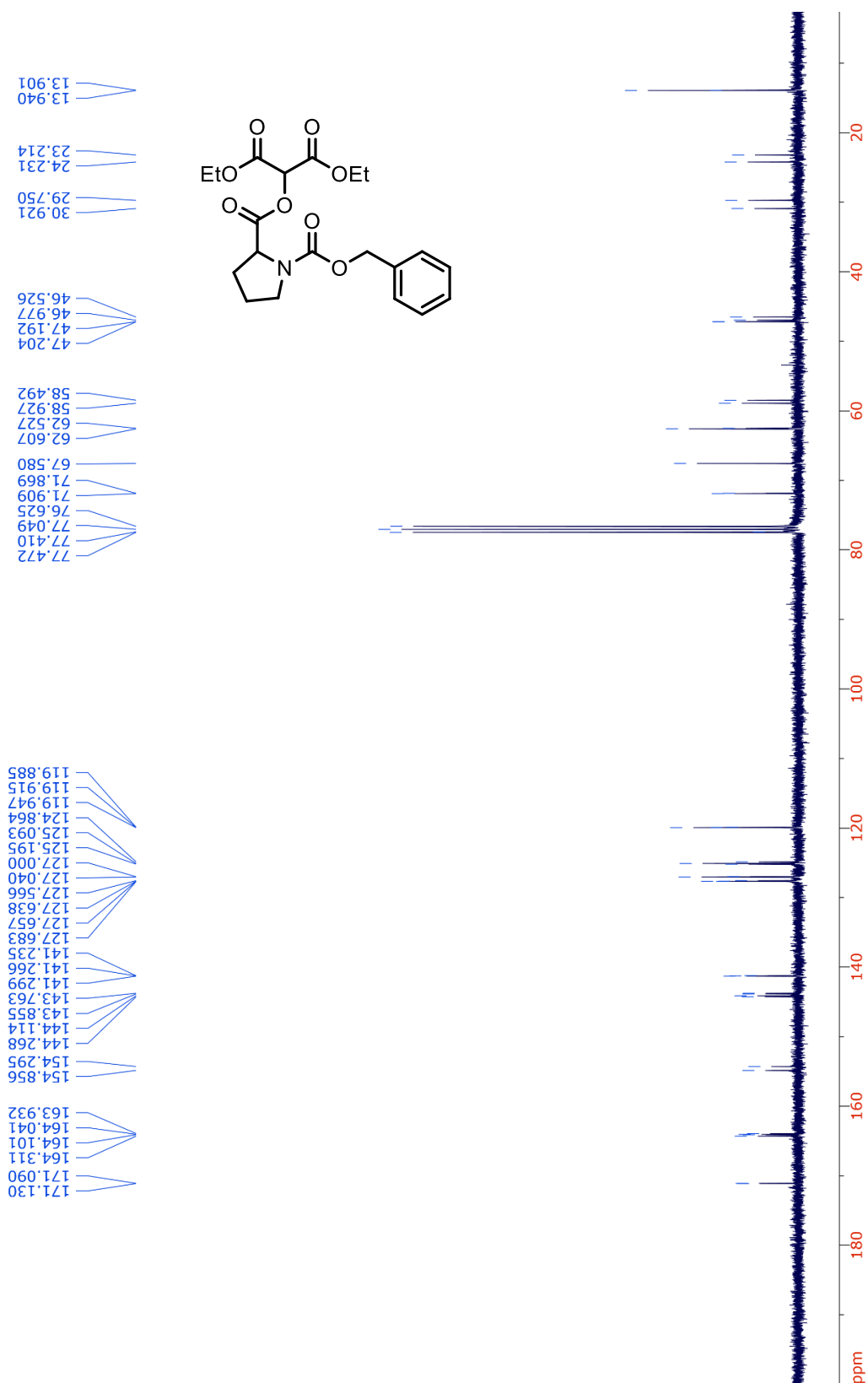
Figure 3.36. ^{1}H NMR (300 MHz, CDCl$_3$) of 1-methoxy-1,3-dioxo-3-(p-tolyl)propan-2-yl (tert-butoxycarbonyl)methioninate (**2-29m**)

180
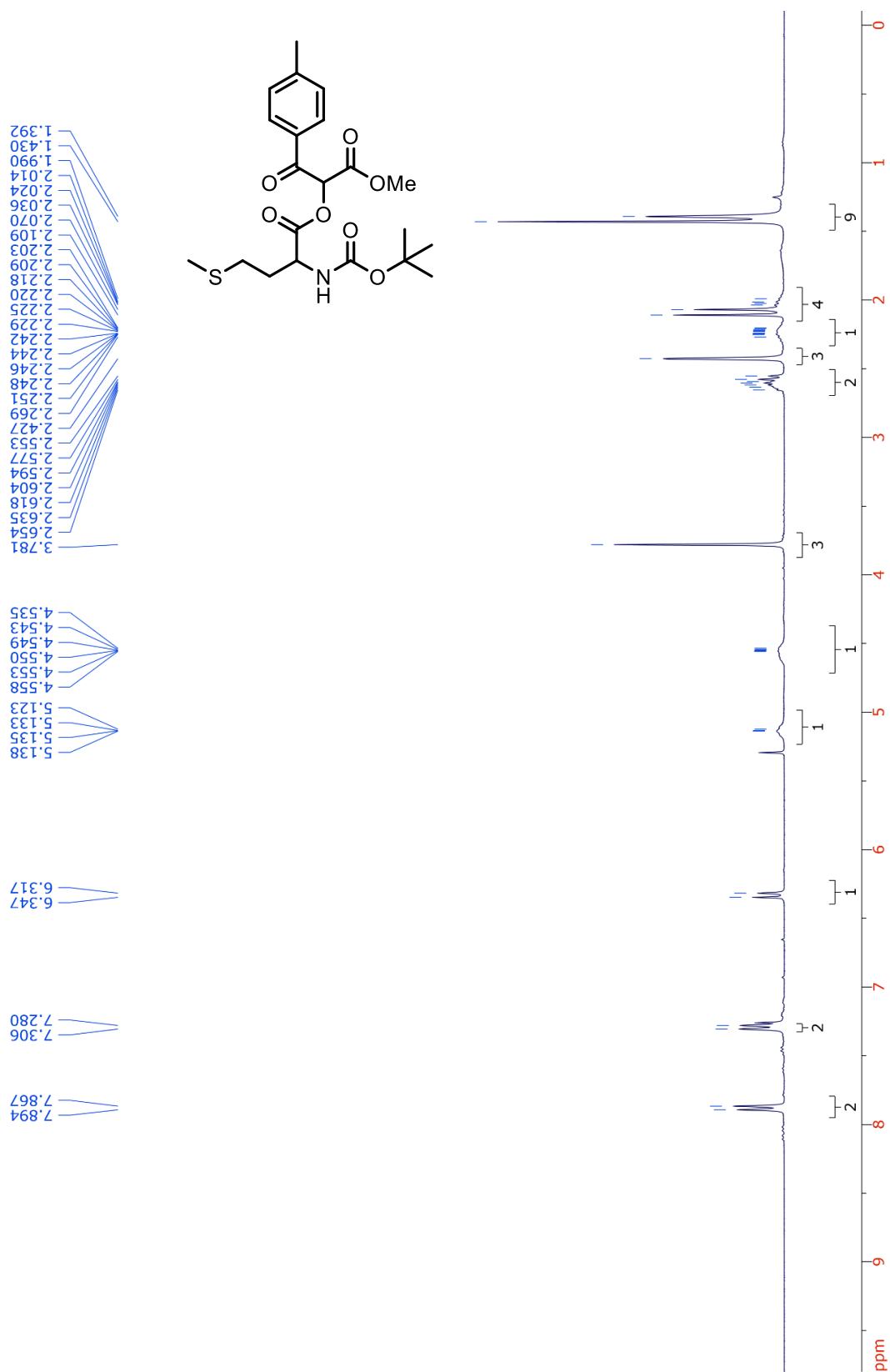
Figure 3.37. ^{13}C NMR (75 MHz, CDCl$_3$) of 1-methoxy-1,3-dioxo-3-(p-tolyl)propan-2-yl (tert-butoxycarbonyl)methioninate (**2-29m**)
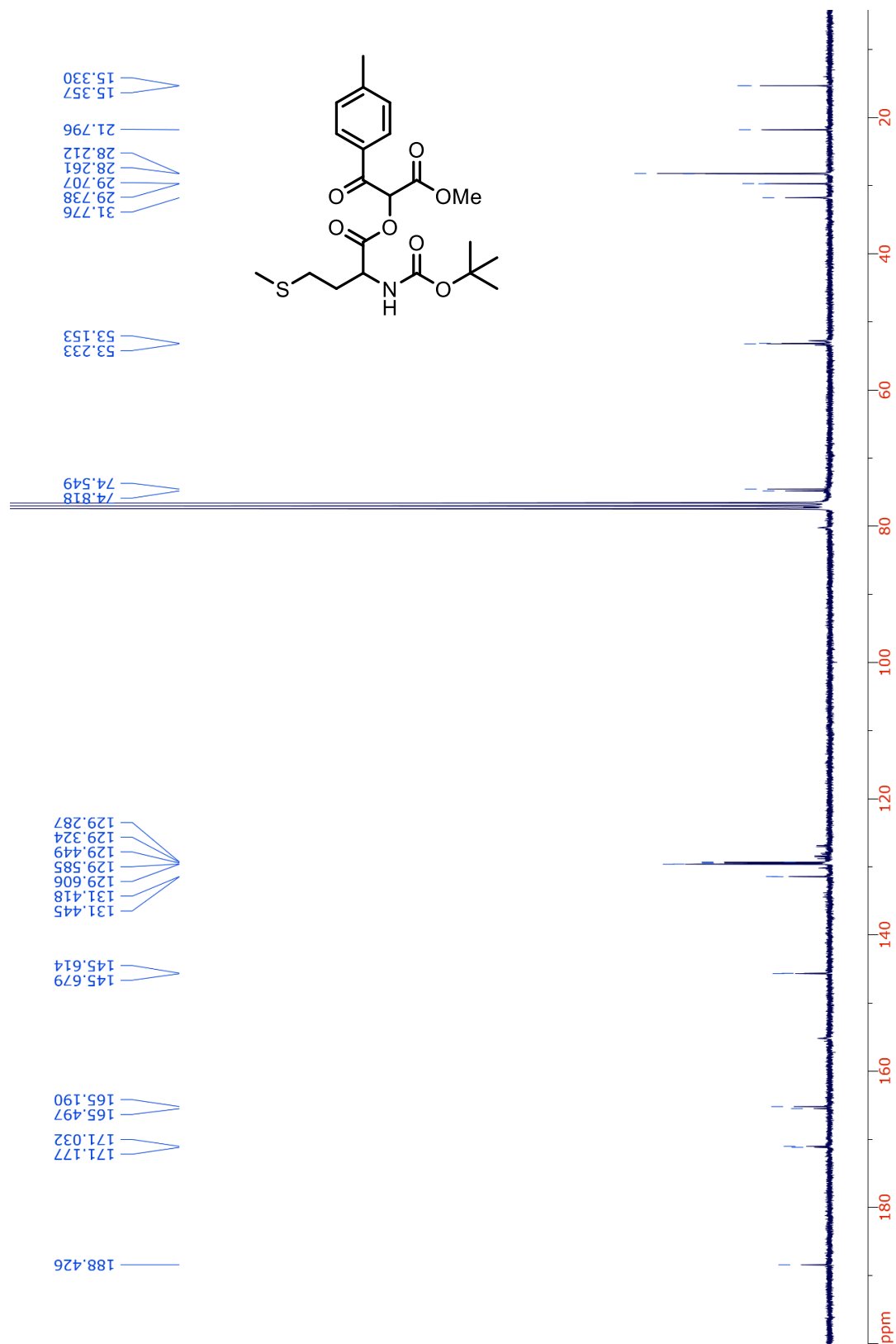
Figure 3.38. ^{1}H NMR (300 MHz, CDCl$_3$) of diethyl 2-((2-(((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-(tert-butoxy)phenyl)propanoyl)oxy)malonate (**2-29n**)
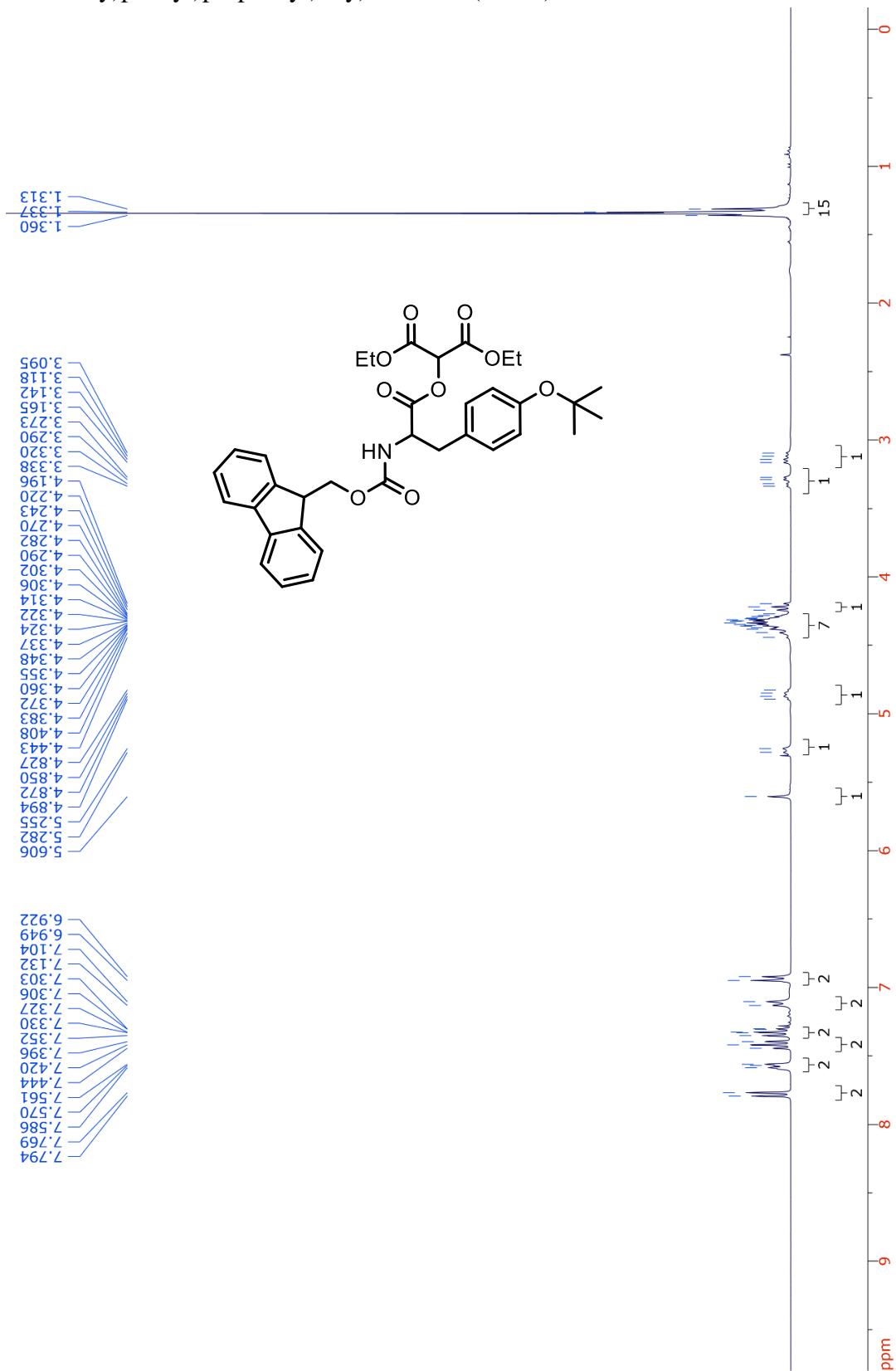
Figure 3.39. ^{13}C NMR (75 MHz, CDCl$_3$) of diethyl 2-((2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-(4-(tert-butoxy)phenyl)propanoyl)oxy)malonate (**2-29n**)

3.762
3.933
4.092

7.273
7.285
7.294
7.302
7.310
7.312
7.317
7.328
7.336
7.353
7.358
7.379
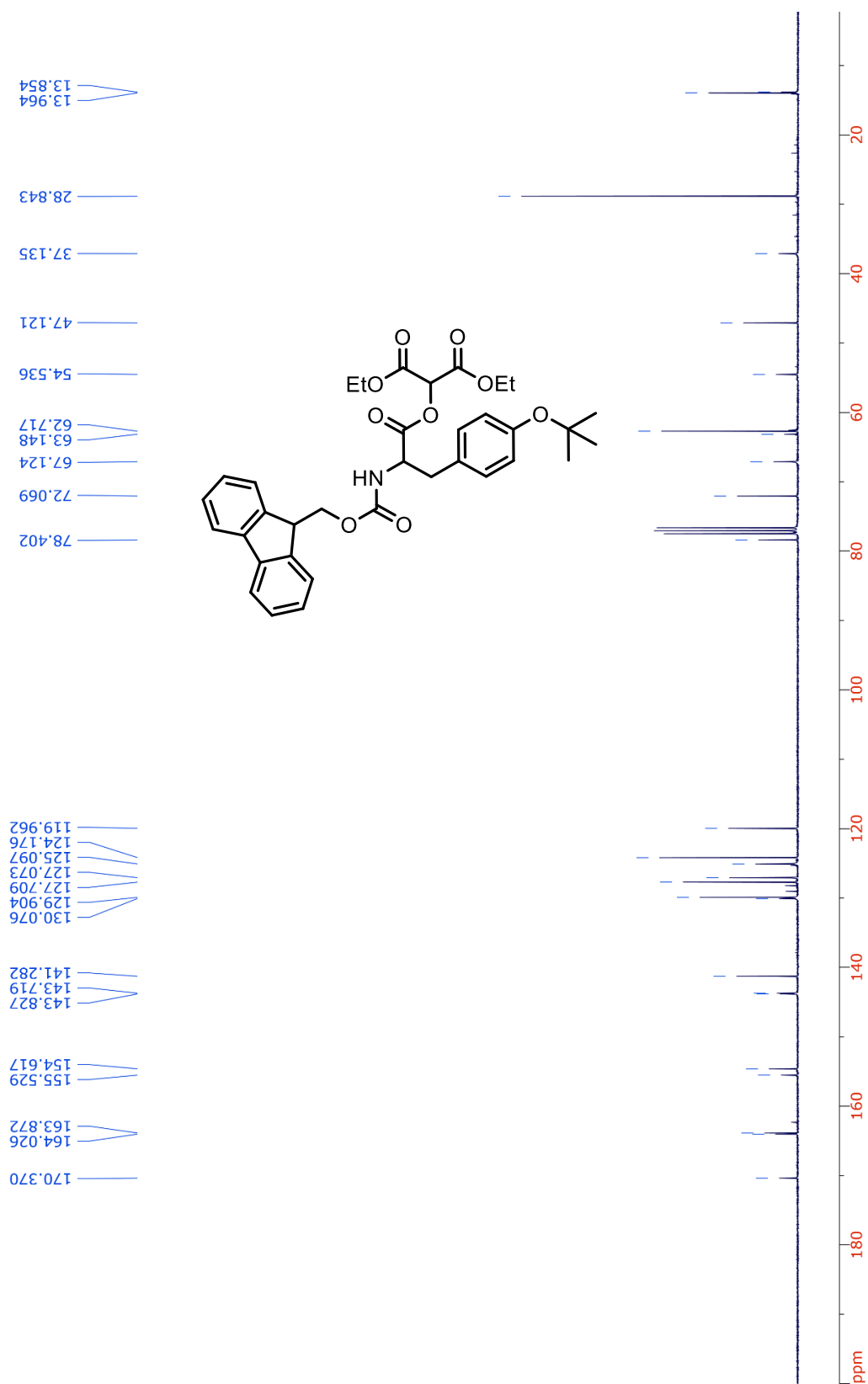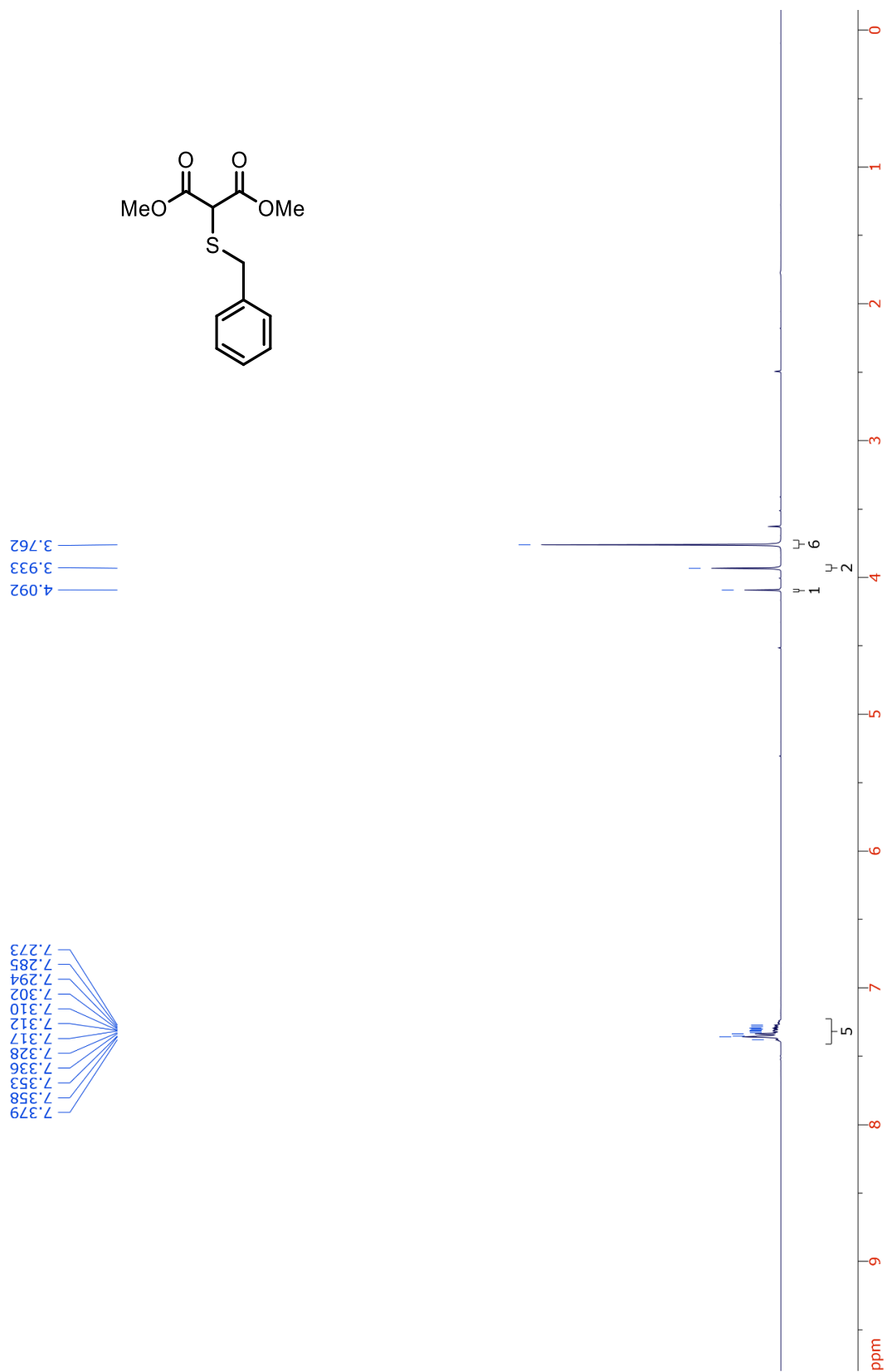
Figure 3.41. ^{13}C NMR (75 MHz, CDCl$_3$) of dimethyl 2-(benzylthio)malonate (**2-43a**)

35.926

49.716
53.152

127.517
128.619
129.200

136.400

167.138
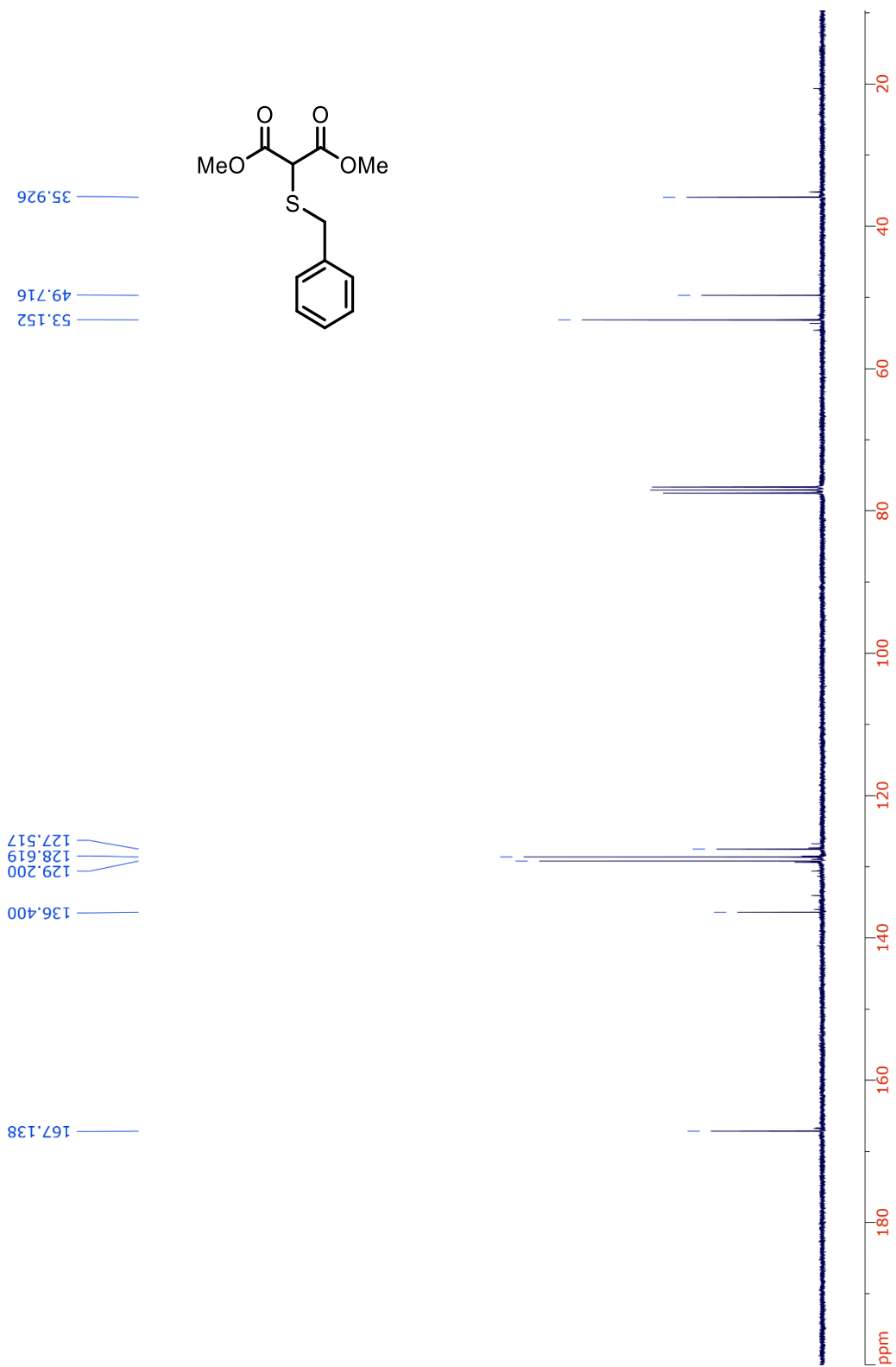
Figure 3.42. ^{1}H NMR (300 MHz, CDCl$_3$) of dimethyl 2-((2,3,5,6-tetramethylphenyl)thio)malonate (**2-43b)**
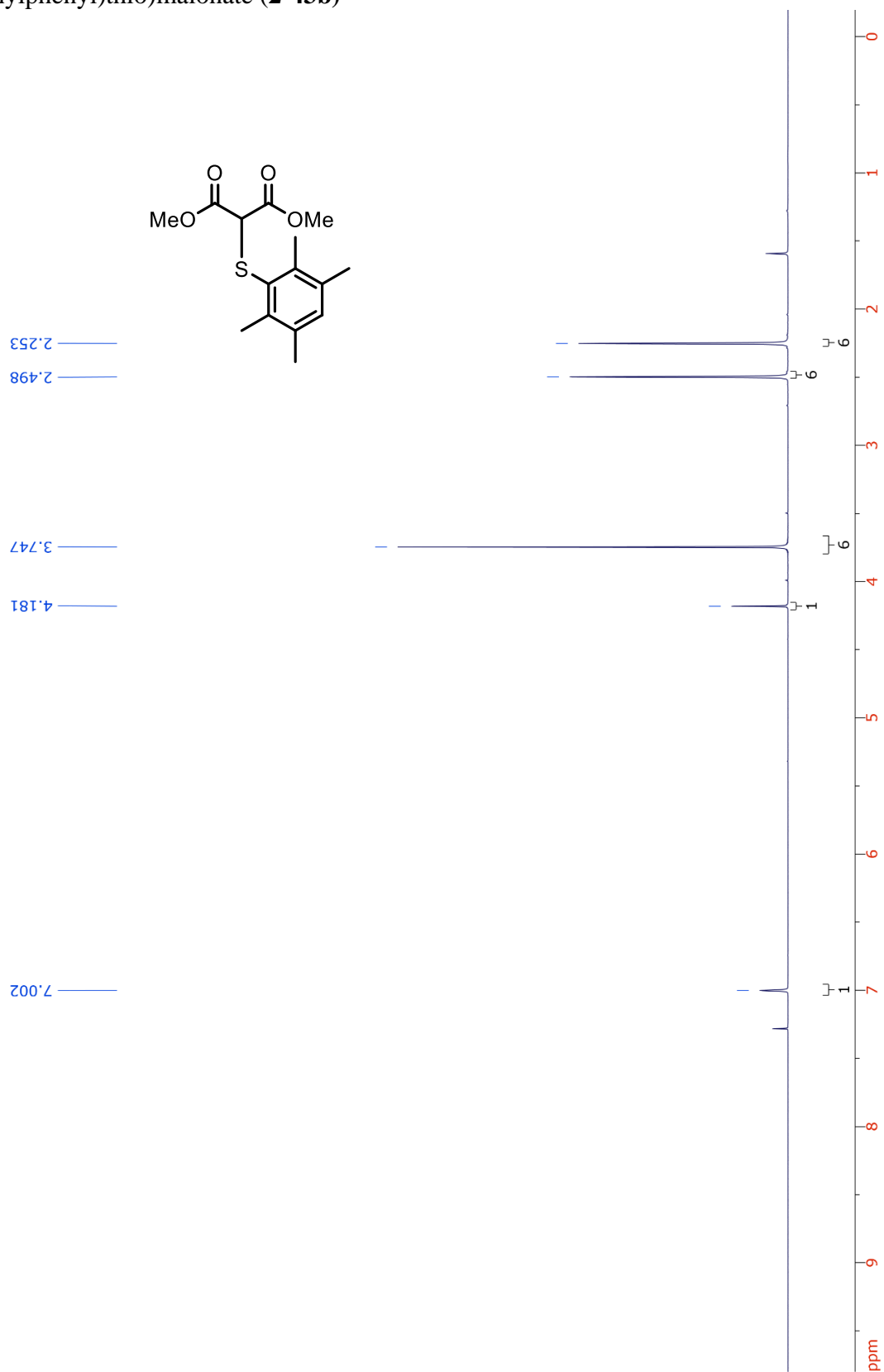
Figure 3.43. ^{13}C NMR (75 MHz, CDCl$_3$) of dimethyl 2-((2,3,5,6-tetramethylphenyl)thio)malonate (**2-43b**)
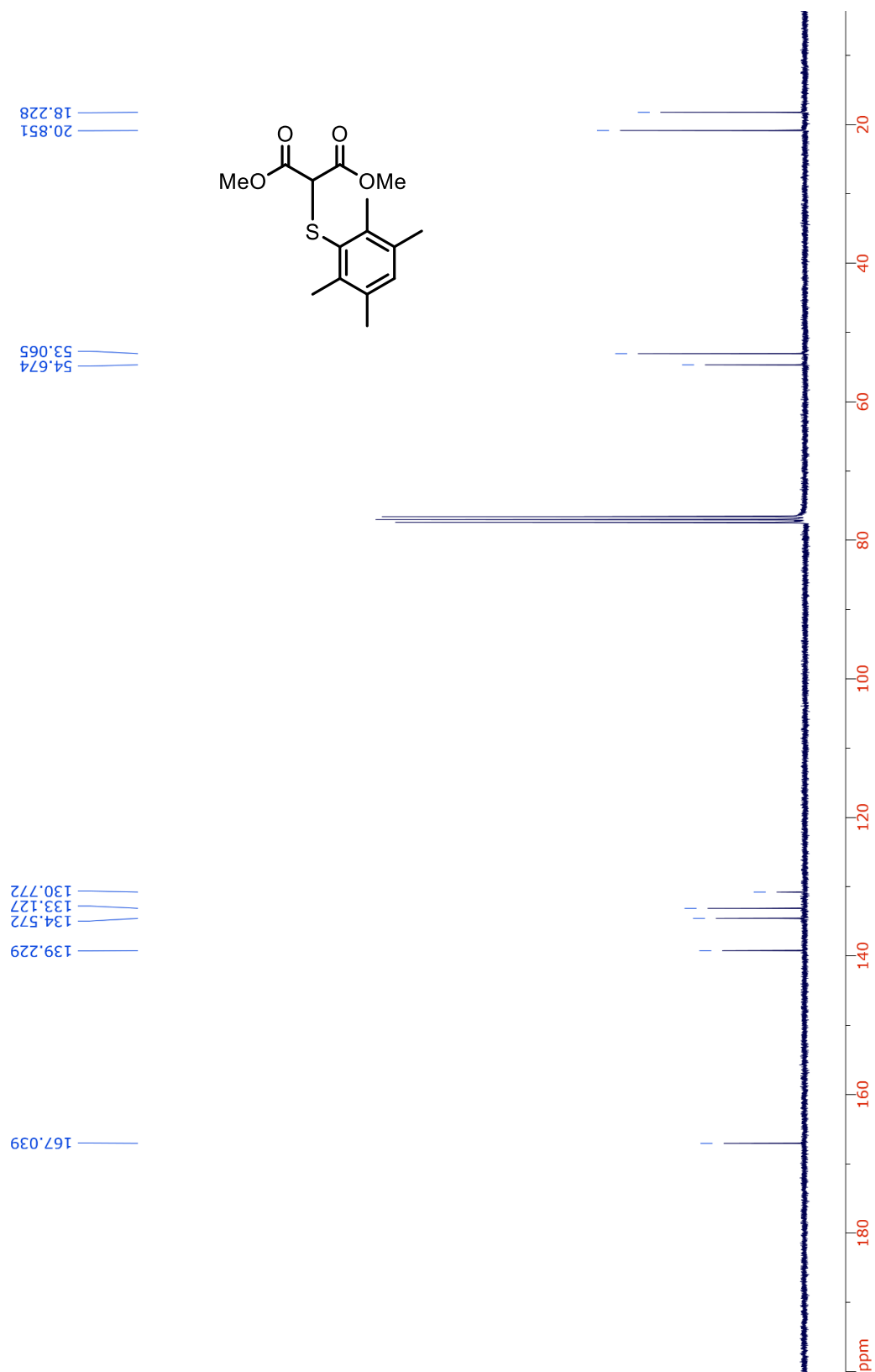
Figure 3.44. ^{1}H NMR (300 MHz, CDCl$_3$) of dimethyl 2-((2,6-dimethylphenyl)thio)malonate (**2-43c**)
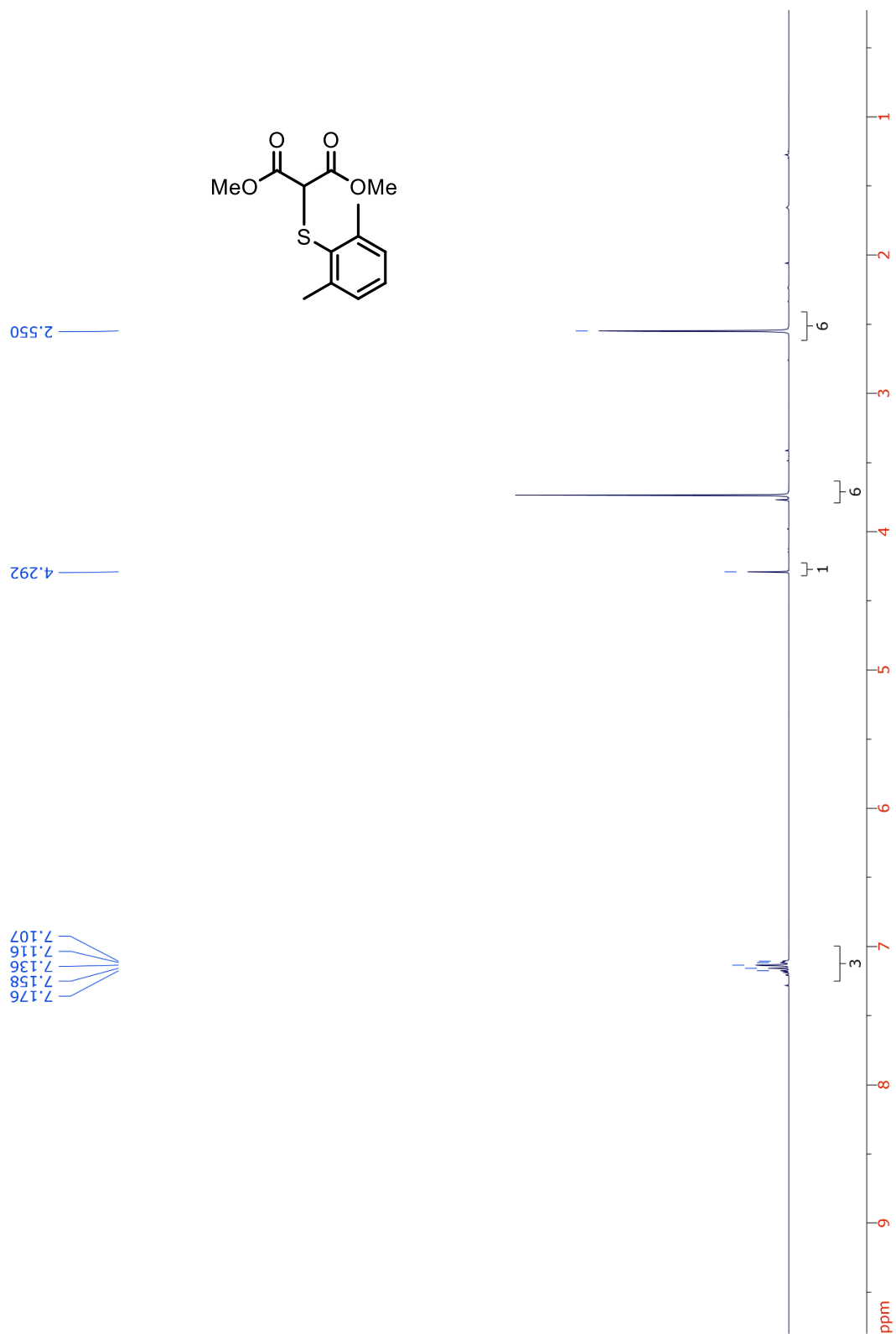
Figure 3.45. ^{1}H NMR (300 MHz, CDCl$_3$) of dimethyl 2-(o-tolylthio)malonate (**2-43d**)

189
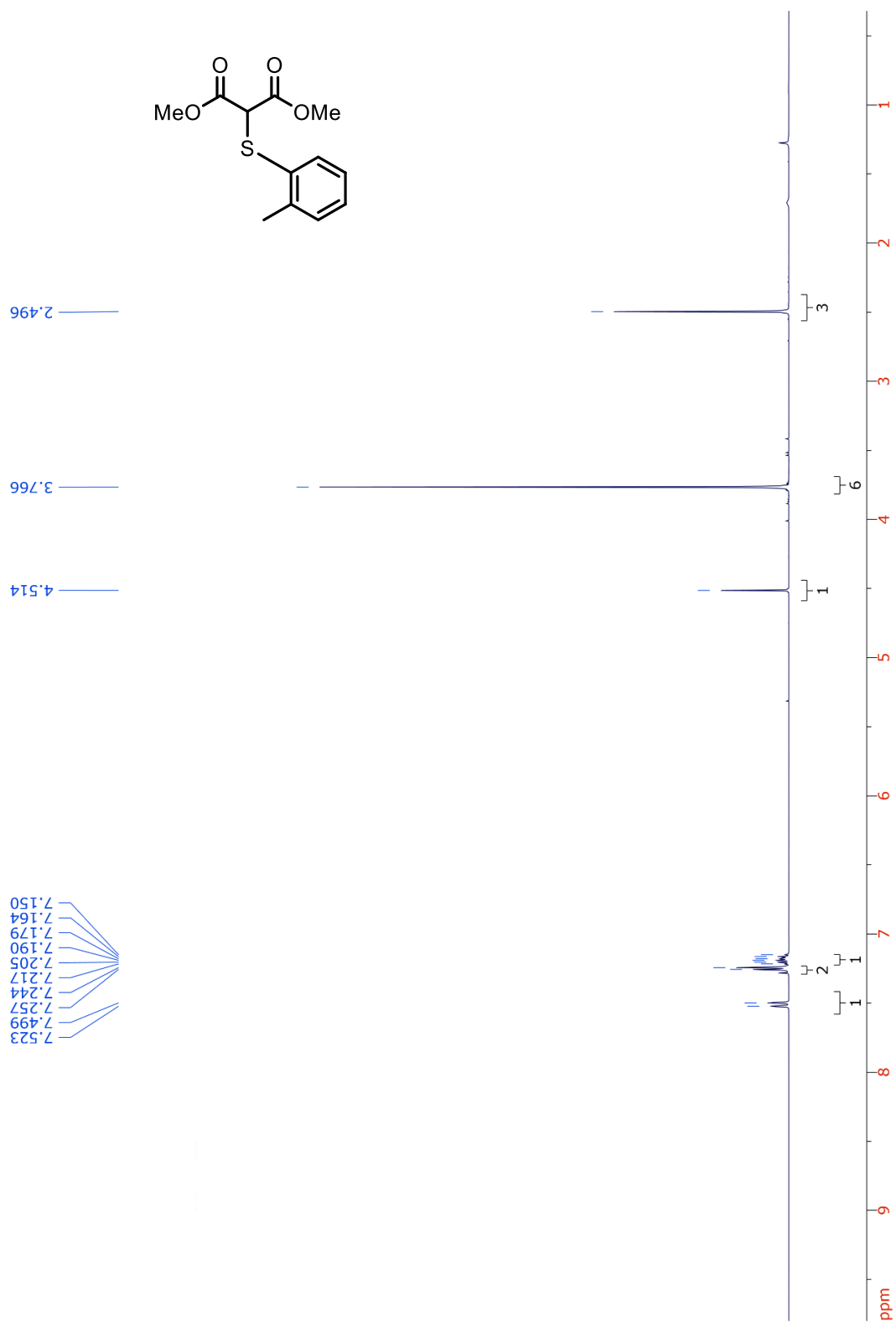
Figure 3.46. ^{1}H NMR (300 MHz, CDCl$_3$) of dimethyl 2-((4-bromophenyl)thio)malonate (**2-43e**)
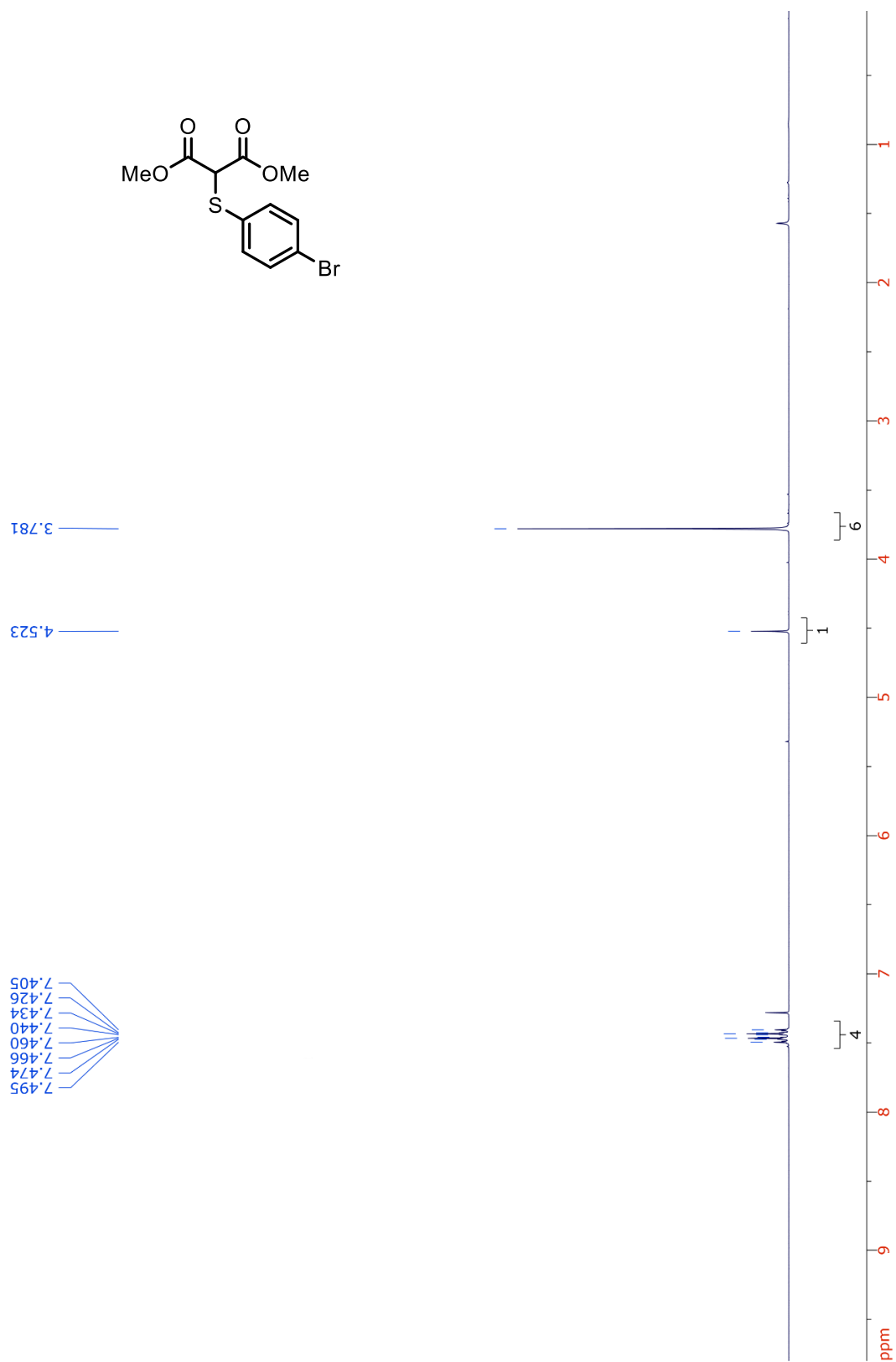
Figure 3.47. ^{1}H NMR (300 MHz, CDCl$_3$) of dimethyl 2-(naphthalen-1-ylthio)malonate (**2-43f**)

191
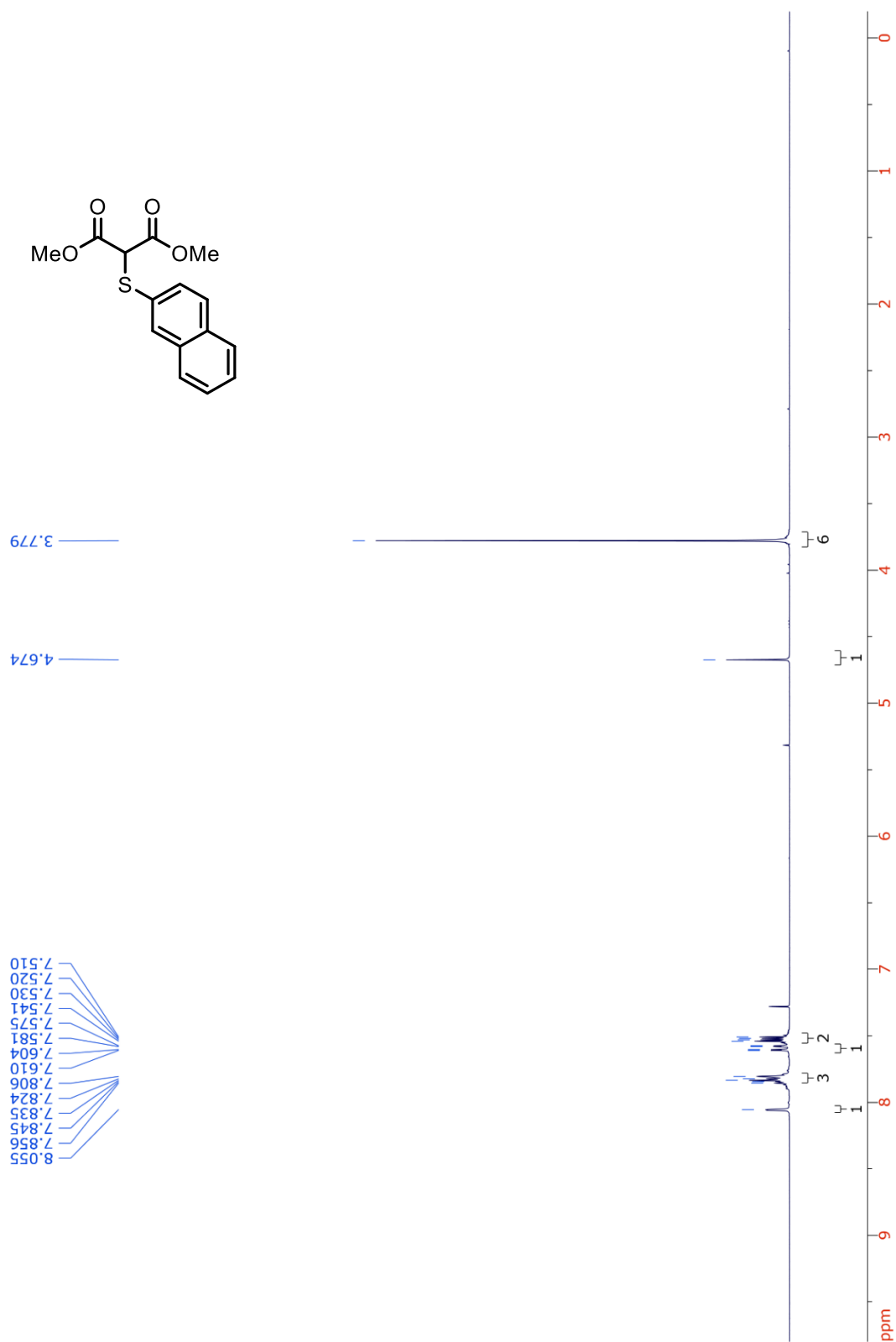
Appendix B – NMR spectra for Chapter 3

Figure 3.48. ^{1}H NMR (300 MHz, CDCl$_3$) of 2-((2-(methoxymethyl)phenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium (**3-17h**)


193
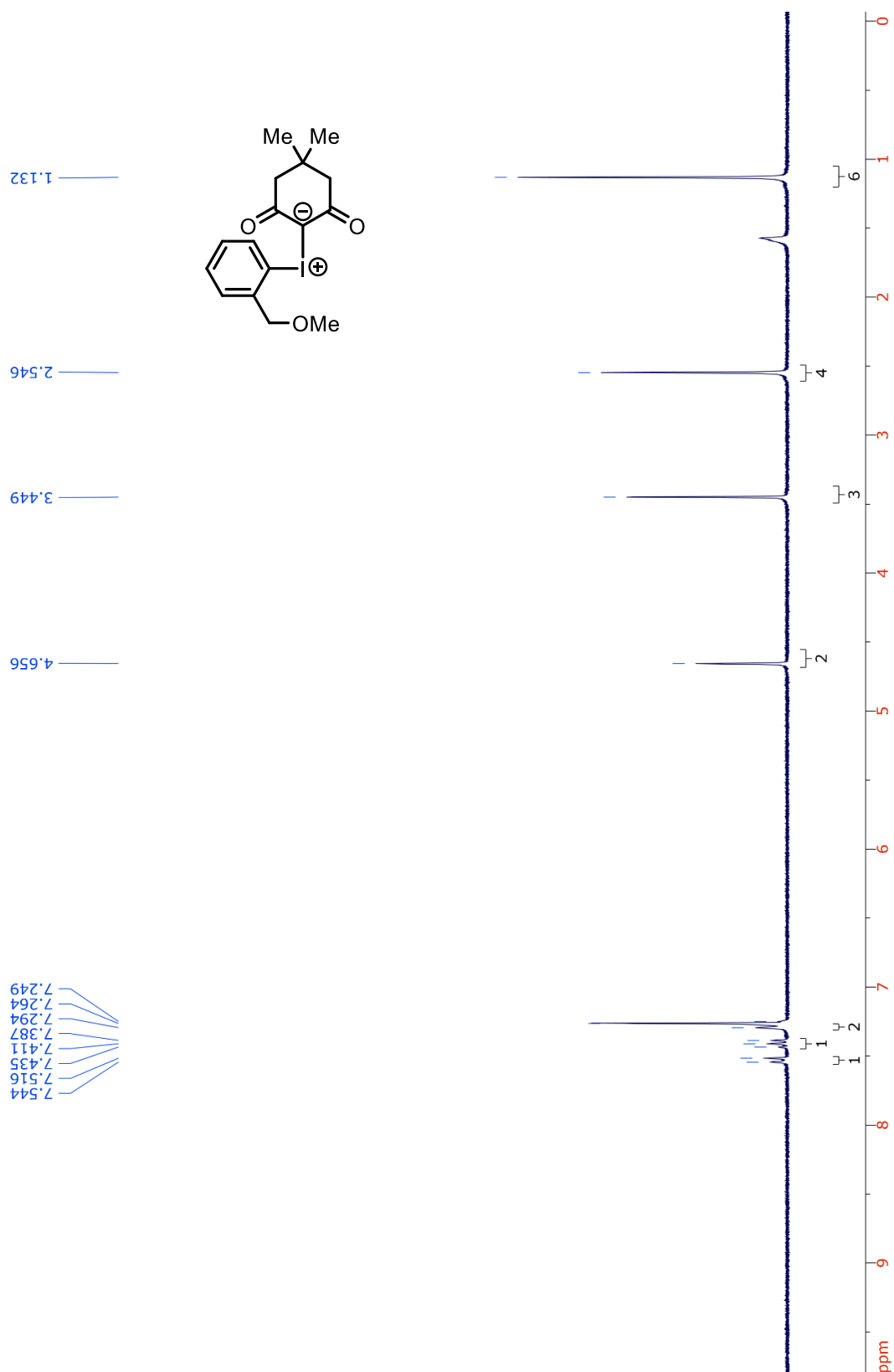
Figure 3.49. ^{13}C NMR (75 MHz, CDCl$_3$) of 2-((2-(methoxymethyl)phenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium (**3-17h**)
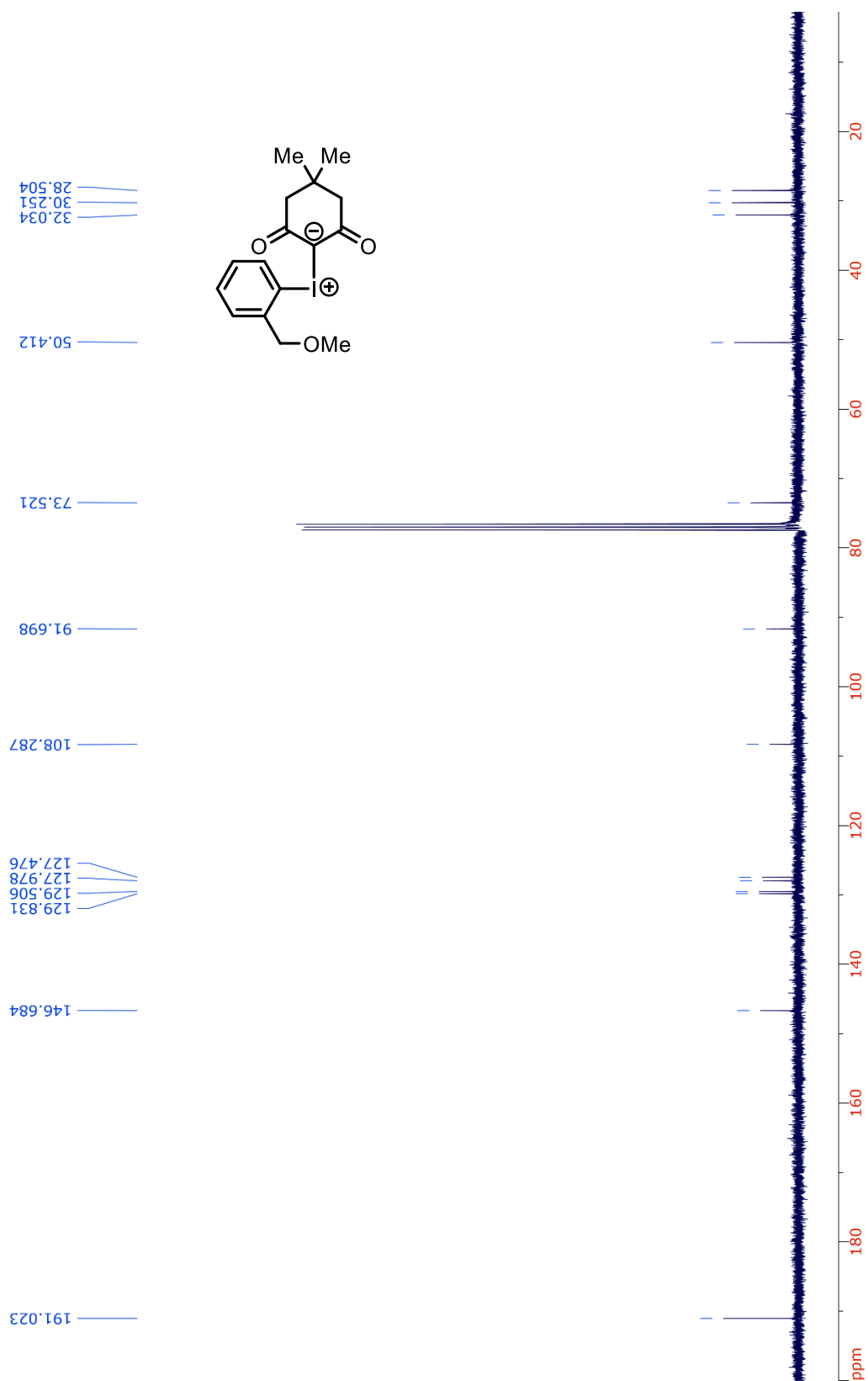
Figure 3.50. HMQC (75 MHz, CDCl₃) of 2-((2-(methoxymethyl)phenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium (**3-17h**)
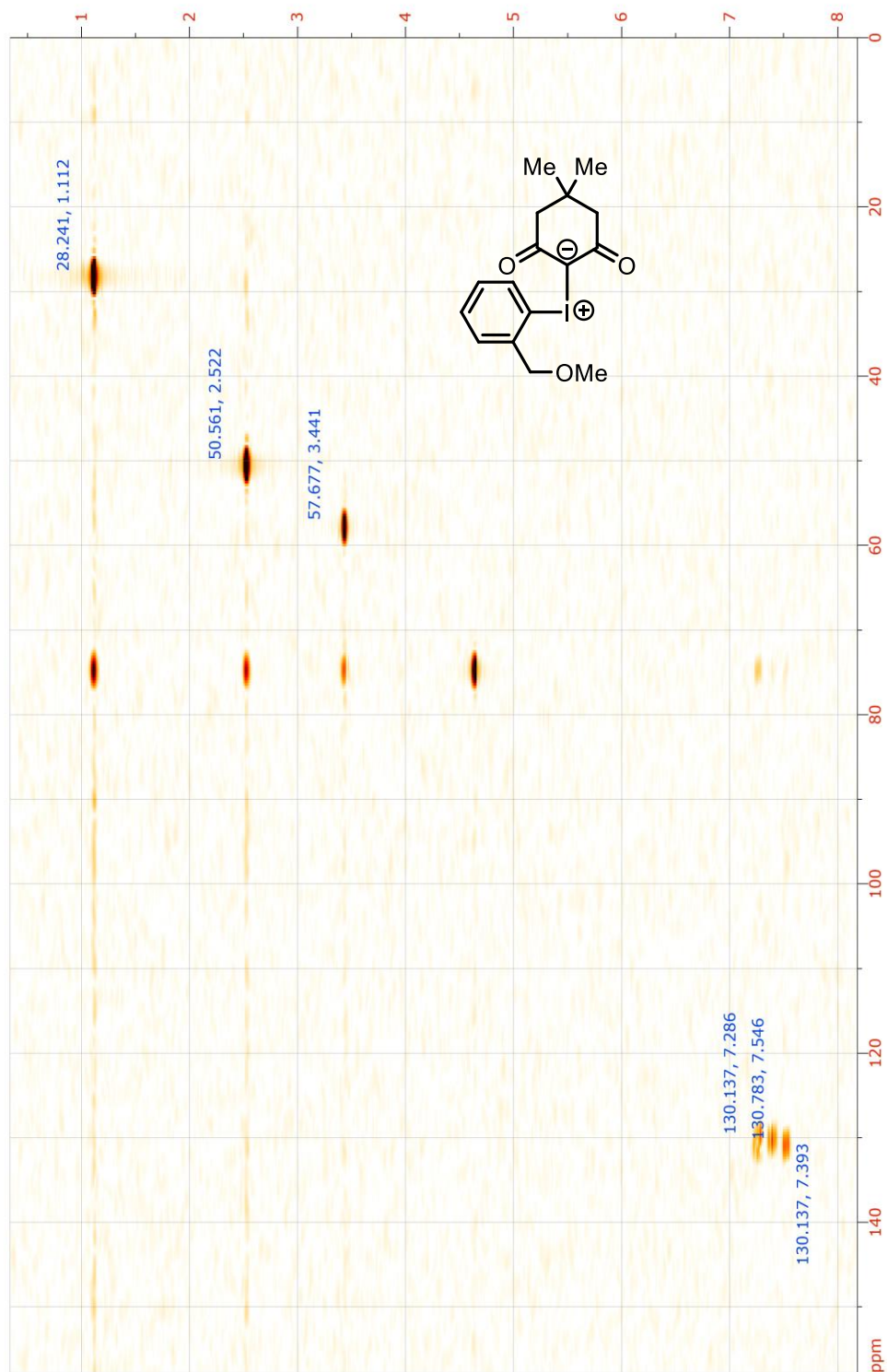
Figure 3.51. HMBC (75 MHz, CDCl₃) of 2-((2-(methoxymethyl)phenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium (**3-17h**)
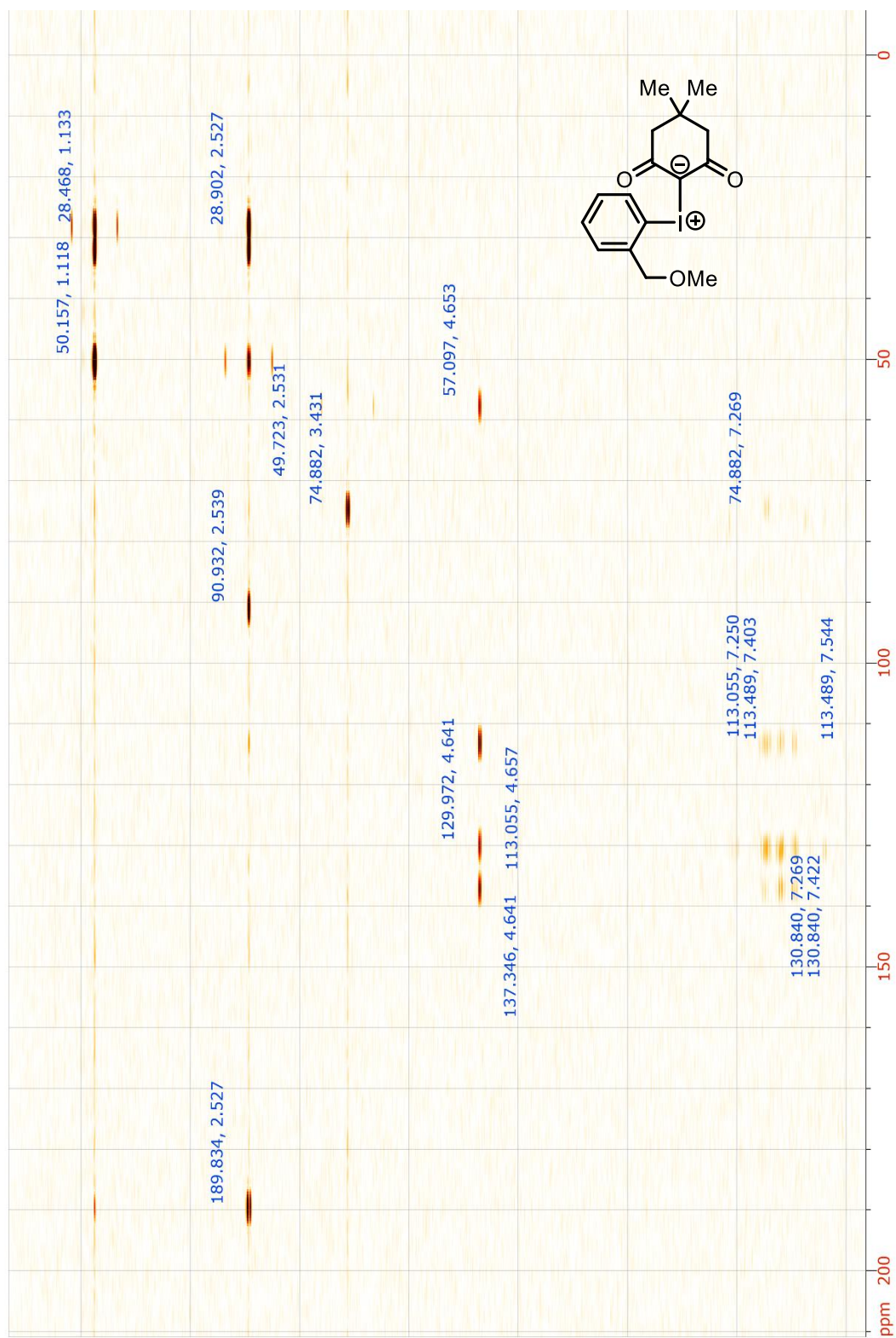
Figure 3.52. ^{1}H NMR (300 MHz, CDCl$_3$) of 2-((2-(methoxypropan)phenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium (**3-17i**)
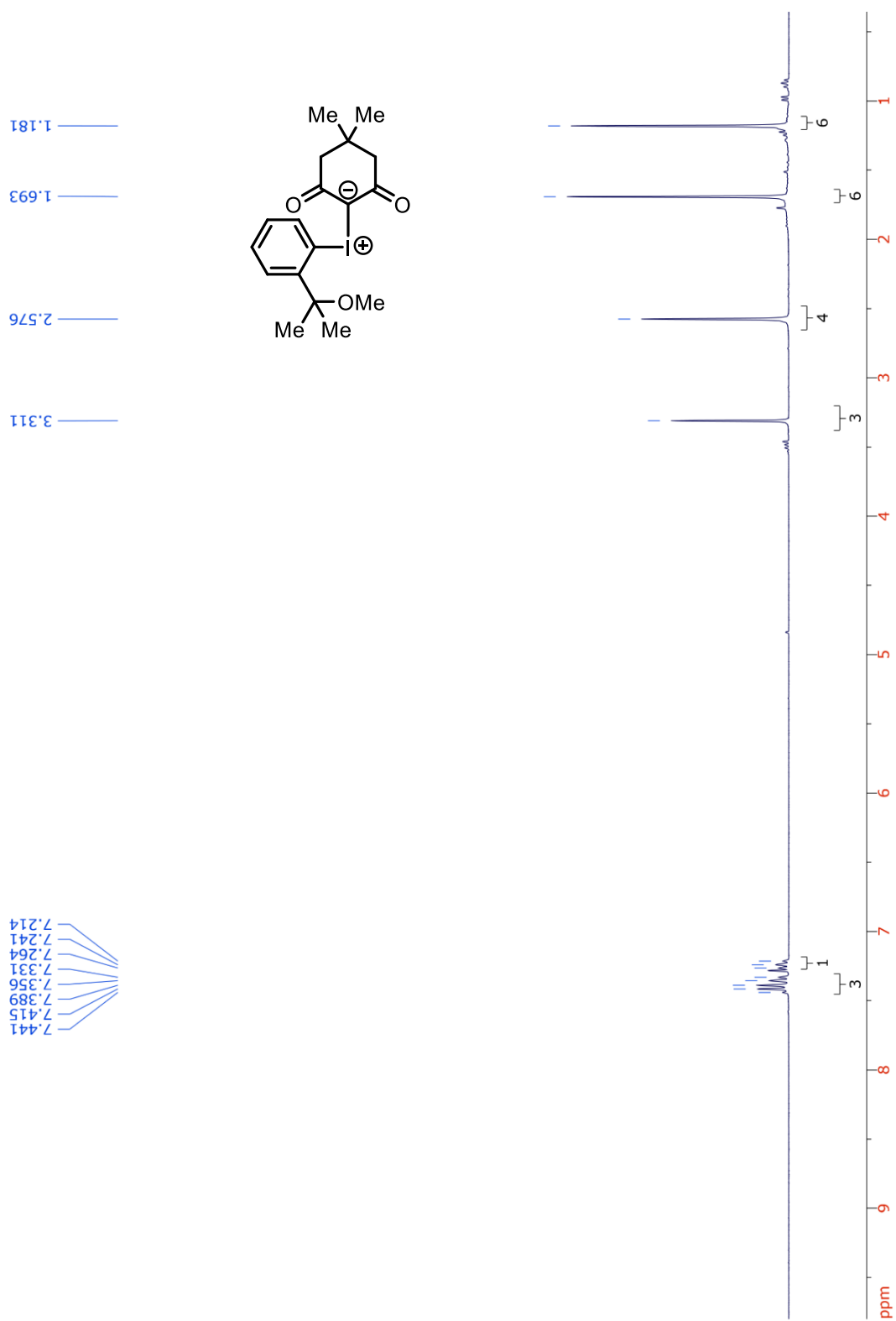
Figure 3.53. ^{13}C NMR (75 MHz, CDCl$_3$) of 2-((2-(methoxypropan)phenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium (**3-17i**)
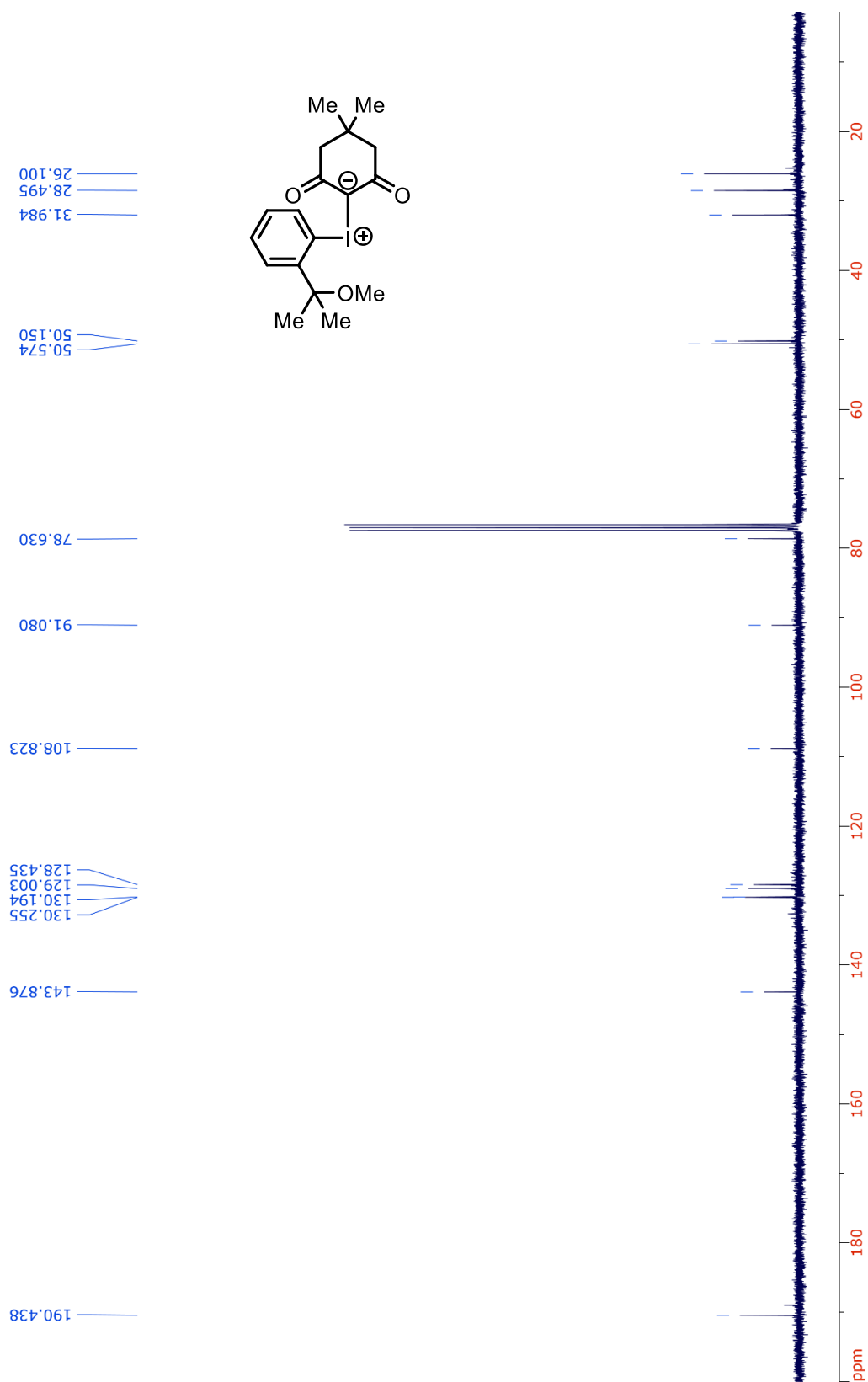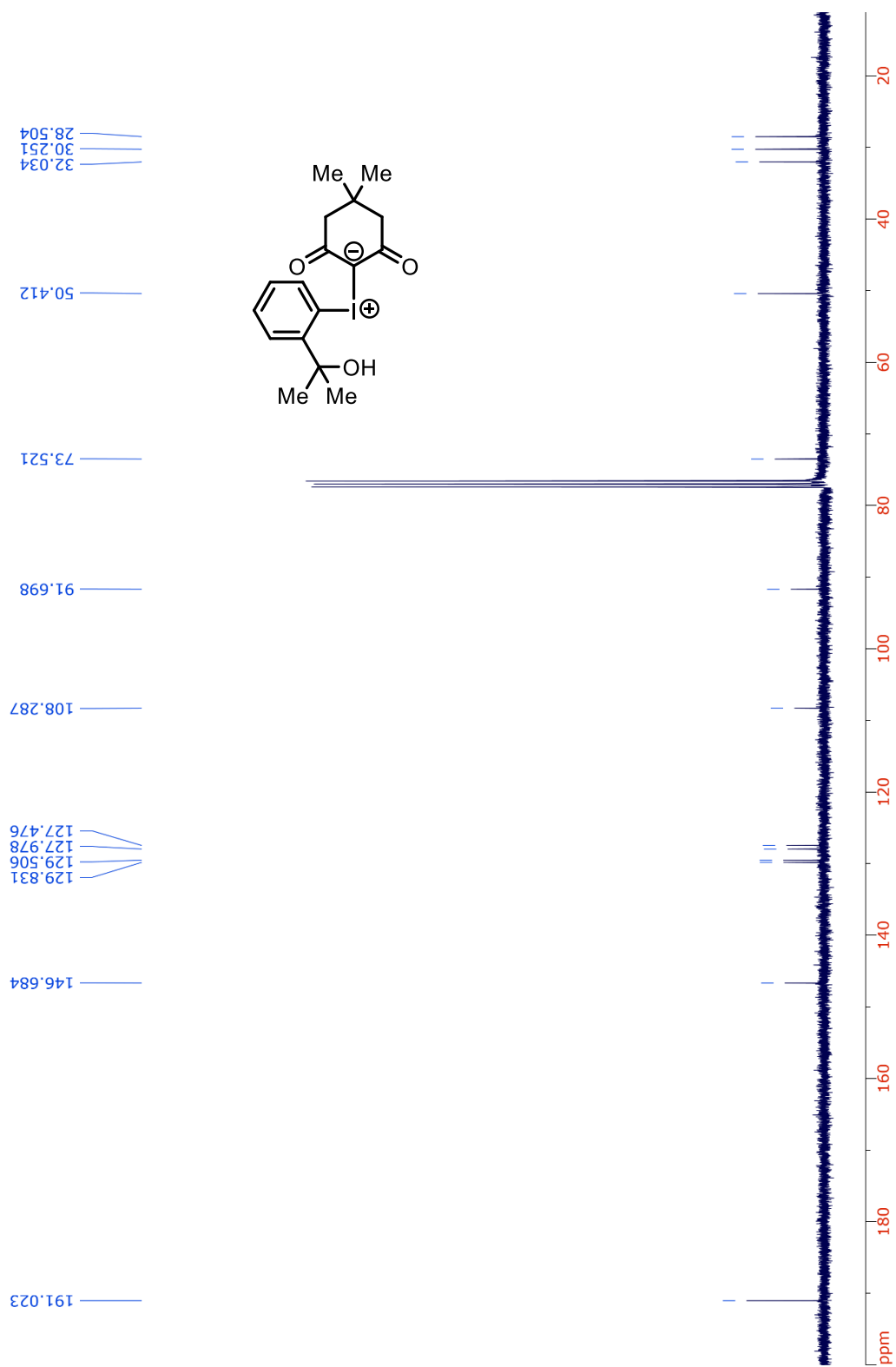
Figure 3.54. ^{1}H NMR (300 MHz, CDCl$_3$) of (2-nitrophenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium (**3-17j**)

199
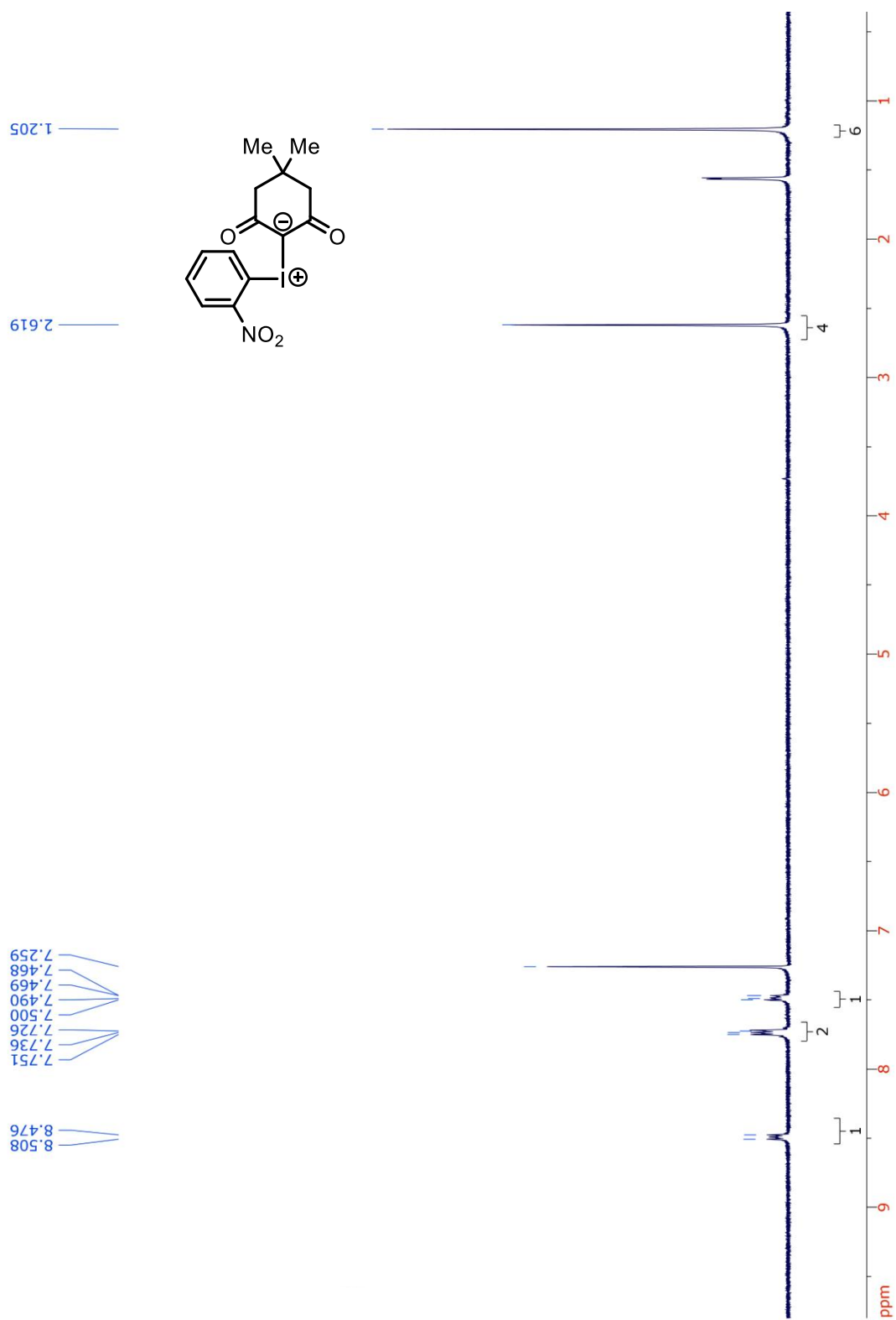
Figure 3.55. ^{13}C NMR (75 MHz, CDCl$_3$) of (2-nitrophenyl)(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium (**3-17j**)
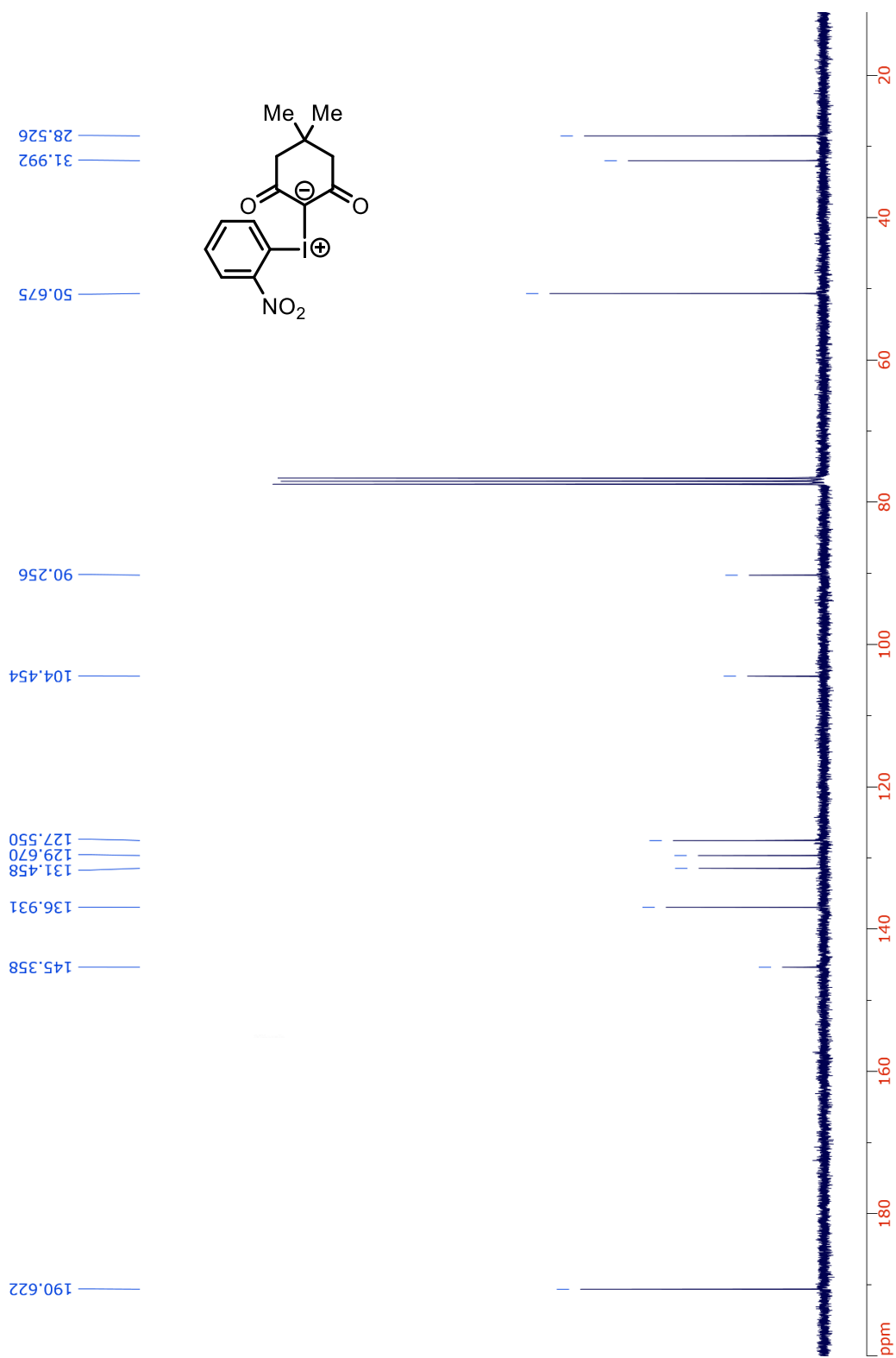
Figure 3.56. ^{1}H NMR (300 MHz, CDCl$_3$) of 2-((2-(2-hydroxypropan-2-yl)phenyl))(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium (**3-17l**)
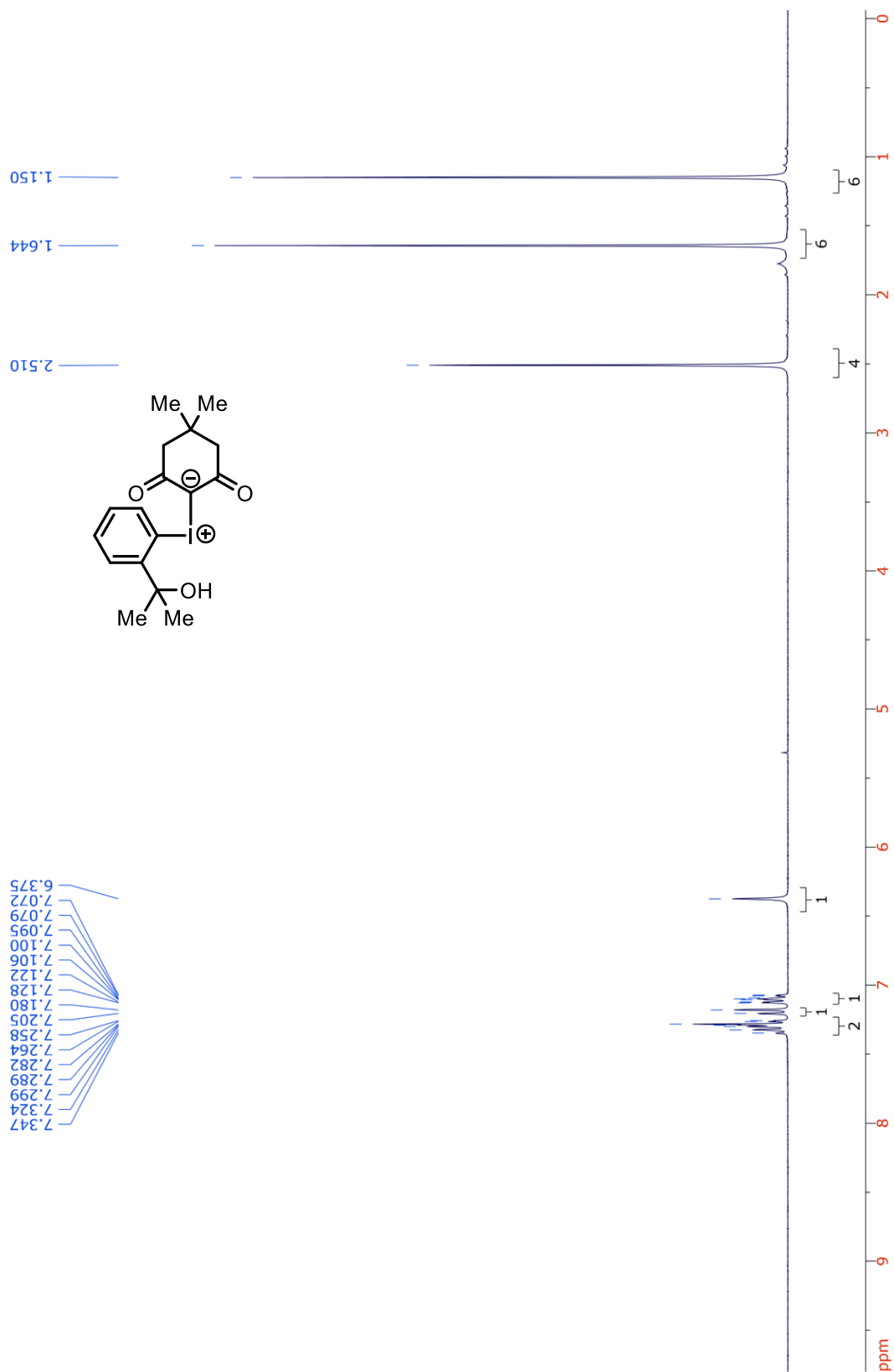
Figure 3.57. ^{13}C NMR (75 MHz, CDCl$_3$) of 2-((2-(2-hydroxypropan-2-yl)phenyl))(4,4-dimethyl-2,6-dioxocyclohexyl)iodonium (**3-17l**)

Figure 3.58. ^{1}H NMR (300 MHz, CDCl$_3$) of 1,1,1-trifluoro-3-(phenyl- λ^3-iodaneylidene)pentane-2,4-dione (**3-23**)

203
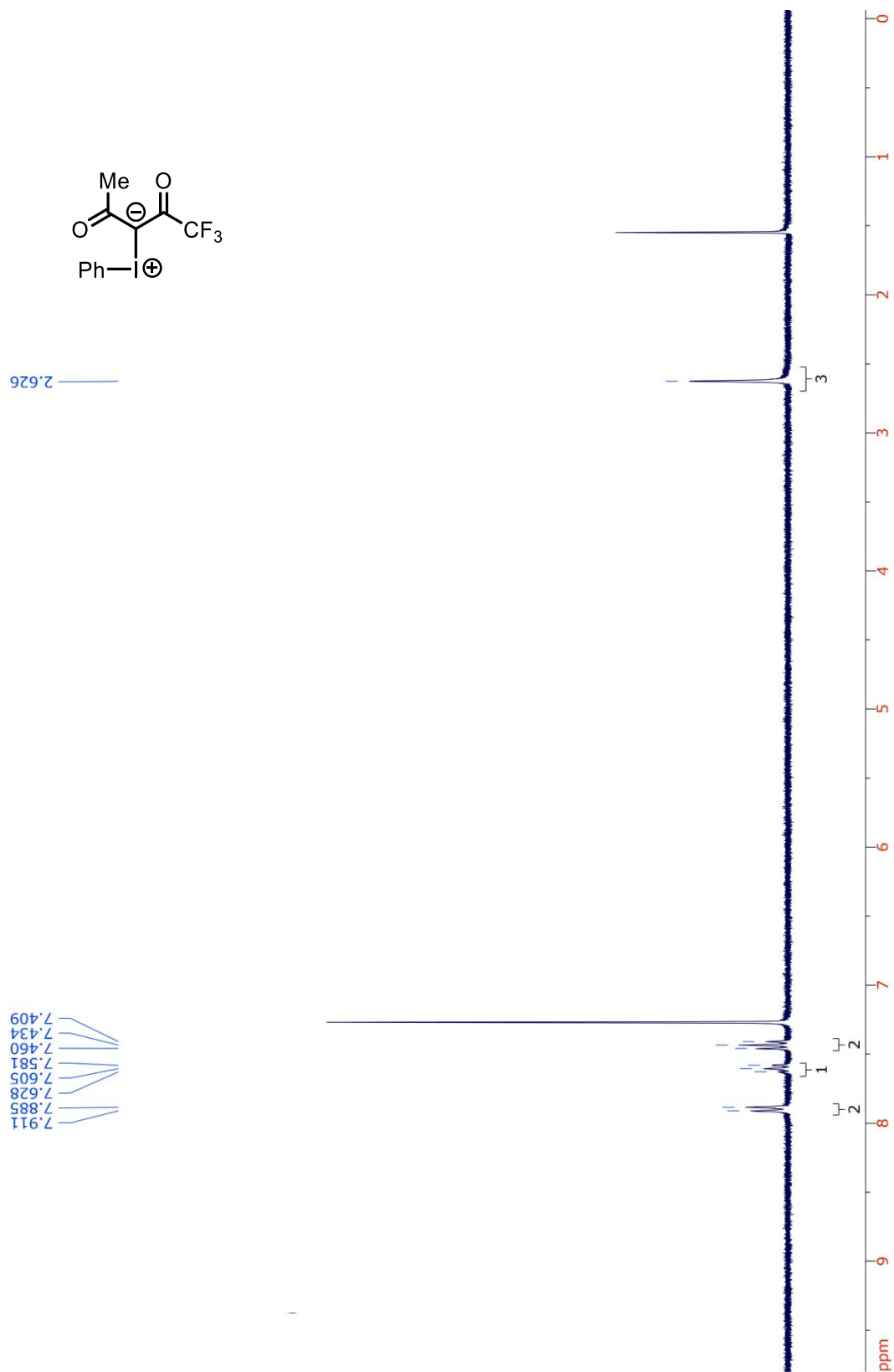
Figure 3.59. ^{19}F NMR (282 MHz, CDCl$_3$) of 1,1,1-trifluoro-3-(phenyl-λ^3-iodaneylidene)pentane-2,4-dione (**3-23**)

-67.981

Figure 3.60. ^{1}H NMR (300 MHz, CDCl$_3$) of ethyl 4,4,4-trifluoro-3-oxo-2-(phenyl–λ^3-iodaneylidene)butanoate (**3-24**)
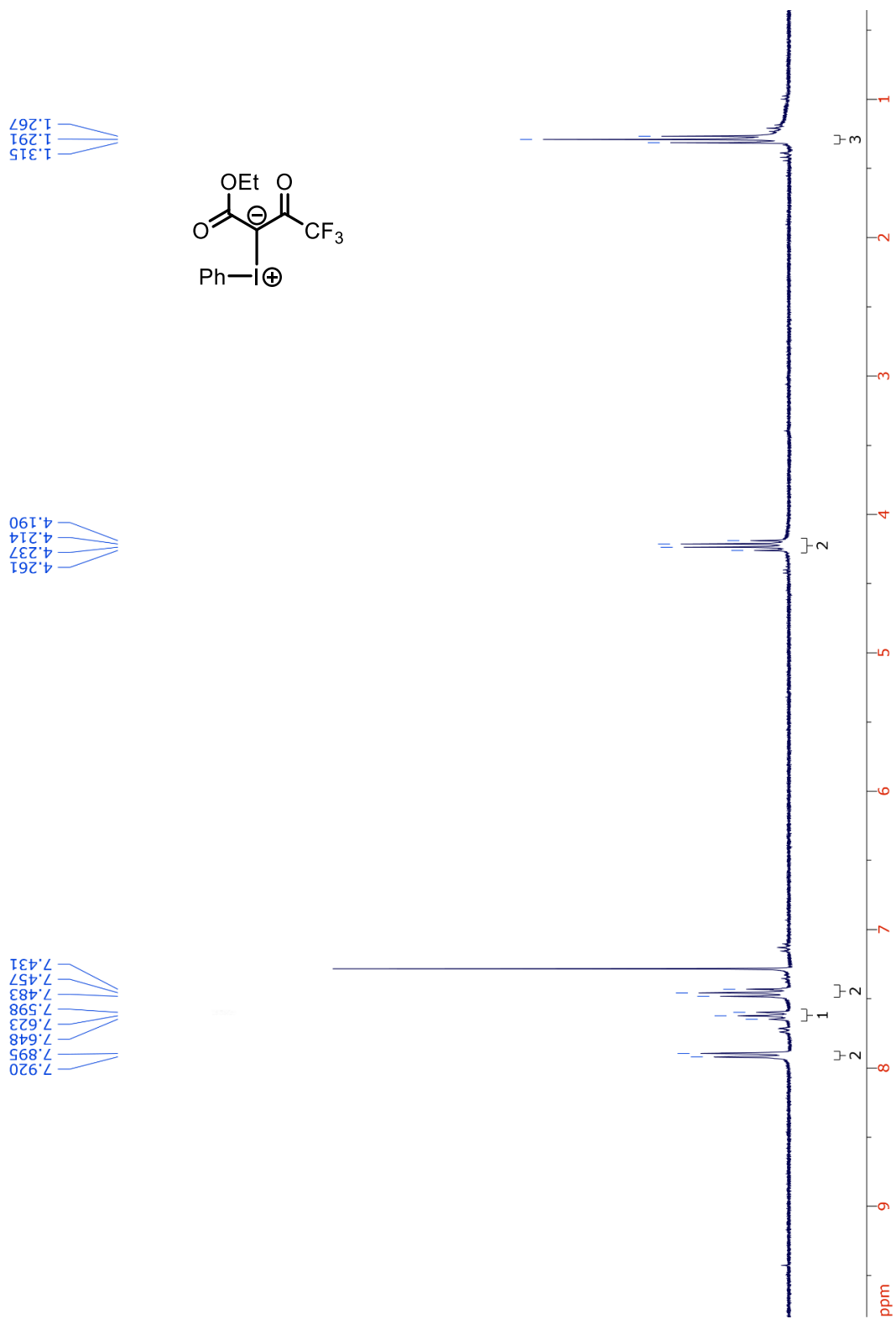
Figure 3.61. ^{19}F NMR (282 MHz, CDCl$_3$) of ethyl 4,4,4-trifluoro-3-oxo-2-(phenyl–λ^3-iodaneylidene)butanoate (**3-24**)

Figure 3.62. ^{1}H NMR (300 MHz, CDCl$_3$) of 1,1,1-trifluoro-3-((2-nitrophenyl)-λ^3-iodaneylidene)pentane-2,4-dione (**3-42**)
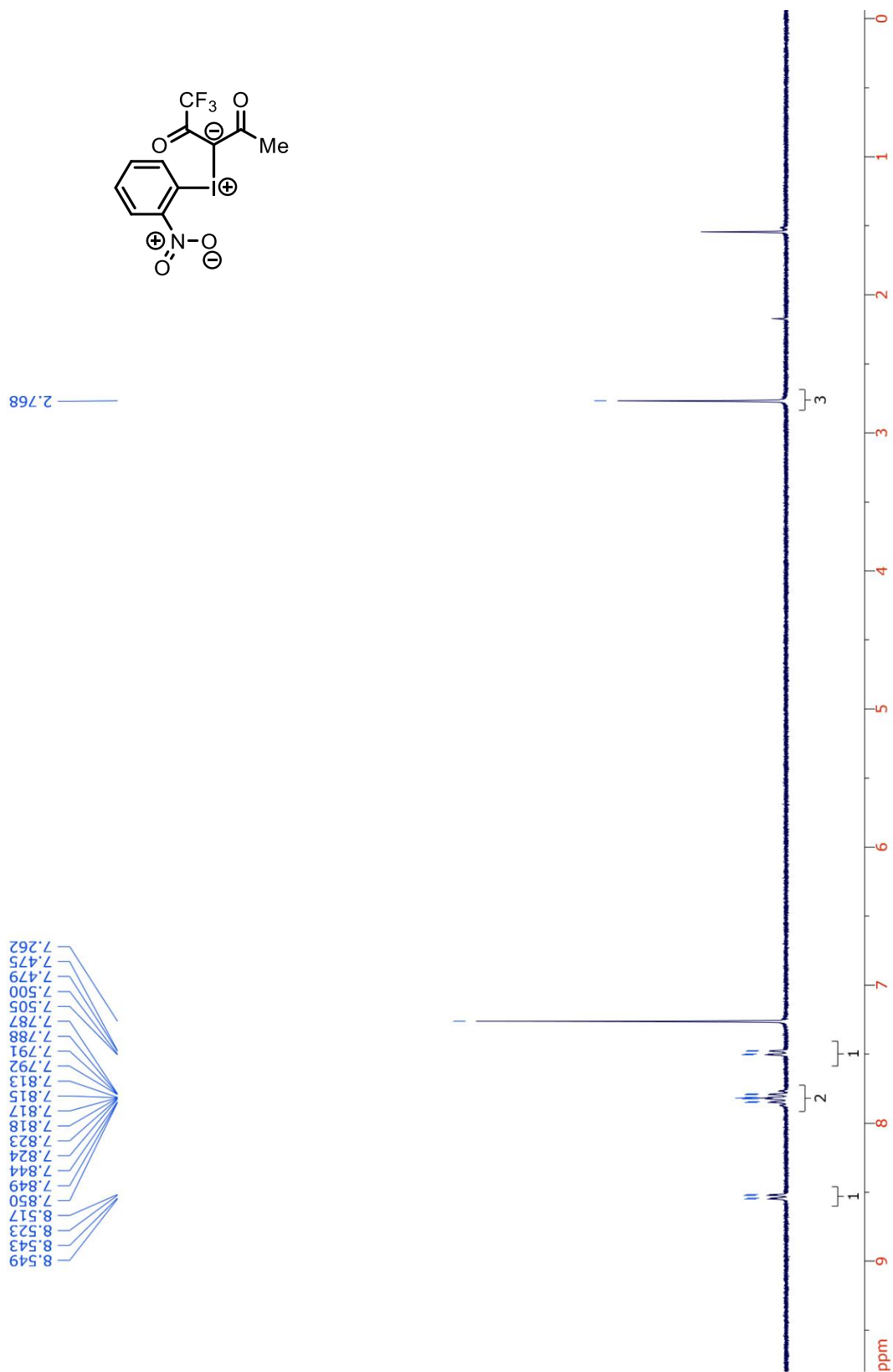
Figure 3.63. ^{19}F NMR (282 MHz, CDCl$_3$) of 1,1,1-trifluoro-3-((2-nitrophenyl)- λ^3-iodaneylidene)pentane-2,4-dione (**3-42**)

-68.834

Figure 3.64. ^{1}H NMR (300 MHz, CDCl$_3$) of 1,1,1-trifluoro-3-((2-(methoxymethyl)phenyl)-λ^3-iodaneylidene)pentane-2,4-dione (**3-43**)
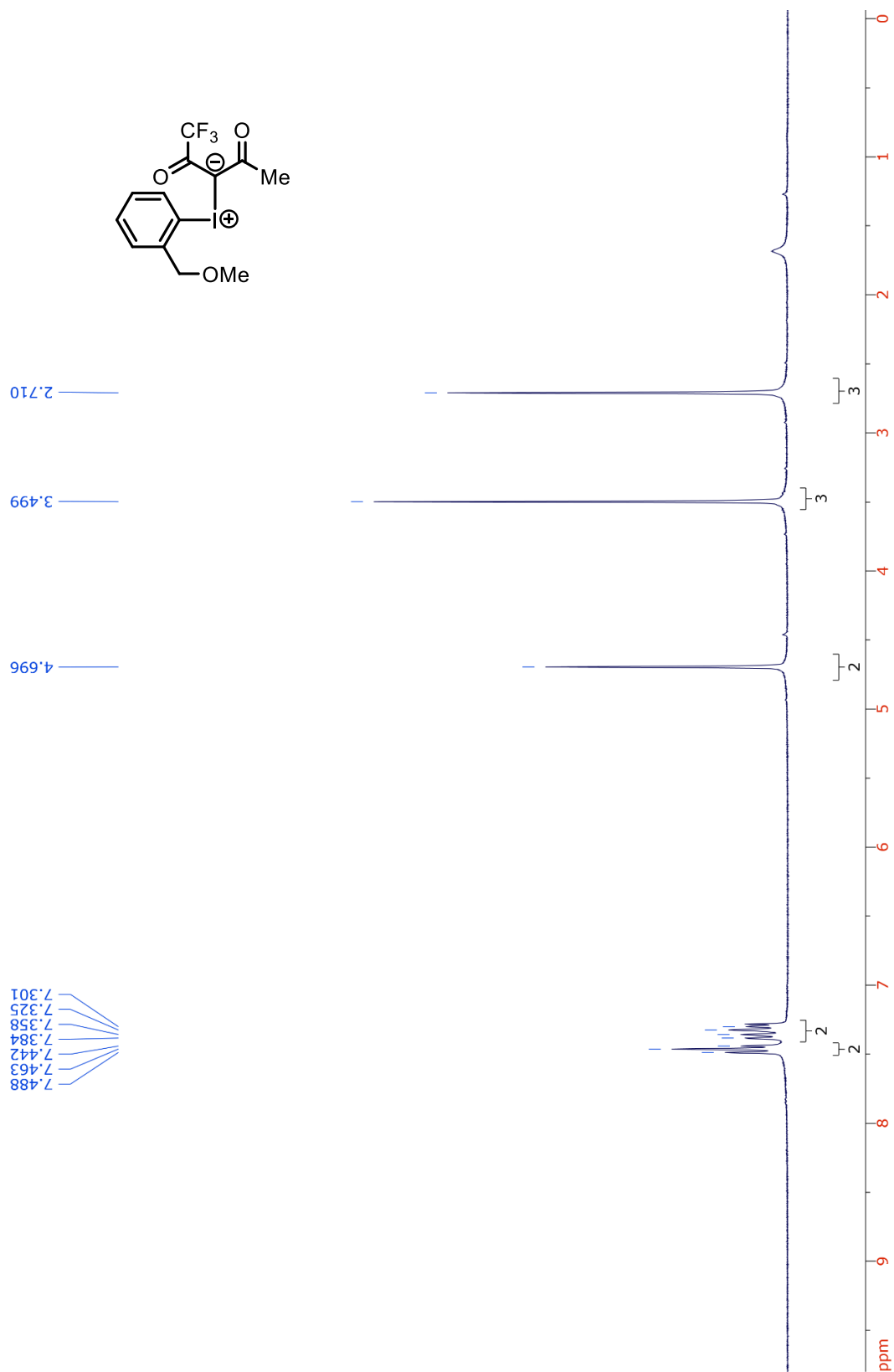
Figure 3.65. ^{19}F NMR (282 MHz, CDCl$_3$) of 1,1,1-trifluoro-3-((2-(methoxymethyl)phenyl)- λ^3-iodaneylidene)pentane-2,4-dione (**3-43**)
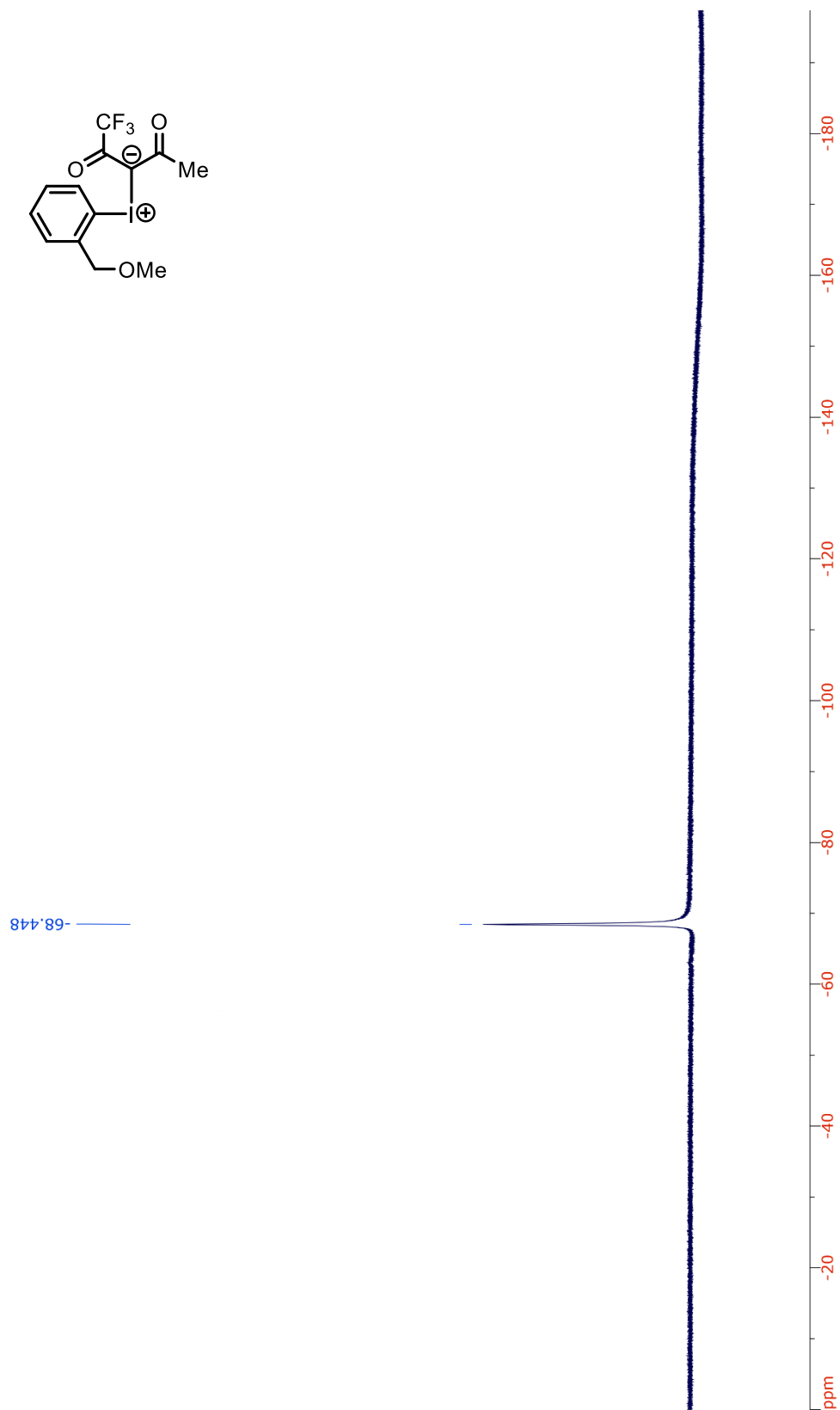

−69.448

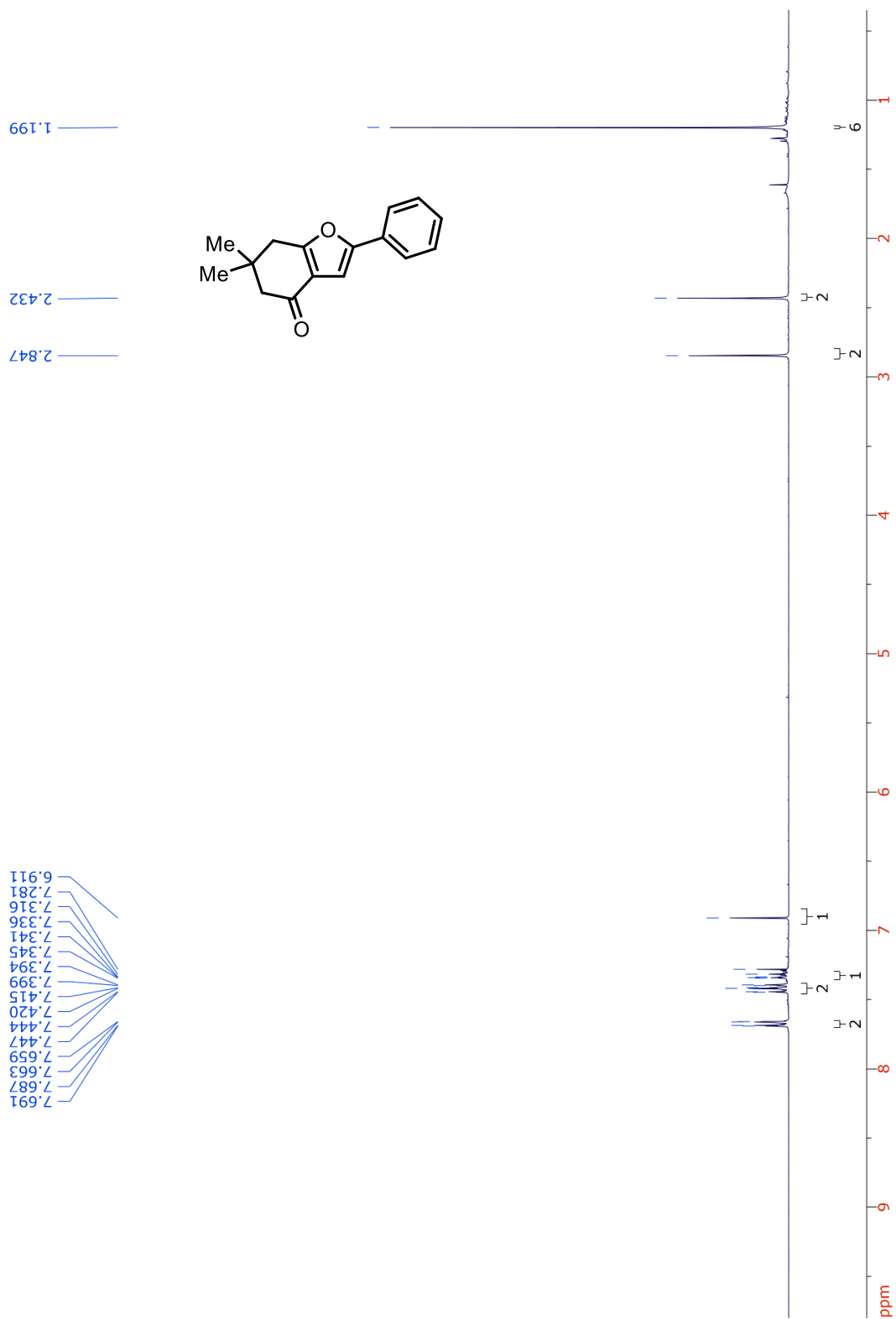**Figure 3.66.** ^{1}H NMR (300 MHz, CDCl$_3$) of 6,6-dimethyl-2-phenyl-6,7-dihydrobenzofuran-4(5H)-one (**3-25**)

Figure 3.67. ^{1}H NMR (300 MHz, CDCl$_3$) of 2-(4-methoxyphenyl)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5H)-one (**3-25a**)
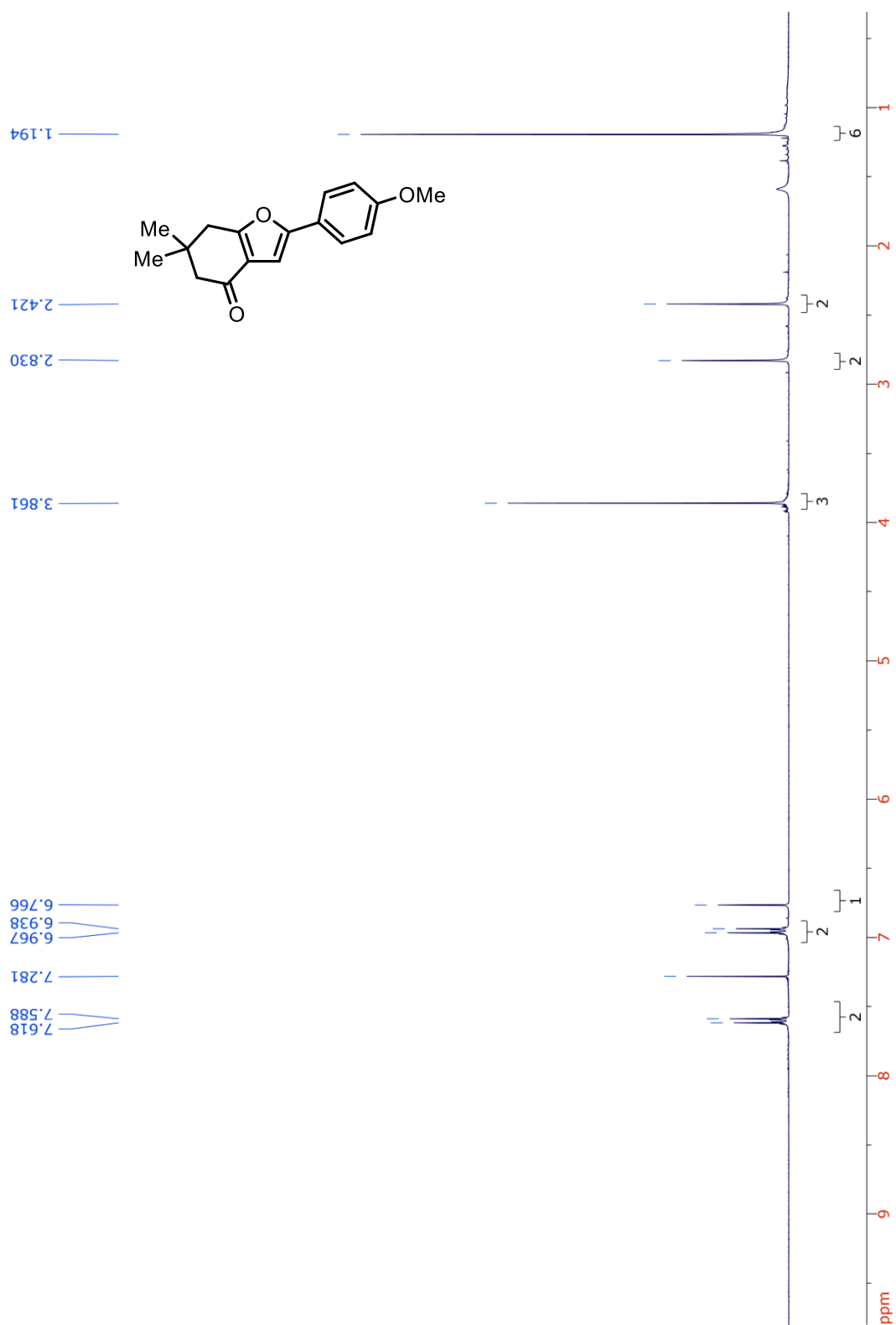
Figure 3.68. ^{1}H NMR (300 MHz, CDCl$_3$) of 2-(2-(dimethylamino)phenyl)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5H)-one (**3-25b**)
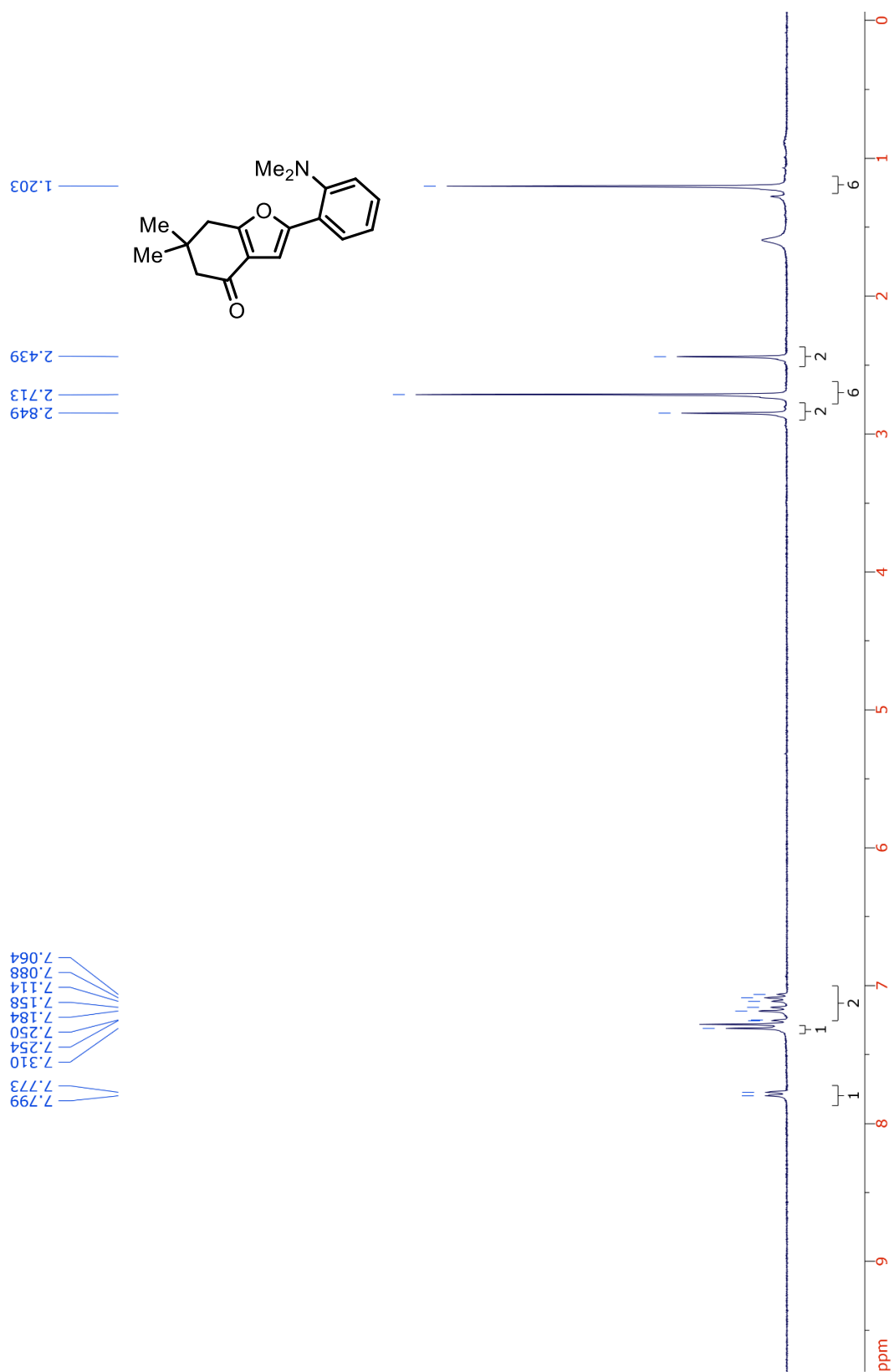

1.203

2.439

2.713
2.849

7.064
7.088
7.114
7.158
7.184
7.250
7.254
7.310

7.773
7.799

Figure 3.69. ^{13}C NMR (75 MHz, CDCl$_3$) of 2-(2-(dimethylamino)phenyl)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5H)-one (**3-25b**)

29.663
36.254
38.481
45.041
53.090

105.557

120.453
122.780
123.602
124.678
128.005
129.601

151.951
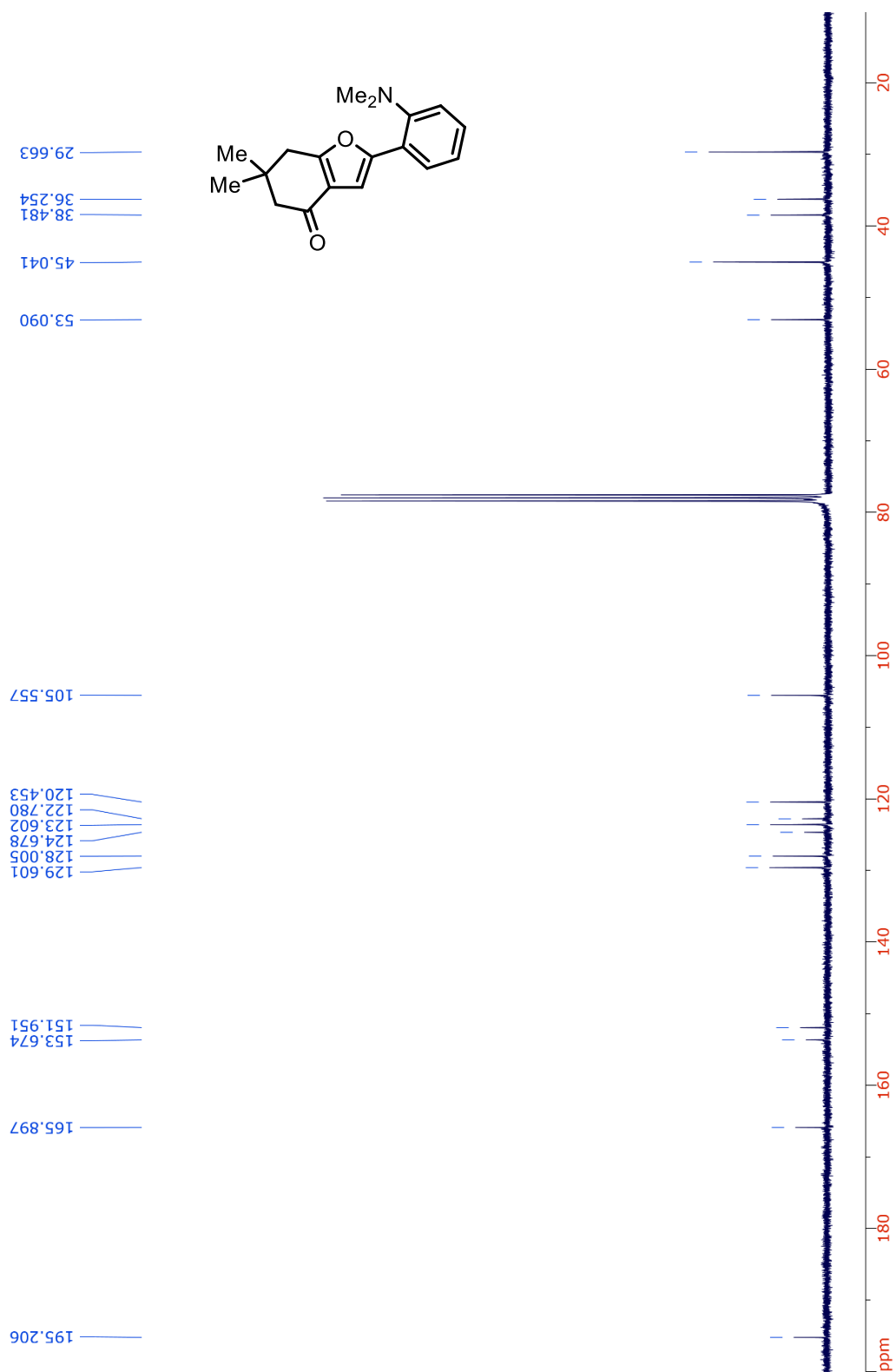153.674

165.897

195.206

Figure 3.70. ^{1}H NMR (300 MHz, CDCl$_3$) of 2-(4-(tert-butyl)phenyl)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5H)-one (**3-25c**)

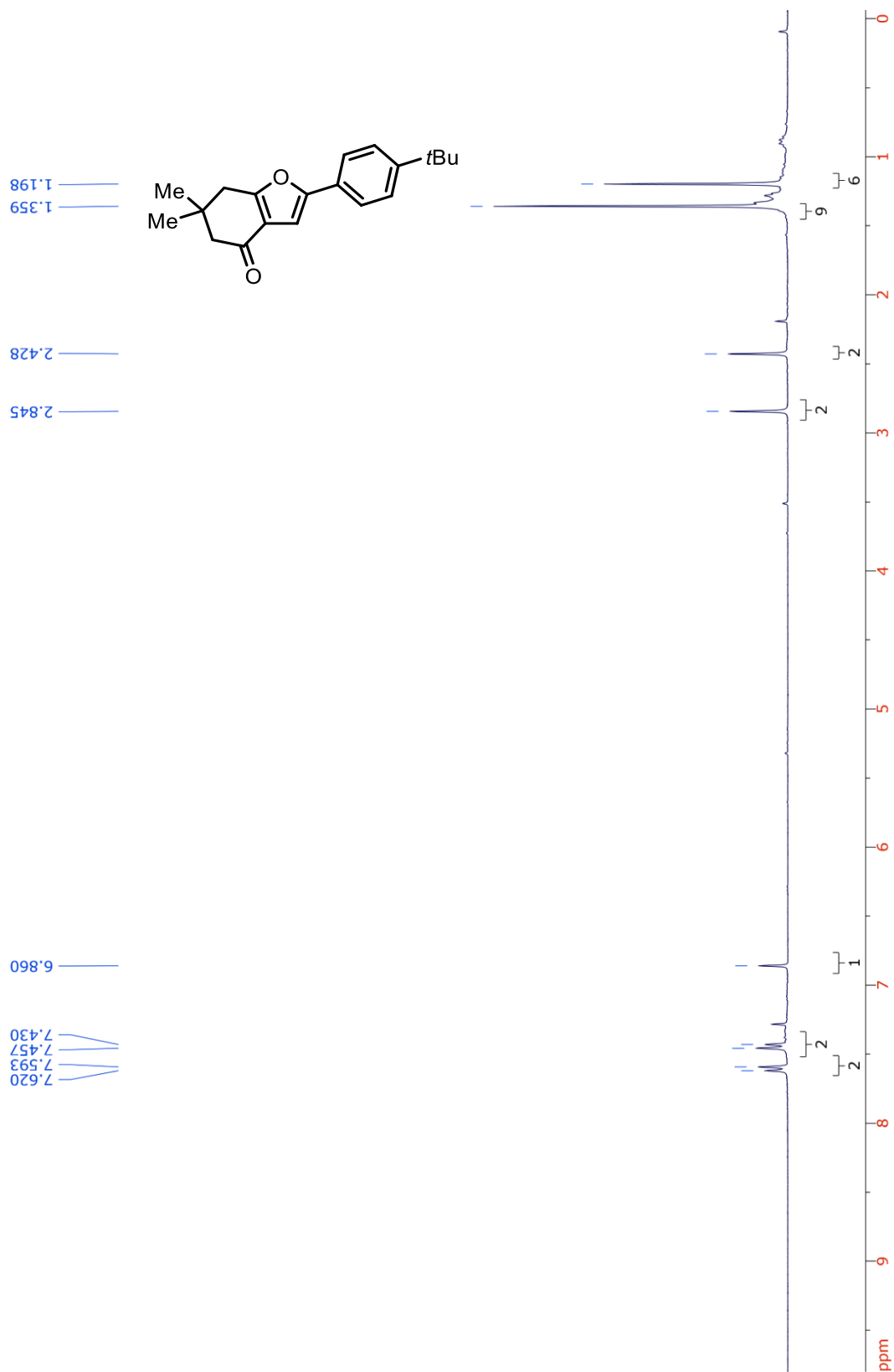**Figure 3.71.** ^{13}C NMR (75 MHz, CDCl$_3$) of 2-(4-(tert-butyl)phenyl)-6,6-dimethyl-6,7-dihydrobenzofuran-4(5H)-one (**3-25c**)
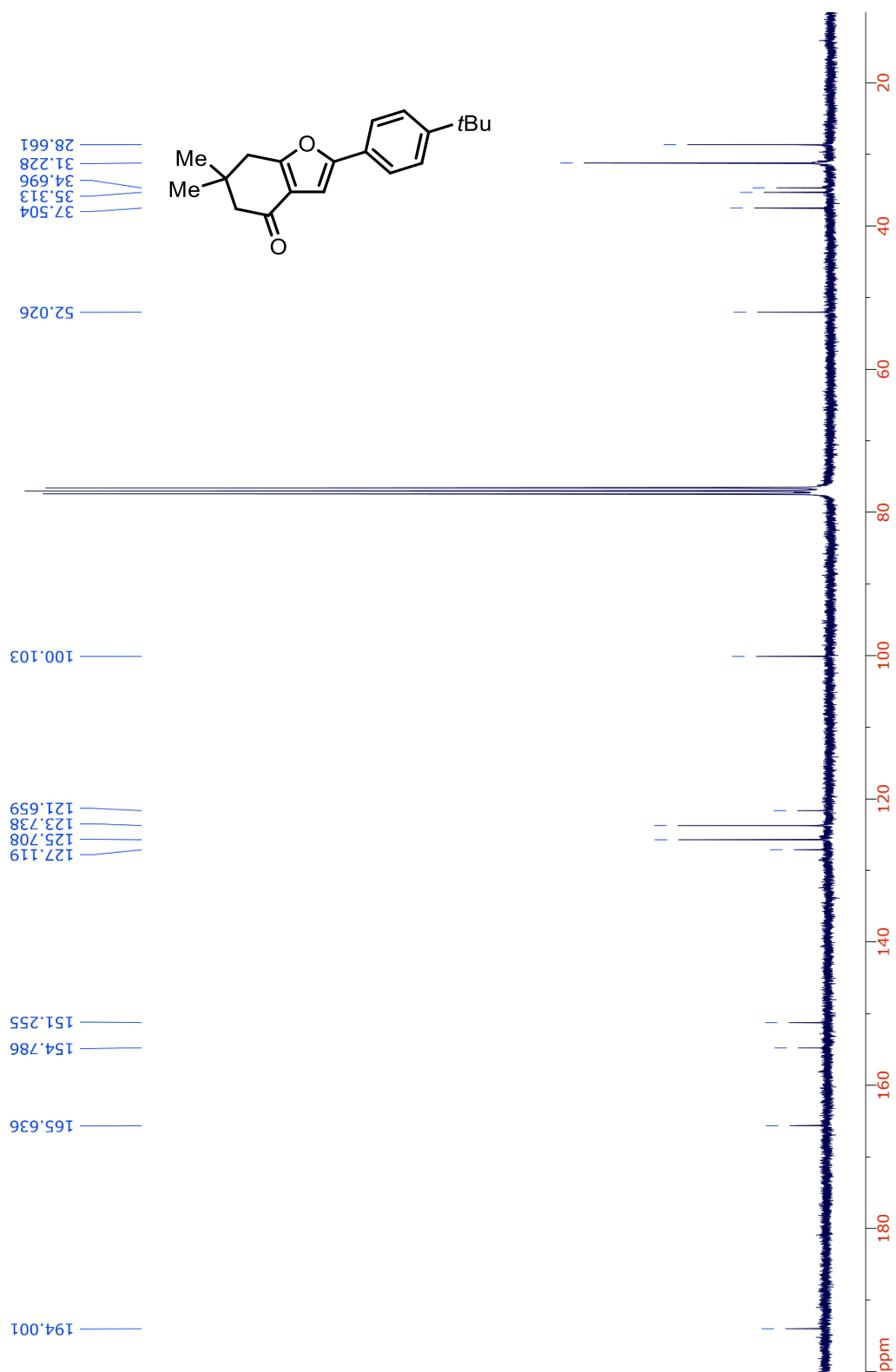

28.661
31.228
34.696
35.313
37.504

52.026

100.103

121.659
123.738
125.708
127.119

151.255
154.786

165.636

194.001

Figure 3.72. ^{1}H NMR (300 MHz, CDCl$_3$) of 1-(5-phenyl-2-(trifluoromethyl)furan-3-yl)ethan-1-one (**3-25**)

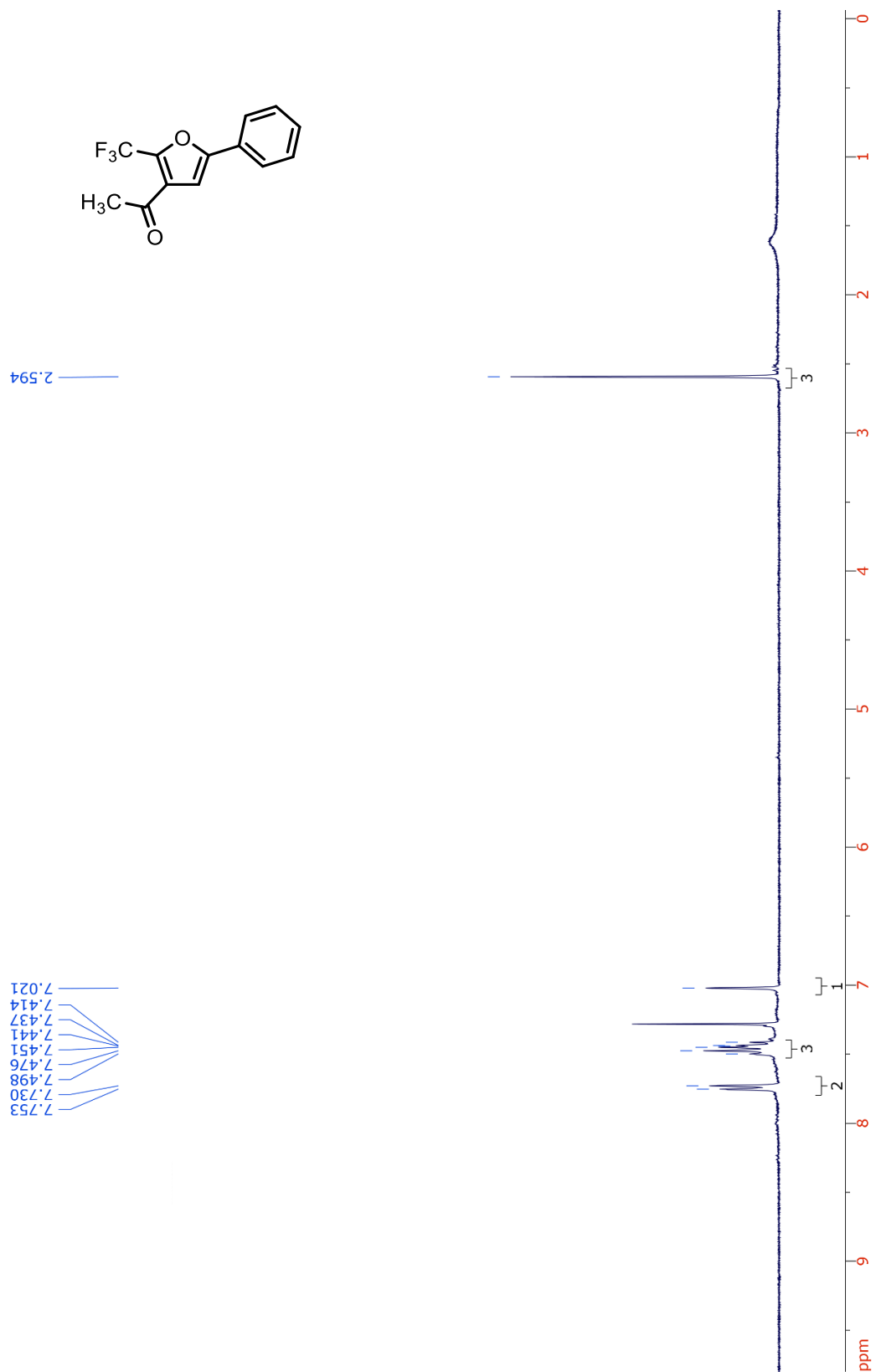**Figure 3.73.** ^{13}C NMR (600 MHz, CDCl$_3$, H and F decoupling) of 1-(5-phenyl-2-(trifluoromethyl)furan-3-yl)ethan-1-one (**3-25**)
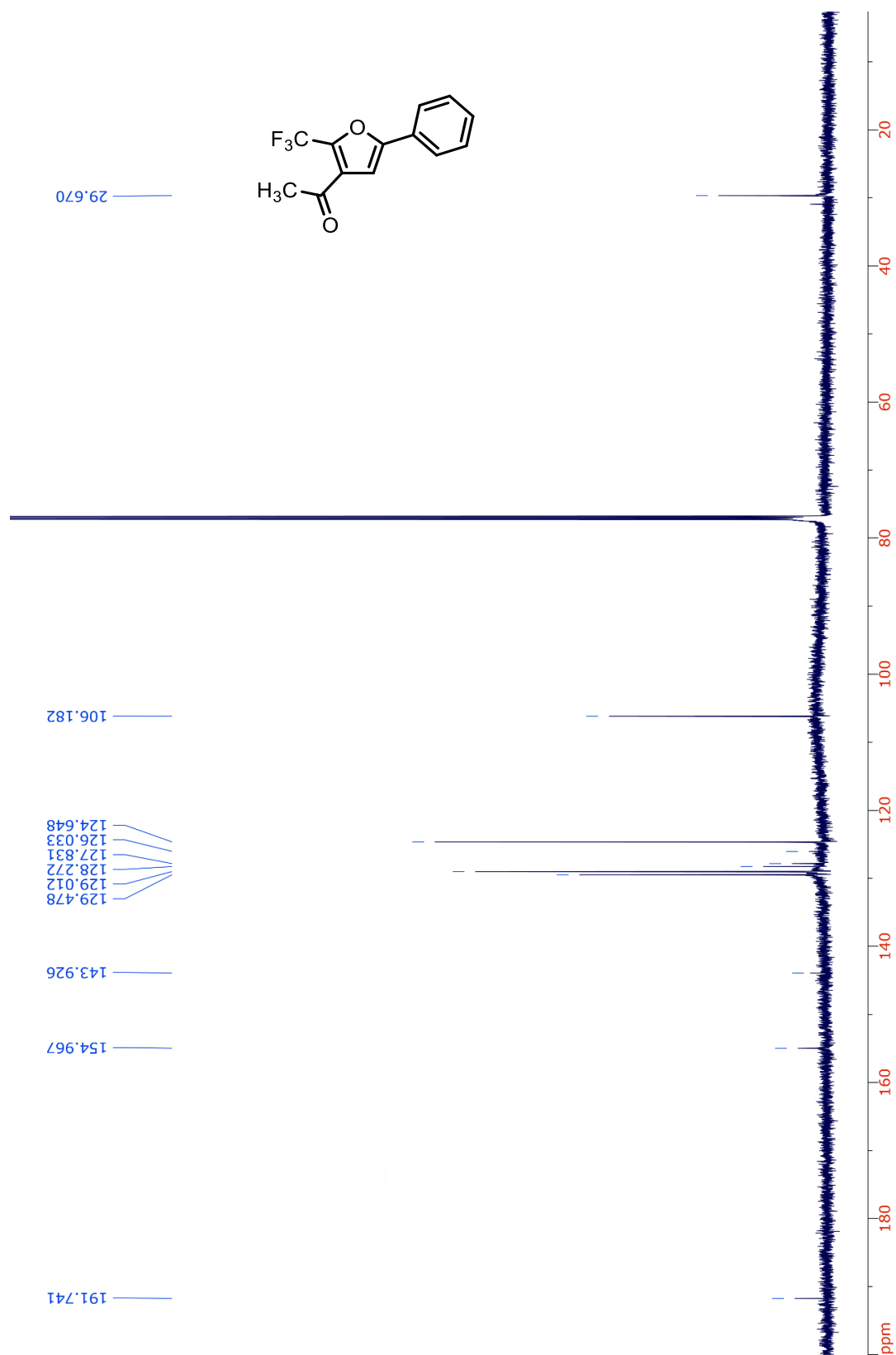

29.670

106.182

124.648
126.033
127.831
128.272
129.012
129.478

143.926

154.967

191.741

Figure 3.74. ^{19}**F** NMR (600 MHz, CDCl$_3$) of 1-(5-phenyl-2-(trifluoromethyl)furan-3-yl)ethan-1-one (**3-25**)

-60.624