HYPERVALENT IODINE REAGENTS FOR TOSYL TRANSFER REACTIONS IN ORGANIC SYNTHESIS

A THESIS
SUBMITTED TO THE FACULTY OF THE GRADUATE SCHOOL
OF THE UNIVERSITY OF MINNESOTA
BY

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IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
MASTER OF SCIENCE

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July, 2015

ACKNOWLEDGMENTS

I would like to extend my gratitude to the following individuals for their support in the research involved with this thesis starting with my amazing wife Jessica Klasen who has shown unwavering support of my goals during my studies and research here at the University of Minnesota - Duluth. I would like to thank my colleagues Eranda Maligaspe, Steve Koski, Brent Kastern, Khiem Nguyen, Jonathan Fuchs, Paul Vue, Mack Liebl, Cody Makitola, Nate Erickson, Tony Wertish, Cole Holstrom and Mahtab Fathi-Rasekh for their support, time and chemical insights. Most importantly, I would like to thank Dr. Viktor Zhdankin, Dr. Akira Yoshimura, and Dr. Victor Nemykin for their guidance, flexibility, and support which has been instrumental to my learning, research, and career goal of becoming a STEM educator during my time here at UMD.

I would like to express my gratitude for the financial support provided by the National Science Foundation (CHE-1262479) as well as for access to important instrumentation used for this research here through the Department of Chemistry & Biochemistry at the University of Minnesota – Duluth.

• Varian ^{UNITY} INOVA 500 MHz NMR

• Agilent Technologies 7890A GC System with 5975C VL MSD

• Rigaku Rapid II single crystal X-ray diffractometer

• Bruker micrOTOF-Q III with Thermoscientific UltiMate 3000 UHPLC

I would like to give a special thanks to my friends and family who mean so much to me for their support.

DEDICATION

I would like to dedicate this thesis to my wife and son

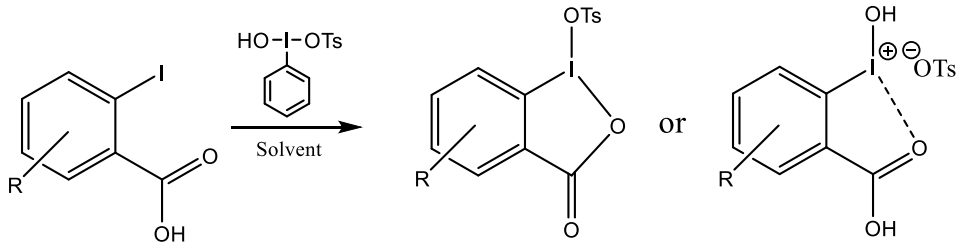
Jessica Ruth Klasen

and

Elliott Scott Klasen

ABSTRACT

In recent years, organohypervalent iodine compounds have emerged as environmentally friendly and efficient reagents for various synthetically useful oxidative transformations. The purpose of this research is to take a closer look at newer five membered heterocyclic hypervalent iodine compounds similar to the hydroxy(tosyloxy)iodobenzene (HTIB) studied by G.F. Koser in the 1980's, which utilized different variations of iodobenzene with different functional groups in the *para*-position of a benzene ring in order to perform ligand transfer reactions. Utilizing Koser's framework new heterocyclic hypervalent iodine reagents have been synthesized using 2-iodobenzoic acid as well as other similar substrates as a starting material along with HTIB.



Different variations of these heterocycles have been synthesized in order to analyze the structural and kinetic nature of these less studied derivatives and their overall reactivity for selective oxidations and tosyl-transfer reactions in organic synthesis.

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ABBREVIATIONS

HTIB – Hydroxy(tosyloxy)Iodobenzene

PET – Positron Emission Tomography

RAI – Radioactive Iodine

IDB – (Dichloroiodo)benzene

DIB – (Diacetoxyiodo)benzene

BTI – [Bis(trifluoroacetoxy)iodo]benzene

BPI – Diphenyliodoium Chloride

IBA – 2-Iodosobenzoic acid

IBX – 2-Iodoxybenzoic acid

DMP – Dess-Martin Periodinane

PTSA – *p*-Toluenesulfonic acid

p-TsOH – *p*-Toluenesulfonic acid

HOMO – Highest Occupied Molecular Orbital

3c-4e – 3 center 4 electron bond

OTs – Tosylate Group

Ts – *p*-toluene sulfonyl

OTf – Triflate Group

Tf – Trifluoromethane sulfonyl

OMs – Mesylate group

Ms – Methane sulfonyl

ONs – Nosylate group

Ns – *p*-Nitrobenzene sulfonyl

OCs – (+)-10-Camphorsulfonyloxy group

Cs – (+)-10-Camphorsulfonyl

NBS – *N*-bromosuccinimide

NCS – *N*-chlorosuccinimide

*m*CPBA – *meta*-chlroperoxybenzoic acid

DMF – Dimethylformamide

HFIP – Hexafluoroisopropanol

EAS – Electrophilic Aromatic Substitution

EDG – Electron Donating Group

EWG – Electron Withdrawing Group

THF – Tetrahydrofuran

DCM – Dichloromethane or Methylene Chloride

DMSO – Dimethyl Sulfoxide

NMR – Nuclear Magnetic Resonance

TMS – Tetramethylsilane

DBU – 1,8-Diazabicyclo[5.4.0]undec-7-ene

ABX – 1-Acetoxy-1,2-benziodoxle-3(1*H*)-one

TFE – 2,2,2-Trifluoroethanol

Section 1:

Review

1.1. Introduction to Iodine and Polyvalent Iodine Compounds

Iodine is a unique element in the periodic table in that it is the largest nonmetal, least electronegative and most polarizable out of all the halogens. Since the initial discovery of iodine by Bernard Courtois in 1811, iodine has been found to be biologically important for stimulating tissue and cell growth and has found a number of applications including medical imaging technology using Positron Emission Tomography (PET) in conjunction with radioactive iodine (RAI) also known as I-131, which can also be used for cancer treatment in human thyroids. Other applications include the use of silver iodide for cloud seeding in agriculture or for the development of film photographs. Many pharmaceuticals and biological compounds have an iodine component and iodine containing compounds have successfully been used as versatile oxidants in organic synthesis for a range of products including biologically active reagents for over 200 years.[1–4] The versatility of iodine is due in part to its large size and electronic nature that allows iodine to exist in a large number of different oxidation states (-1, +1,+3,+5,+7) much like a transition metal, and easily exists with an expanded octet. These characteristics allow iodine to form chemical compounds commonly referred to as polyvalent iodine compounds or hypervalent iodine compounds.

In general, the Martin-Arduengo system (*N*-*X*-*L*) for designating hypervalent molecules is used when classifying different types of polyvalent iodine complexes, where the system identifies the number of valence electrons around the central atom (*N*), the

chemical symbol of central atom (*X*), and the number of ligands joined to the central atom by sigma bonds (*L).* Figure 1 below, show the geometries associated with different polyvalent iodine compounds along with their Martin-Arduengo classifications.[1]

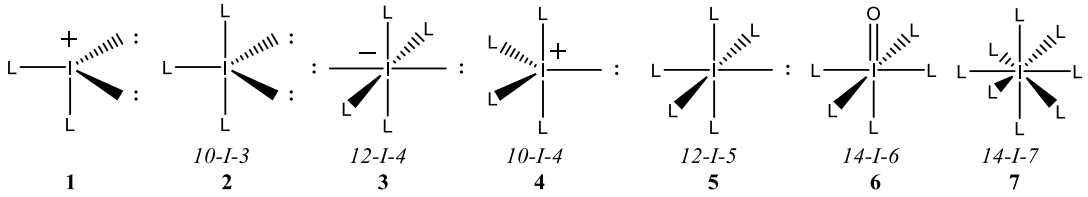


Figure 1: Structure of polyvalent iodine compounds with Martin-Arduengo classification.

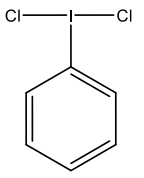
As mentioned previously, due to iodine's large size and electronic nature, it can exist in higher oxidation state with expanded octets to form different variations of polyvalent iodine species. For example structure **2** is considered a variation of a trivalent iodine(III) species (λ^3-iodanes). Structure **1** as depicted only contains eight valence electrons but is the typical structure of an iodonium salt, which is associated with an anionic ligand making it a trivalent salt. Structures **4** and **5** are considered variations of pentavalent iodine(V) species (λ^5-iodanes). Structures **6** and **7** are examples of heptavalent iodine(VII) species, which are only known to exist as different fluoride species or as different derivatives of periodic acid (HIO_4).[1]

The first example of a synthesized polyvalent iodine compound was isolated by German chemist C. Willgerodt by reacting iodobenzene with chlorine gas to form (dichloroiodo)benzene (**8**) in 1886. Many other important examples were synthesized shortly after including (diacetoxyiodo)benzene in 1892 (**10**), iodosylbenzene in 1892 (**14**), and 2-iodooxybenzoic acid in 1893 (**16**) as well as reported examples of diaryliodonium salts in 1894. By 1914 over 500 different polyvalent iodine compounds

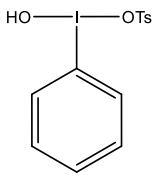
were synthesized, which were described in a book published by Willgerodt. However, the rate of research on polyvalent iodine compounds slowed significantly after its initial discovery with only three significant reviews that were published by Sandin (1943) and Banks (1966), and another by Beringer providing comprehensive tabulation of physical properties of polyvalent iodine compounds in 1956.[1] Table 1 lists some of the most common hypervalent iodine reagents with their common abbreviations and classes.

Table 1: Common Pentavalent and Trivalent Iodine Reagents used in Organic Synthesis.

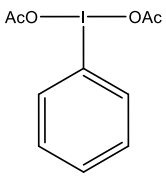
Examples of λ^3-Iodanes



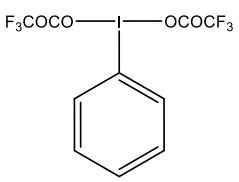
8
(Dichloroiodo)benzene **(IDB)**
Chloride



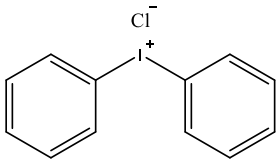
9
Hydroxy(tosyloxy)iodobenzene **(HTIB)**
Sulfonate



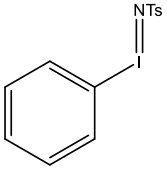
10
(Diacetoxyiodo)benzene **(DIB)**
Carboxylate



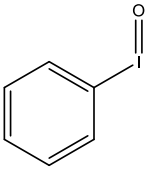
11
[Bis(trifluoroacetoxy)iodo]benzene **(BTI)**
Carboxylate



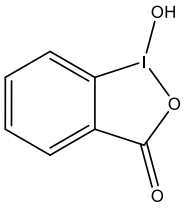
12
Diphenyliodonium Chloride **(DPI)**
Iodonium Salt



13
(*N*-Tosylimino)phenyliodinane
imide

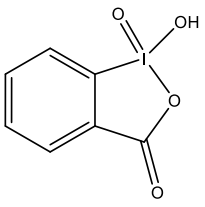


14
Iodosylbenzene
Iodosylarene

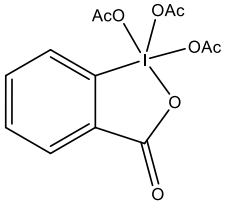


15
2-Iodosobenzoic acid **(IBA)**
Benziodoxle

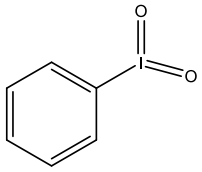
Examples of λ^5-Iodanes



16
2-Iodoxybenzoic acid **(IBX)**
Benziodoxle

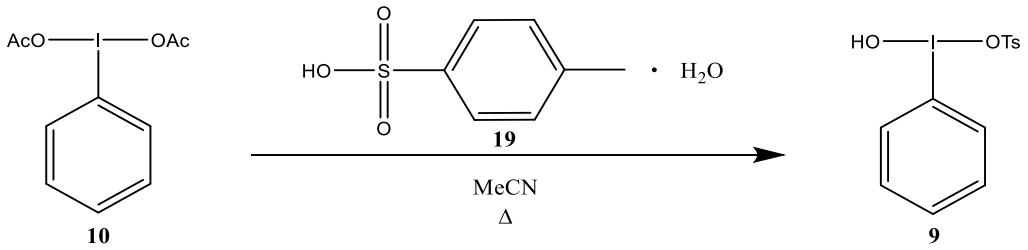


17
Dess-Martin periodinane **(DMP)**
Benziodoxle



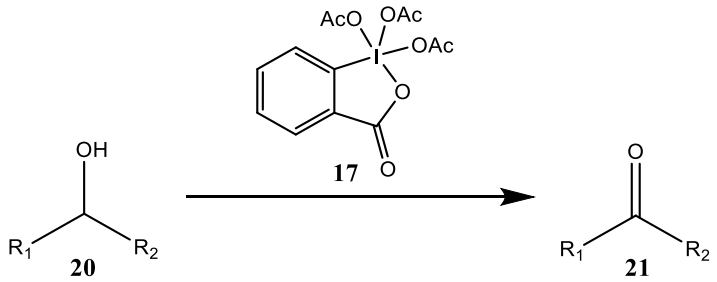
18
Iodoxybenzene
Iodylarene

Starting in the 1980's the area of polyvalent iodine chemistry experienced a renaissance with researchers discovering new applications for previously synthesized polyvalent iodine compounds. For example, 2-iodoxybenzoic acid (**16**) found new catalytic applications over a 100 years after its initial discovery. HTIB or hydroxy(tosyloxy)iodobenzene (**9**), which was discovered by Neilands and Karele in 1970, is synthesized by reacting diacetoxyiodobezene (**10)** with *p*-toluenesulfonic acid monohydrate or PSTA (**19**), as shown in Scheme 1, and has been found to be useful for a number of useful oxidative transformations.[1]



Scheme 1

A number of other hypervalent iodine compounds were discovered in the 1980's, including new variations of benziodoxles, iodonium salts, and Dess-Martin Periodinane (**17**) or DMP. DMP is one of the most commonly known polyvalent iodine reagents due its ability to selectively oxidize primary and secondary alcohols (**20**) to their perspective ketones and aldehydes (**21**) as shown in Scheme 2.[1]



Scheme 2

1.2. General Reactivity and Structure of Polyvalent Iodine Compounds

These polyvalent iodine compounds are of interest to researchers due in large part to their mild-moderate oxidative behavior that has reactivity similar to their transition metal counterparts. However, hypervalent iodine compounds with their low toxicity make them an environmentally friendly alternative to similar transition metals like mercury, lead, osmium, chromium and others without dealing with the toxic heavy metal congeners. The reactivity pattern of hypervalent iodine is commonly referred to in terms of oxidative addition, ligand exchange, reductive elimination, and ligand coupling similar to transition metals. A generic variation of this process with hypervalent iodine compounds in shown below in Figure 2. The reactivity of iodobenzene is able to undergo oxidative additions to form stable complexes and then also acts as a strong leaving group during the reductive elimination of a hypervalent iodine complex. The presence of iodobenzene as a leaving group allows for a number of S_N2 reactions by nucleophilic displacement, for example, makes these reagents a powerful tool for selective oxidations and comparable to transition metals in many regards.[1,2]

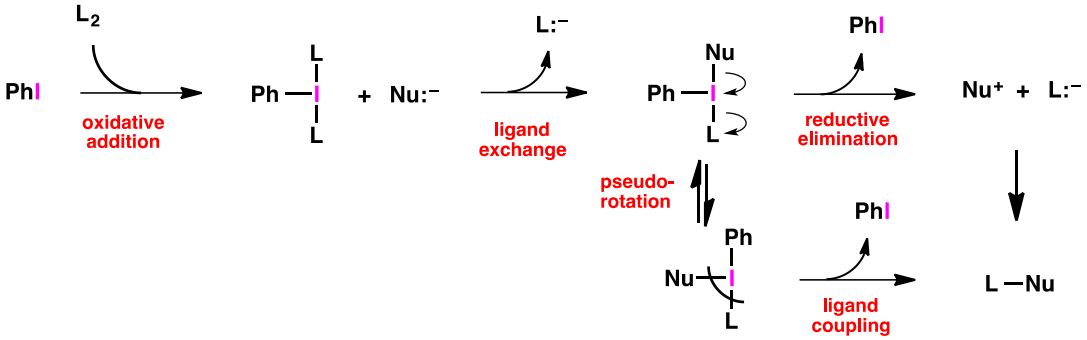


Figure 2: General reactivity of Hypervalent iodine complexes.

The hypervalent bonding of these compounds is typically described by molecular orbital theory involving a three-center-four-electron bond (3c-4e). Both G.C. Pimentel and R.E. Rundle independently proposed this idea based on molecular orbital theory in 1951, where there are two bonding electrons, and two nonbonding electrons in the highest occupied molecular orbital (HOMO) across the 3c-4e bond for L-X-L causing these Hypervalent compounds to be highly polarized in nature with a charge distribution of almost -0.5 on each ligand (L) and +1.0 on the central atom (X) as depicted below.

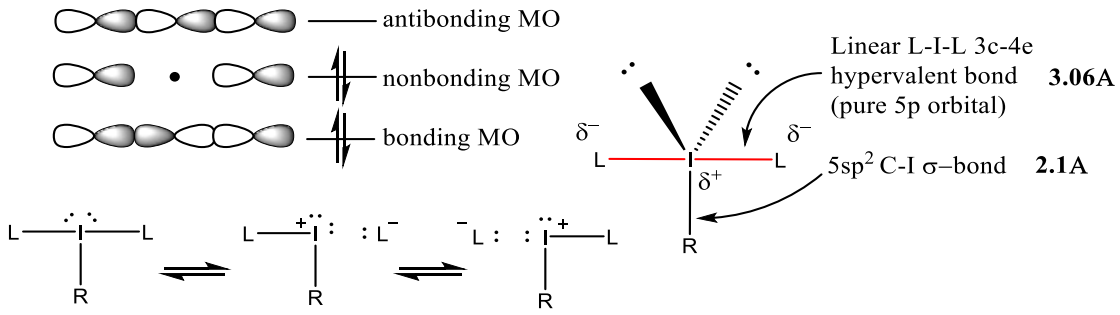


Figure 3: Molecular orbital description of 3c-4e bonds in trivalent iodine complexes.

Figure 3 represents the typical description for a trivalent iodine complex where the molecular structure is T-shaped in nature allowing for the linear L-I-L 3c-4e bond to form with the two electronegative ligands in the axial position of the distorted trigonal bipyramidal structure and the less electronegative R group to exist in the equatorial position. Pentavalent iodine structures are similar, except they consist of two linear L-I-L 3c-4e bonds that are orthogonal to each other to form with 4 electronegative ligands in a distorted pseudo-octahedral geometry as depicted below in Figure 4.

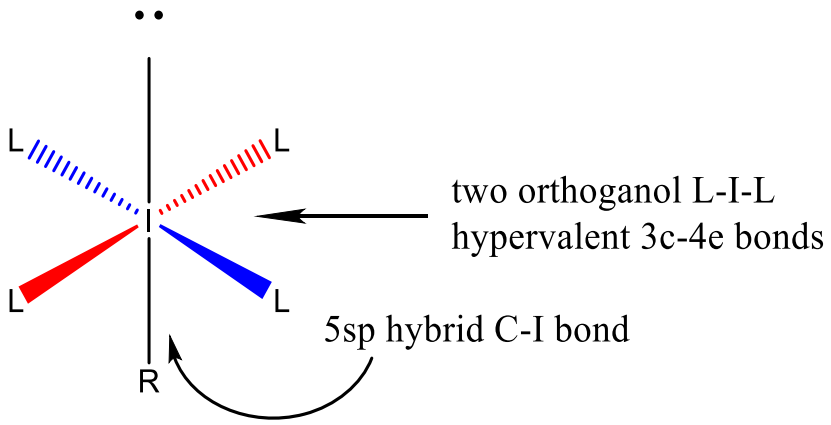
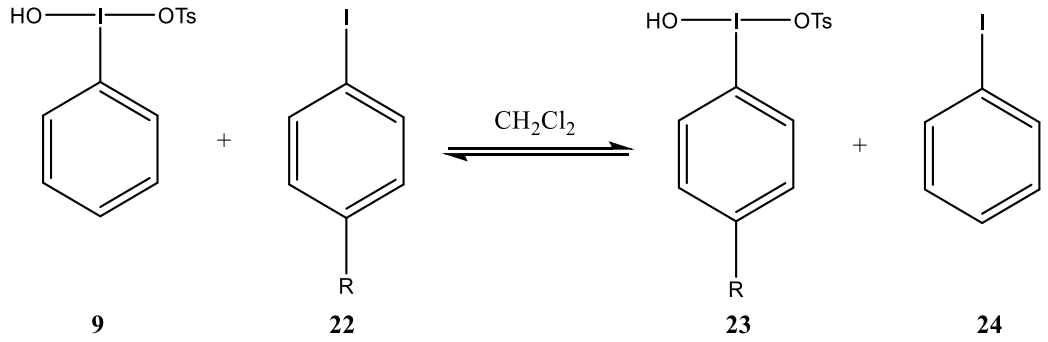


Figure 4: Description of bonding in pentavalent iodine complexes.

The structural chemistry of these polyvalent iodine compounds is governed by noncovalent electrostatic interactions due to the highly polarized 3c-4e bond and is attributed to the general reactivity of these compounds.[1]

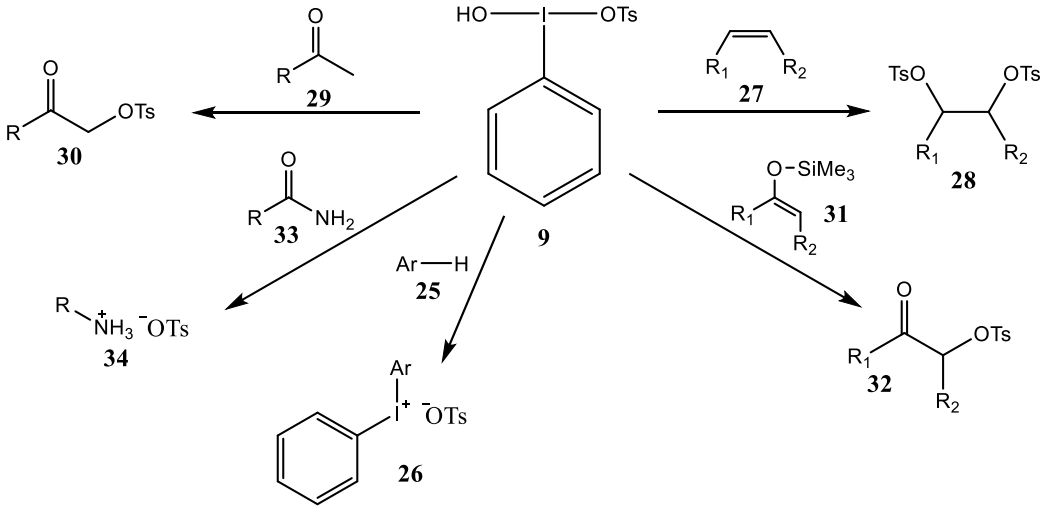
1.3 Introduction to the Synthetic Utility of HTIB

As previously mentioned, hypervalent iodine compounds are known for their mild to moderate oxidative behavior, which has been explored in order to selectively oxidize specific functional groups or to perform a ligand transfer reaction. Compounds like hydroxy(tosyloxy)iodobenzene are sulfonates have been found to have special applications for a range of oxytosylations, phenyliodination, and Hofmann-type rearrangements.[5,6] Gerald F. Koser in 1980 published an article on the mild oxidative behavior of HTIB (**9**), also known as Koser's Reagent, on aryl iodides (**22**) through a ligand transfer reaction as depicted below in Scheme 3 to produce new *p*-substituted variations of HTIB (**23**) and iodobenzene as a by-product of HTIB (**24**).[6]



Scheme 3

In a short period of time, Koser and others continued exploring the synthetic utility of HTIB (**9**) in the 1980's as a new reagent for iodonium salt synthesis (**26**) from arenes (**25**),[7] *cis*-tosyloxylations of alkenes (**27,28**),[8] α-tosyloxylation of ketones (**29,30**),[9] α-sulfonyloxylation of carbonyl compounds (**32**) using trimethylsilyl enol ethers (**31**),[7] as well as Hoffman type preparation of amine salts (**34**) using various aliphatic amides (**33**)[11,12], which are some of common applications for Koser's reagent that will be discussed in further detail. Scheme 4 below shows some of these general reactions.



Scheme 4

Zefirov's reagent $O(I(Ph)OSO_3CF_3)_2$ reacts in a similar manner as HTIB (Koser's reagent) with alkenes in order to produce *cis*-bis triflates.[5] Other variations of HTIB are commonly produced by substituting the tosylate ligand (**9)** with other anionic ligands such as mesylate (**35**), triflate (**36**), nosylate (**37**), (+)-10-camphorsulfonyloxy (**38**) in order to introduce other ligands to substrates during ligand transfer reactions, adjust selectivity, or improve solubility.[2,12–15] Examples of these sulfonates are shown in Figure 5. The most common method for preparing these derivatives of HTIB uses DIB (**10**) and substituting the appropriate sulfonic acid in acetonitrile as described in Scheme 1.[2]

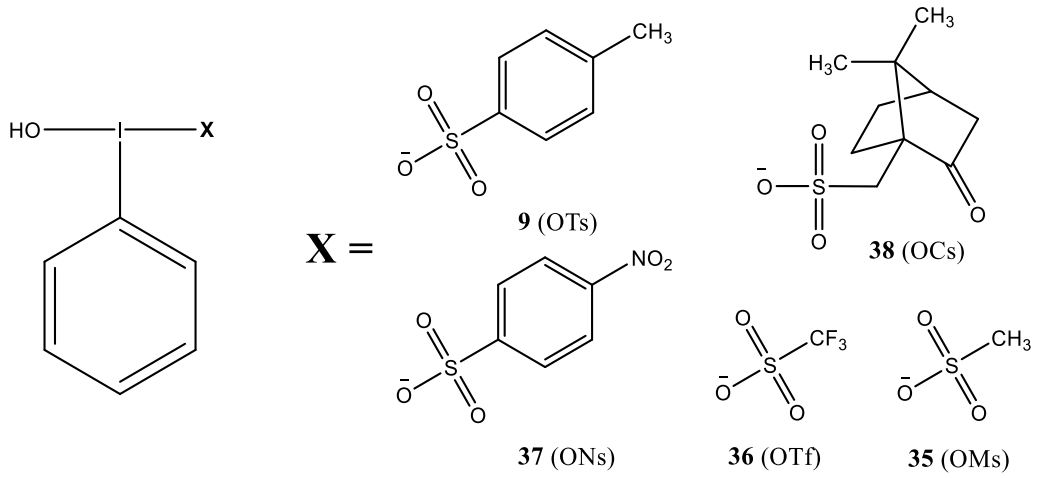


Figure 5: Variations of Koser's reagent by substitution of anionic sulfonic acid.

The structure of HTIB has been determined with the use of single crystal X-Ray analysis to confirm the T-shape of the trivalent iodine atom as shown in Figure 6. The electronegative ligands (OH and OTs) are co-linear with an I-OTs bond length of 2.473A and a short I-OH bond of 1.940A. The sum of the covalent radii or oxygen and iodine is 1.99A indicating the structure is ionic in nature with the tosylate group acting with more anionic character while the hydroxyl group is bound covalently in comparison.[16]

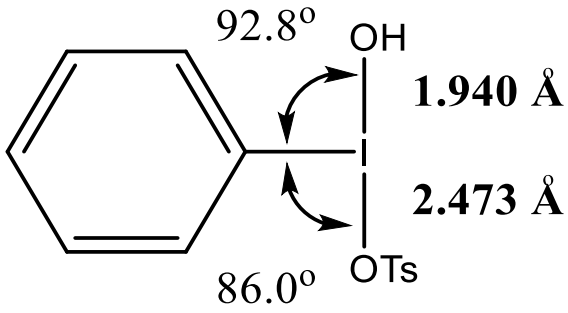
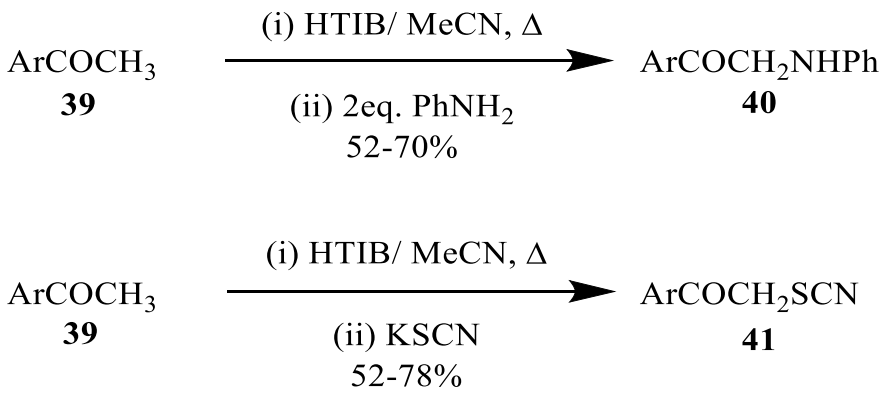


Figure 6: Structure of HTIB based on X-ray analysis.

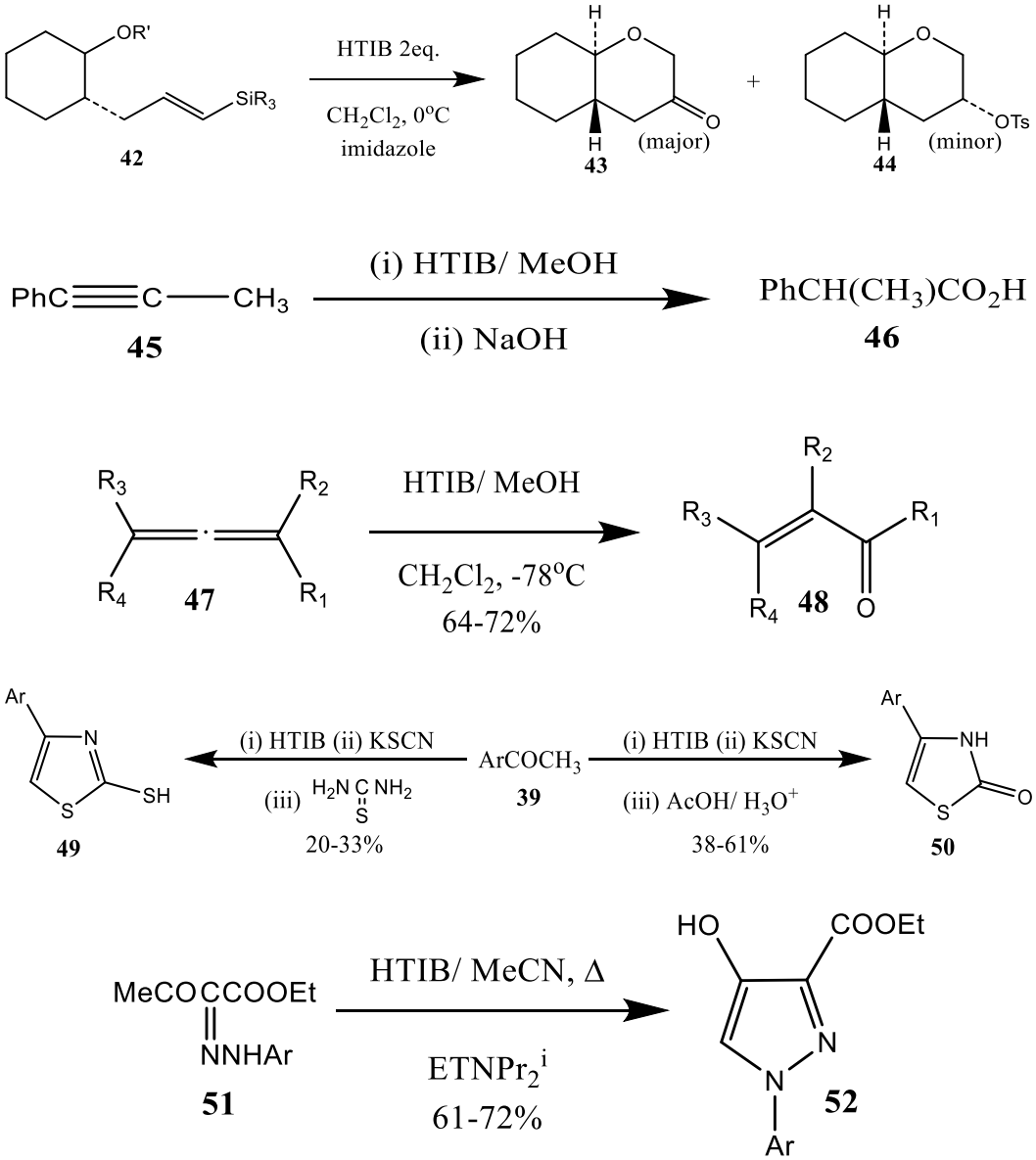
The utility of HTIB by the mid 1990's had also been used for a variety of other applications including the functionalization of acetophenones (**39-41**) with moderate yields as described in Scheme 5.



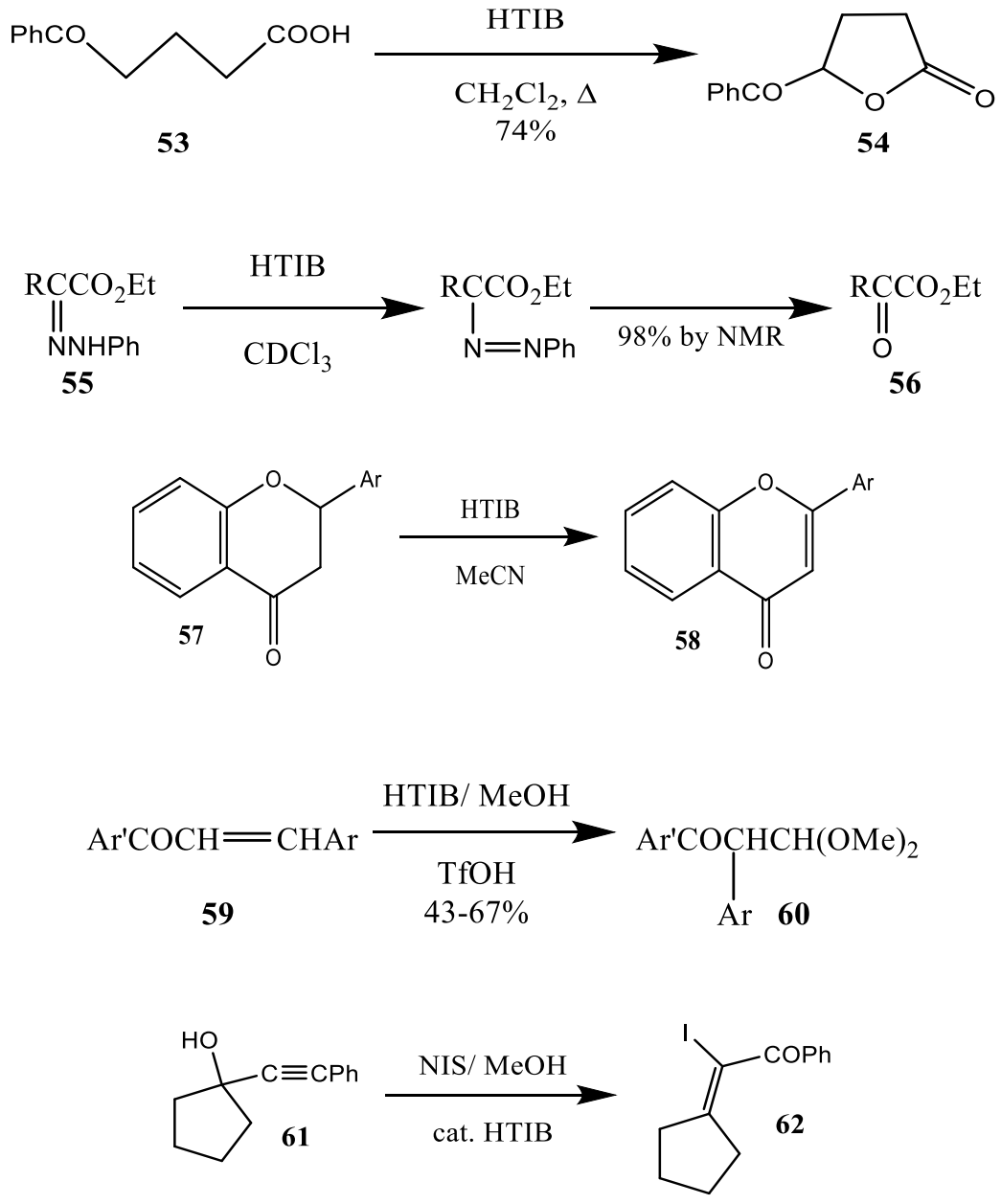
Scheme 5

Other products synthesized using HTIB include of pyran-3-ones (**43**) and minor tosyloxy-tetrahydropyran (**44**) products from silyl-substituted δ,ε–unsaturated alcohols and ethers (**42**), the conversion of alkynes (**45**) to esters (**46**), the conversion of allenes (**47**) to carbonyl compounds (**48**). The synthesis of various heterocycles like thiozoles (**49,50**) from keto compounds (**39**), pyrazoles (**52**) from arylhydrazones (**51**), and keto-γ-lactones (**54**) from 5-ketoacids (**53**), which are shown in Scheme 6. The oxidation of

phentlhydrazones (**55**) to α-keto esters (**56**) as well as oxidative transformations of flavanones (**57)** , chalcones (**59**), and alkynols (**61**) are possible using HTIB to synthesize isoflavones (**58**), rearranged acetals (**60**), and enones (**62**) or enals as shown in Scheme 7, were summarized by Varvoglis (1996) in his book *Hypervalent Iodine In Organic Synthesis*.[5]



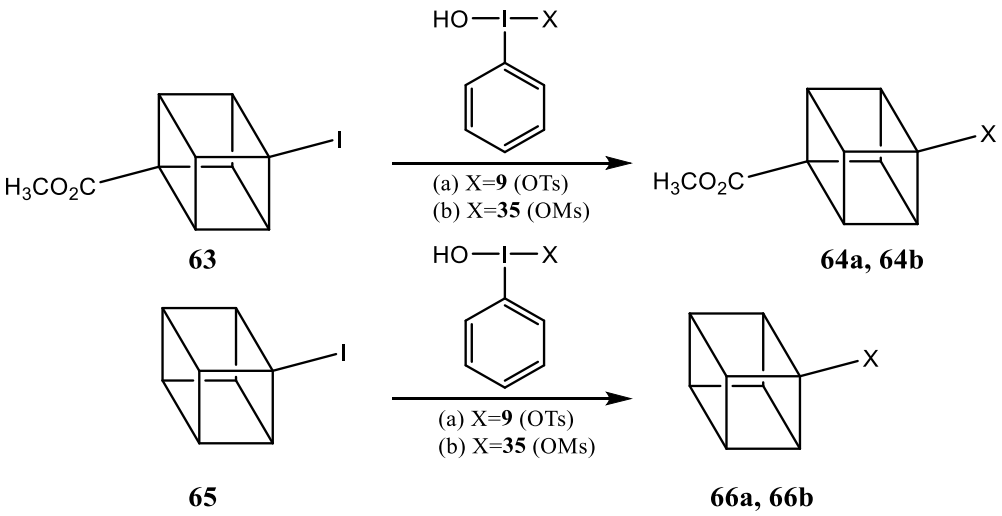
Scheme 6



Scheme 7

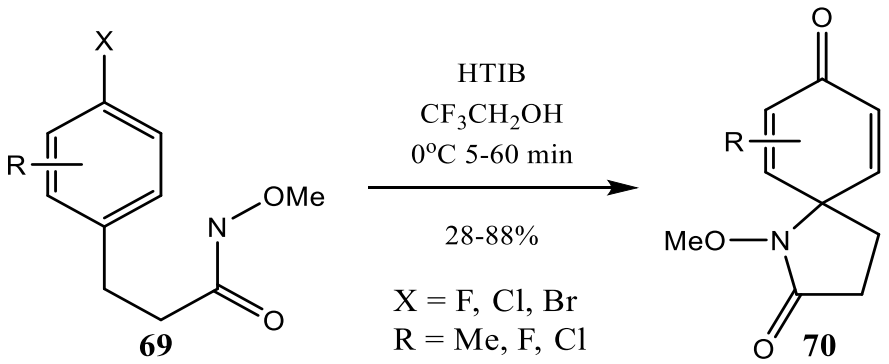
Moriarty also summarized a number of unique applications using HTIB to perform displacement reactions on cubyl iodides (**63,65**) in order to introduce tosylate (**9**) groups, which are shown in Scheme 8. These ligand transfers could also form new

products (**64,66**), using various HTIB derivatives with other anionic groups like mesylate (**35**), triflate (**36**) and chlorine (**8**).[14]

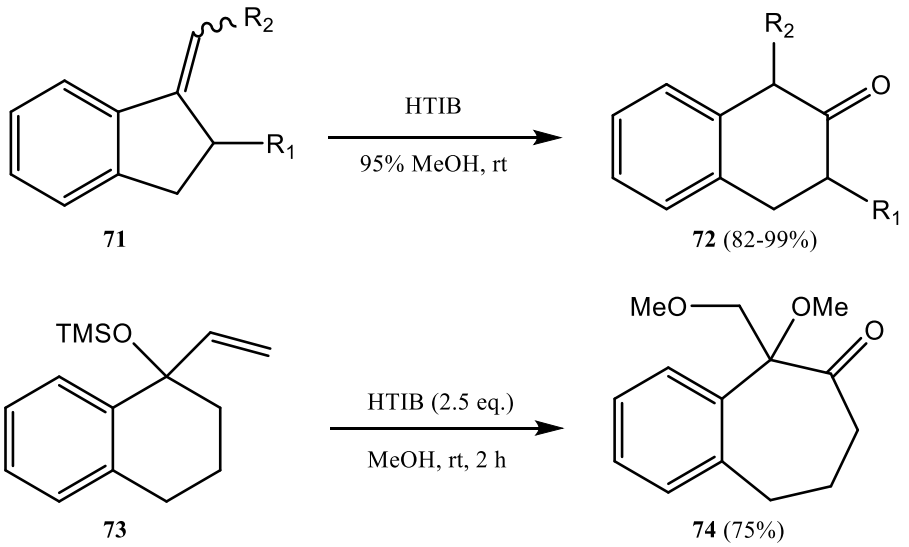


Scheme 8

Other applications of HTIB include its oxidative selectivity towards ring forming reactions (**70**) with appropriate amides (**69**), Scheme 9, and ring expansion reactions (**72,74**) with alkenes (**71**) and 1-vinylcycloalkanol derivatives (**73**) in Scheme 10.[2]



Scheme 9



Scheme 10

Additional discoveries over the last 20 years in regards to the synthetic utility of HTIB includes using new synthetic methods to create recyclable trivalent iodine reagents such as polymer, ion supported, and tetraphenyl based variations of HTIB (**75,76**) are shown in Figure 7.[1,17]

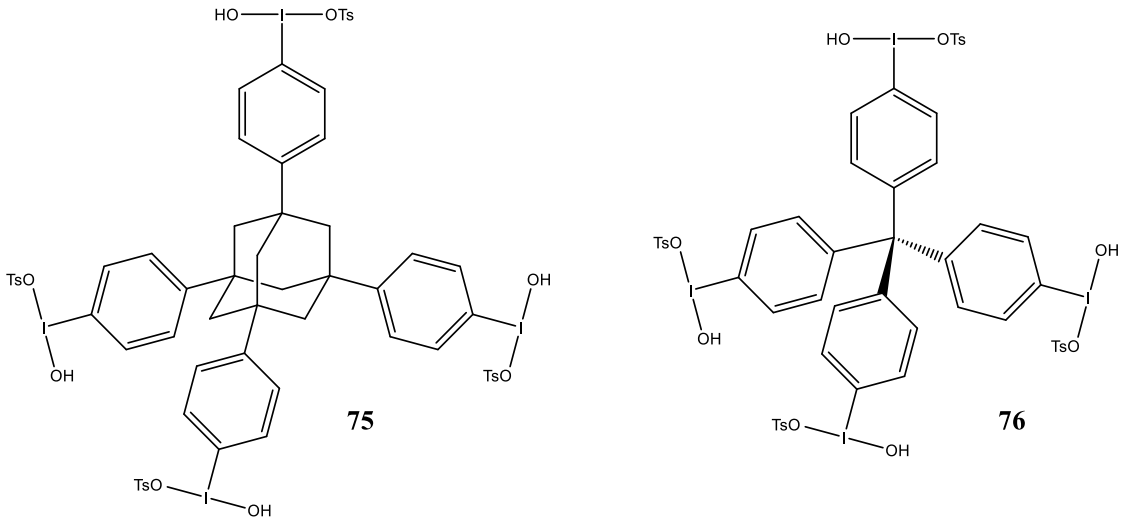
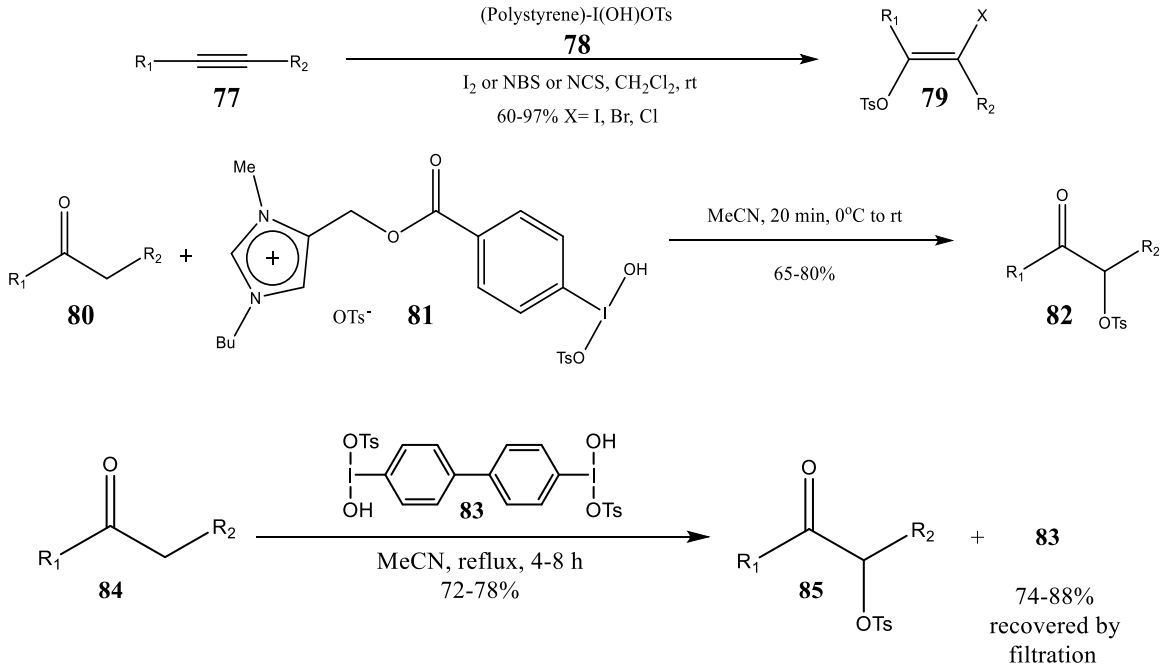


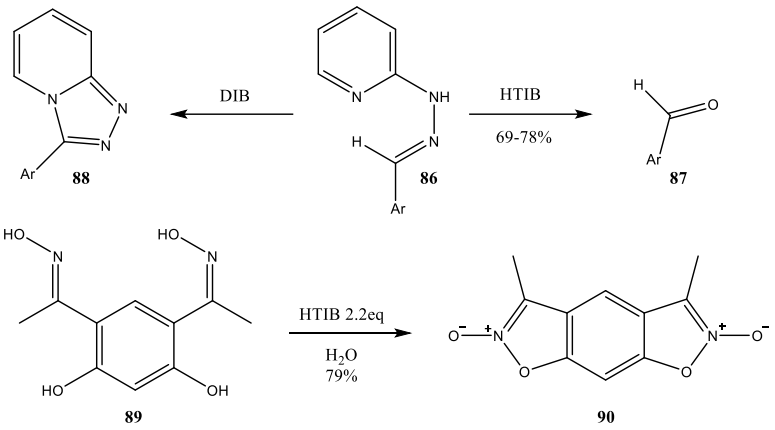
Figure 7: Tetraphenyl based variations of HTIB.

One of the most substantial shortcomings of HTIB or hypervalent iodine compounds in general is there is low atom economy from a green chemistry view point, when utilized as stoichiometric reagents in organic synthesis. The poor atom economy is due to the formation of expensive iodoarenes that are unrecoverable.[18] Thus, a substantial amount of research using recyclable hypervalent iodine complexes has been done in order to improve the atom efficiency of these oxidation reactions and recover these expensive reagents and regenerate them for future reactions. Applications in literature of these HTIB supported reagents include oxidative halotosyloxylayions of alkynes (**77**) with iodine or *N*-bromosuccinimide (NBS) or *N*-chlorosuccinimide (NCS), and a polystyrene HTIB analog (**78**) to produce halotosyloxylated alkenes (**79**). Other recyclable HTIB derivatives include ionic liquid-supported variation of HTIB (**81**) and biphenyl supported HTIB for the α-tosyloxylation of ketones (**80, 82, 84, 85**) and the oxidation of primary and secondary alcohols to their perspective aldehydes and ketones shown in Scheme 11. Sue *et al.* has also done work exploring the use of ion-supported HTIB for α-tosyloxylation of ketones without the observable loss of reactivity upon regeneration of HTIB.[2,17]



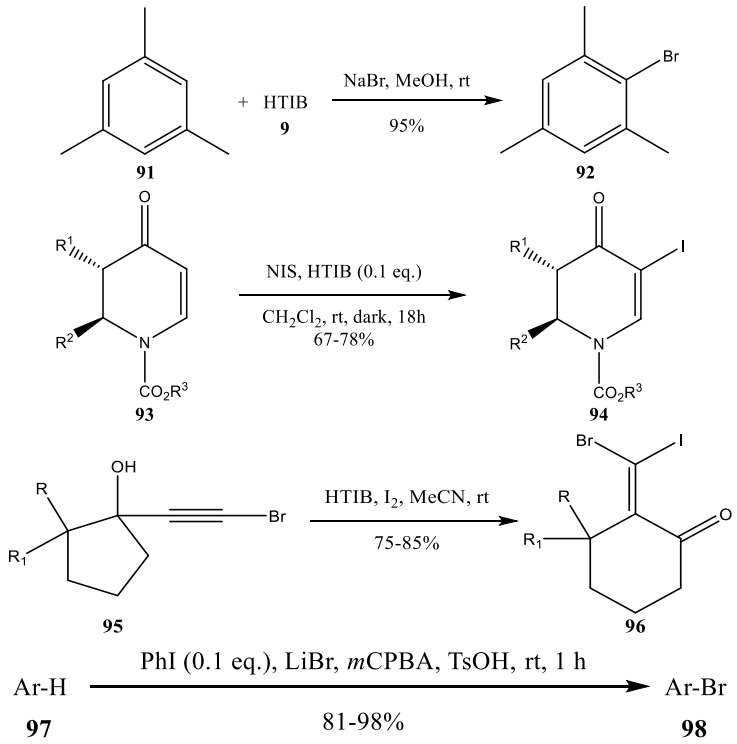
Scheme 11

New one-pot reactions of iodoarenes and *m*CPBA in the presence of sulfonic acids to obtain HTIB *in-situ* have been used effectively in recent years for α-tosyloxylation of ketones, which will be explored later.[2,19] Methods for the regeneration of carbonyl compounds (**87**) have been performed using HTIB. HTIB can be used for the selective cleavage of carbon nitrogen double bonds (**86**) that is very selective in comparison to diacetoxyiodobenzene (**10**) and performs ring cyclization reactions with similar reagents (**88**).[20] HTIB has also been found to be effective for N-O coupling through a HTIB mediated oxidation useful for synthesizing Isoxazoline *N*-oxides (**90**).[21]



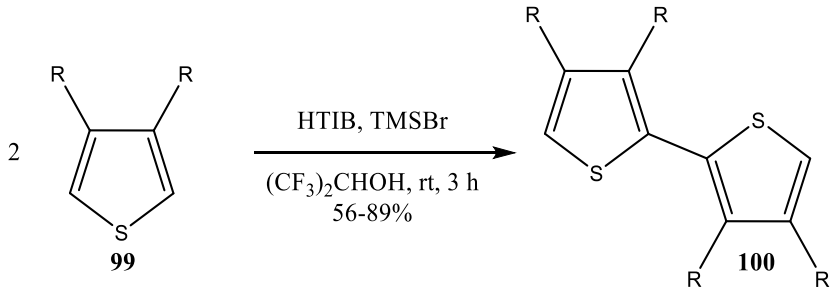
Scheme 12

HTIB is also effective in performing a few oxidative halogenations (**79, 92, 94, 96, 98)** of alkenes (**93**), alkynes (**77, 95**) and other aromatic substrates (**91, 97**) as shown in Scheme 13. No fluorination reactions have been reported using HTIB but a few bromination reactions (**91,97**) as well as iodination reactions (**61, 93, 95)** have been cited in literature.[1]



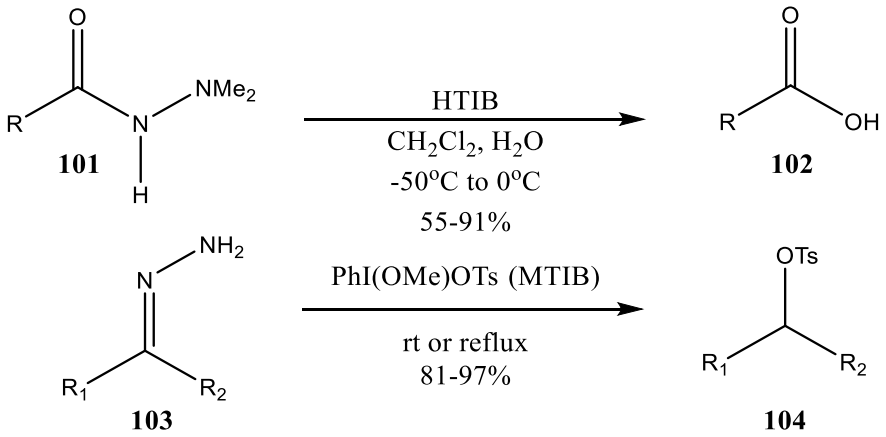
Scheme 13

Oxidative coupling reactions can also be performed using aromatic substrates (**99**) in conjunction with HTIB and tetramethylsilane bromide (TMSBr), depicted in Scheme 14.



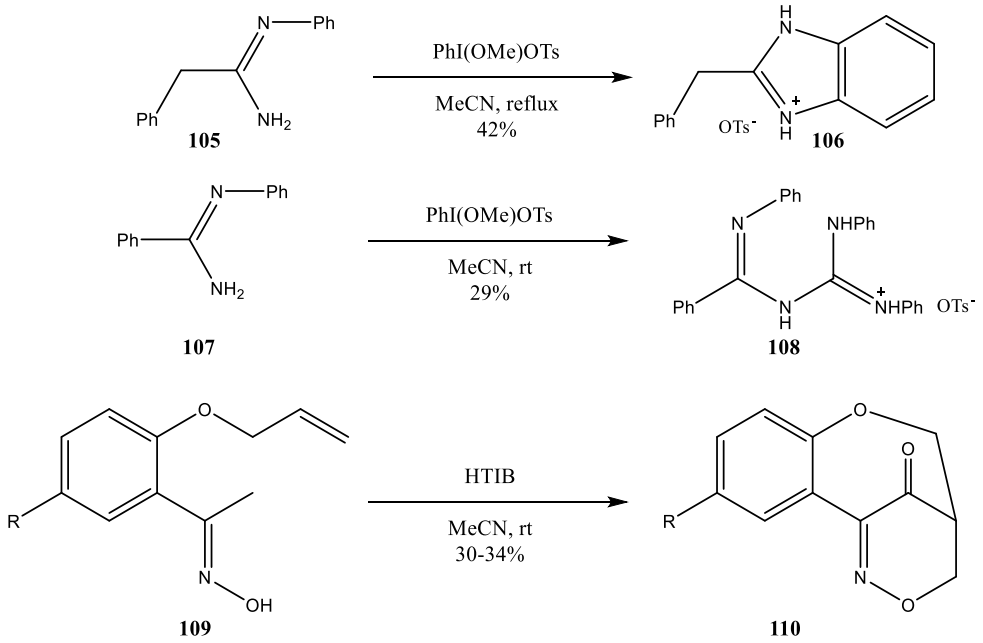
Scheme 14

HTIB and methoxy[(tosyloxy)iodo]benzene (MTIB) is also effective for a number of different rearrangement (**105,107,109**) and fragmentation (**101,103**) reactions to form various products including heterocycles (**106,110**), shown in Scheme 14 and 15. The use of these hypervalent iodine reagents take advantage of electron-deficient centers of nitrogen containing starting materials including ***N***-substituted amines (**105,107**) and aromatic hydrazones (**109**) in Scheme 15.



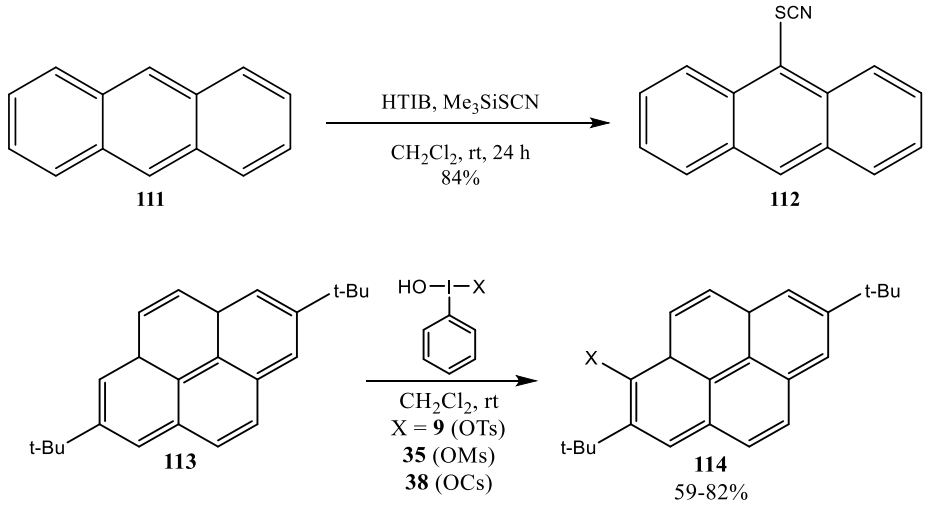
Scheme 15

The synthetic utility of HTIB also can be expanded to the functionalization of aromatic substrates (**111,113**) by transferring various sulfonic acids or using tetramethylsilane thiocyanate to selectively transfer thiocyanate functional groups (**112**). Different variations of HTIB have also been used to selectively transfer different sulfonic acid groups (**9, 35, 38**) to form new products (**114**) as shown in Scheme 17.[1]



Scheme 16

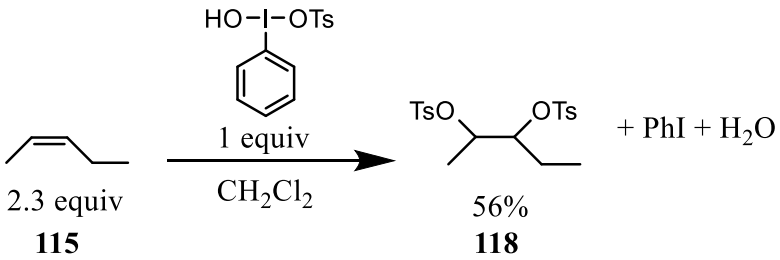
In summary, the use of HTIB for the selective oxidations of various organic substrates have been studied vigorously since the 1980's for a large array of applications. The excellent synthetic utility of HTIB in conjunction with the non-toxic behavior of hypervalent iodine complexes have interested researchers for decades to find useful applications and optimize their efficiency in organic synthesis.[1] The remaining portion of this review will focus on specific synthetic applications of HTIB in organic synthesis.



Scheme 17

1.4. Cis-tosyloxylation of Alkenes using HTIB

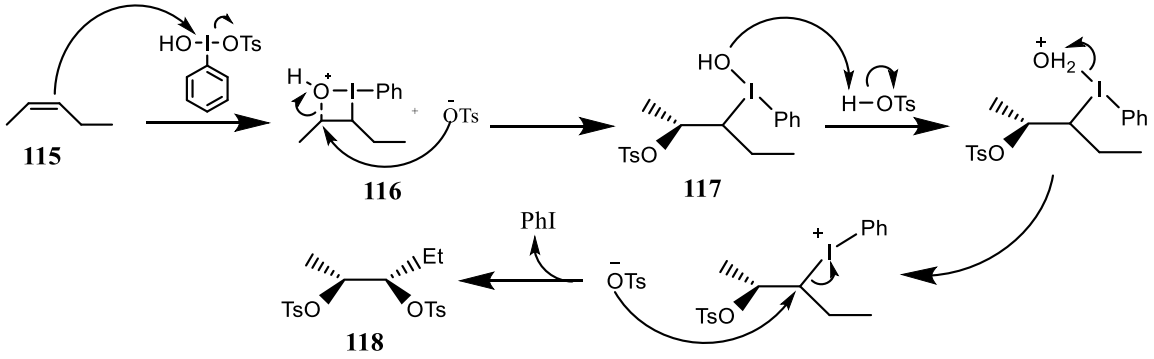
One of the first applications of HTIB involved the *cis*-tosyloxylation of alkenes, which is shown in Scheme 18 below using *cis*-2-pentene (**115**) in excess.



Scheme 18

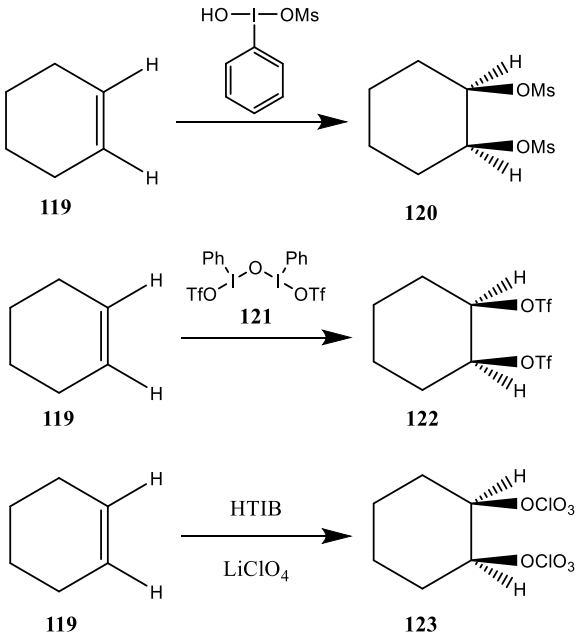
Koser and Rebrovic in 1983 studied the use of HTIB on various alkene substrates. The results from their study suggested that the mechanism is initiated by an electrophilic addition that produces a cyclic organoiodide intermediate (**116**) that undergoes a S_N2 mechanism to collapse the intermediate, initiated by the tosylate leaving group. The hydroxyiodinane (**117**) then undergoes a dehydration followed by an additional S_N2 step

with an additional tosylate to nucleophilically displace phenyliodide to create the *cis*-tosyloxylated product (**118**) as shown in Scheme 19.[8]



Scheme 19

Many researchers performing reactions using HTIB as a chemical reagent will typically use it as a limiting reagent due to its limited solubility, its organic solvents, and its yellow color in methylene chloride, which researchers in some instances can use to indicate if the reaction has gone to completion.[8]

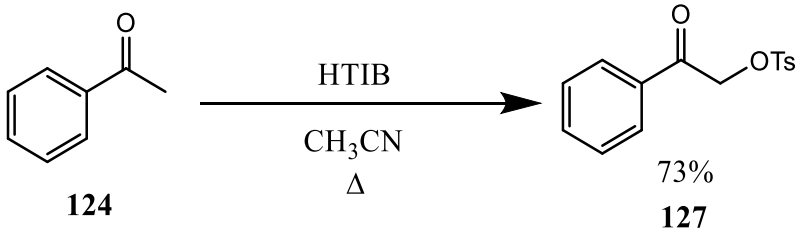


Scheme 20

Other variations of HTIB using different sulfonic acids like methane sulfonic acid (**35**) to transfer mesylate ligands to an alkene (**119**) can be used to produce *cis*-mesylated products (**120**) and triflate ligands (**36**) using Zefirov's reagent (**121**) to form *cis*-triflated products (**122**). HTIB can also be used in the presence of lithium perchlorate to synthesize *cis*-diperchlorates (**123**) as shown in Scheme 20.[16]

1.5. α-Tosyloxylation of Ketones using HTIB

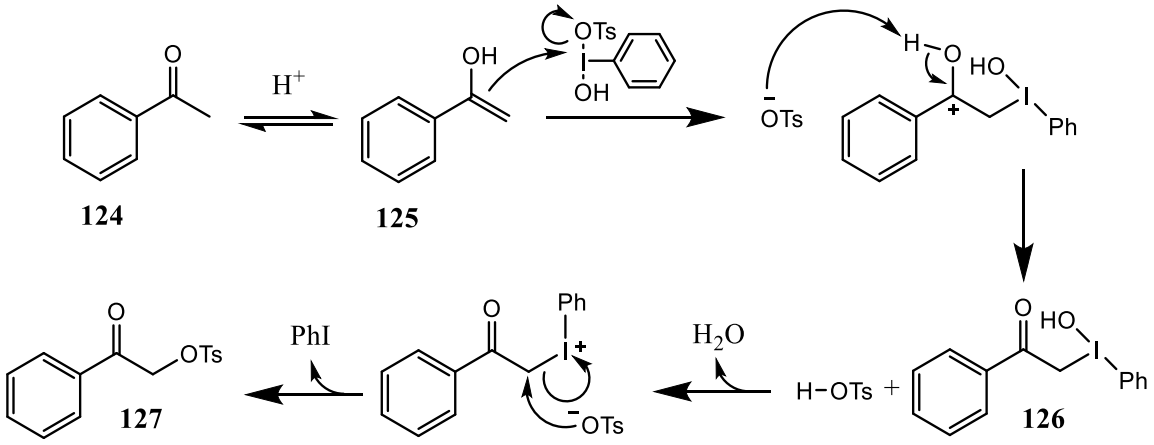
One of the most popular reagents for α-tosyloxylation of ketones is HTIB due to the reagents efficiency and is one of the only reagents capable of producing α-tosyloxylated products directly. Koser, Relenyi, and others published their work in 1982 using HTIB to do one-step α-tosyloxylation of various ketones with yields ranging from 40-99%. Scheme 21 depicts the α-tosyloxylation of acetophenone (**124**).



Scheme 21

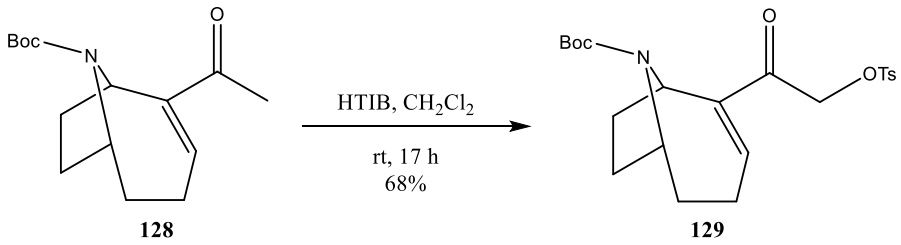
Similar to the *cis*-tosyloxylation for alkenes, the use of HTIB for α-tosyloxylation is initiated by the electrophilic addition of HTIB to the enol tautomer (**125**) to form an intermediate α-phenyliodonio ketone (**126**), which then undergoes a nucleophilic attack by the tosylate ion to displace iodobenzene from the intermediate via an S_N2 mechanism to form the α-tosyloxylated product (**127**) as shown in Scheme 22.[5] These reactions have

also been performed with other variations of HTIB in order to transfer anionic sulfonic acid groups like dinitrobenzene sulfonic acid and (+)-10-camphorsulfonic acid (**38**).[22]



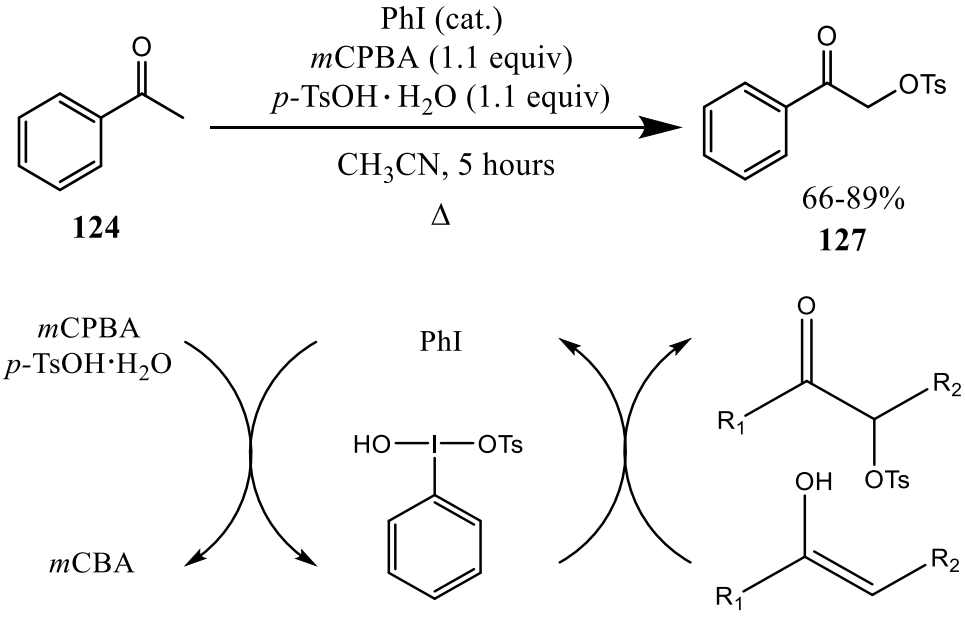
Scheme 22

The reaction is highly chemoselective and a number of functional groups can be tolerated through these α-tosyloxylation reactions including aromatic rings and C-C double bonds. One example being the functionalization of azabicyclic alkaloid anatoxin-a by reaction *N*-Boc anatoxin-a (**128**) with HTIB, in Scheme 23, which is known for its ability to block acetylcholine at nicotinic acetylcholine receptors for peripheral muscle paralysis during surgery.[1]



Scheme 23

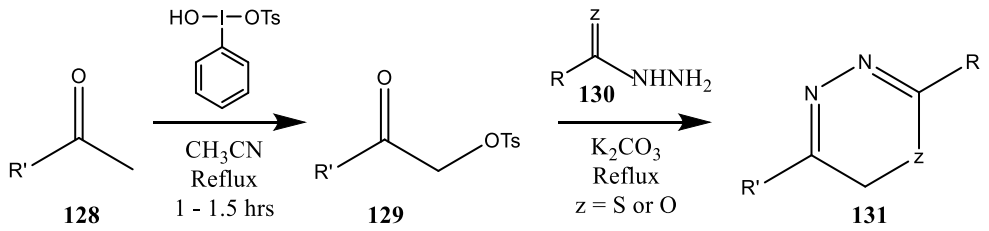
The α-tosyloxylation has also been performed by Yamamoto and coworkers (2006) in a one-pot synthesis using iodobenzene as in various quantities (0.05-1.0 equivalence) with *m*CPBA and *p*-toluenesulfonic acid to form HTIB *in-situ* in order to perform the α-tosyloxylation of acetophenone as shown below in Scheme 24.[19]



Scheme 24

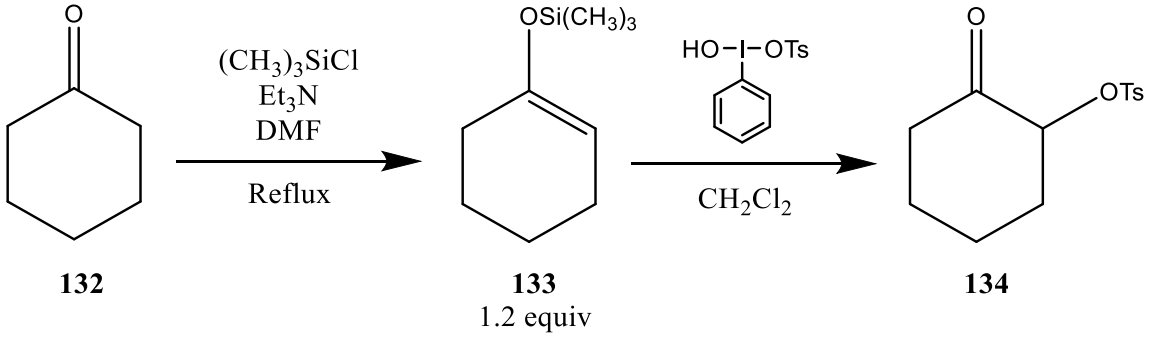
The same reaction in Scheme 24 has been done using polystyrene supported iodobenzene with 1.1 equivalences of *m*CPBA and *p*-toluene sulfonic acid in acetonitrile to produce a recyclable variation of HTIB for the α-tosyloxylation of ketones.[22,23]

Sue *et al.* has also reported the use of ion-supported HTIB for the α-tosyloxylation of ketones that could be recovered and easily regenerated without losing chemical activity.[17] Karade and coworkers in 2009 have used these α-tosyloxyketone products (**129**) and reacted them with different acid hydrazides to synthesize various 1,3,4-oxadizaines and 1,3,4-thiadiazines (**130**) as depicted below in 58-71% yields to form new heterocycles (**131**) shown in Scheme 25.[24]



Scheme 25

In 1989, Moriarty and co-workers used HTIB with trimethylsilyl enol ethers (**29**) to perform α-sulfonyloxylation of carbonyl compounds like cyclohexanone to form α-(tosyloxy)cyclohexanone.[10]

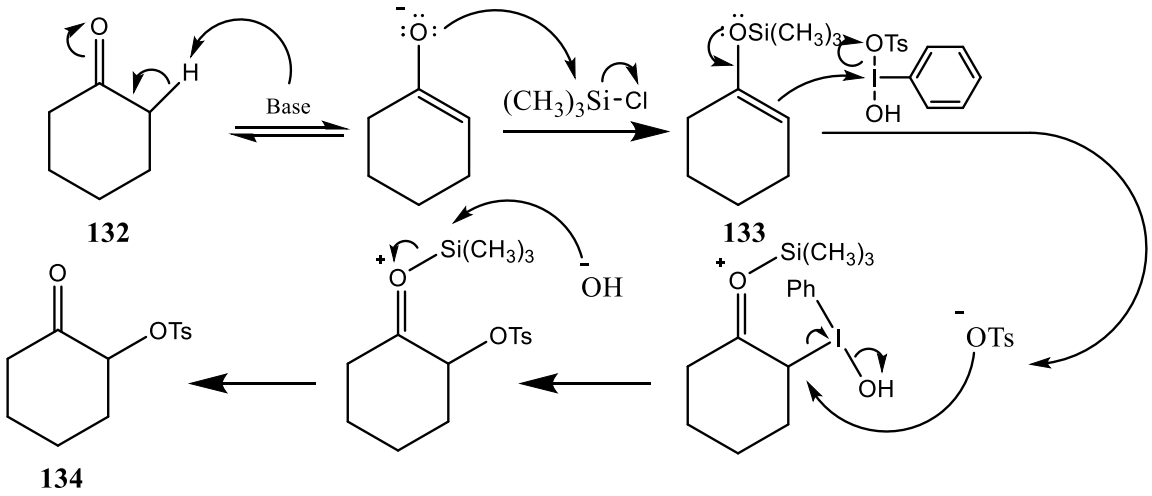


Scheme 26

The use of HTIB for α-sulfonyloxylation of carbonyl compounds is another application that takes advantage of the oxidative behavior of HTIB by the silylation of a ketone in order to form a stable enol ether that can perform an electrophilic addition onto HTIB and regioselectively perform a α-sulfonyloxylation of a large variety of carbonyl compounds including esters, ketones and lactones.[10] The proposed mechanism is shown in Scheme 27.

Yusubov and Wirth have published that the same α-tosylated product (**134**) can be produced by grinding the starting material with DIB and *p*-TsOH for 20 minutes to form α-(tosyloxy)cyclohexanone with a 50% yield, which may suggest that HTIB can be

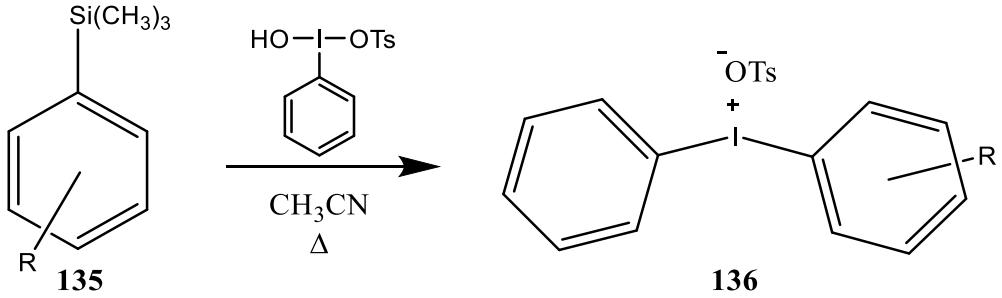
produced in a solvent free one pot synthesis to promote α-sulfonyloxylation of carbonyl compounds.[25]



Scheme 27

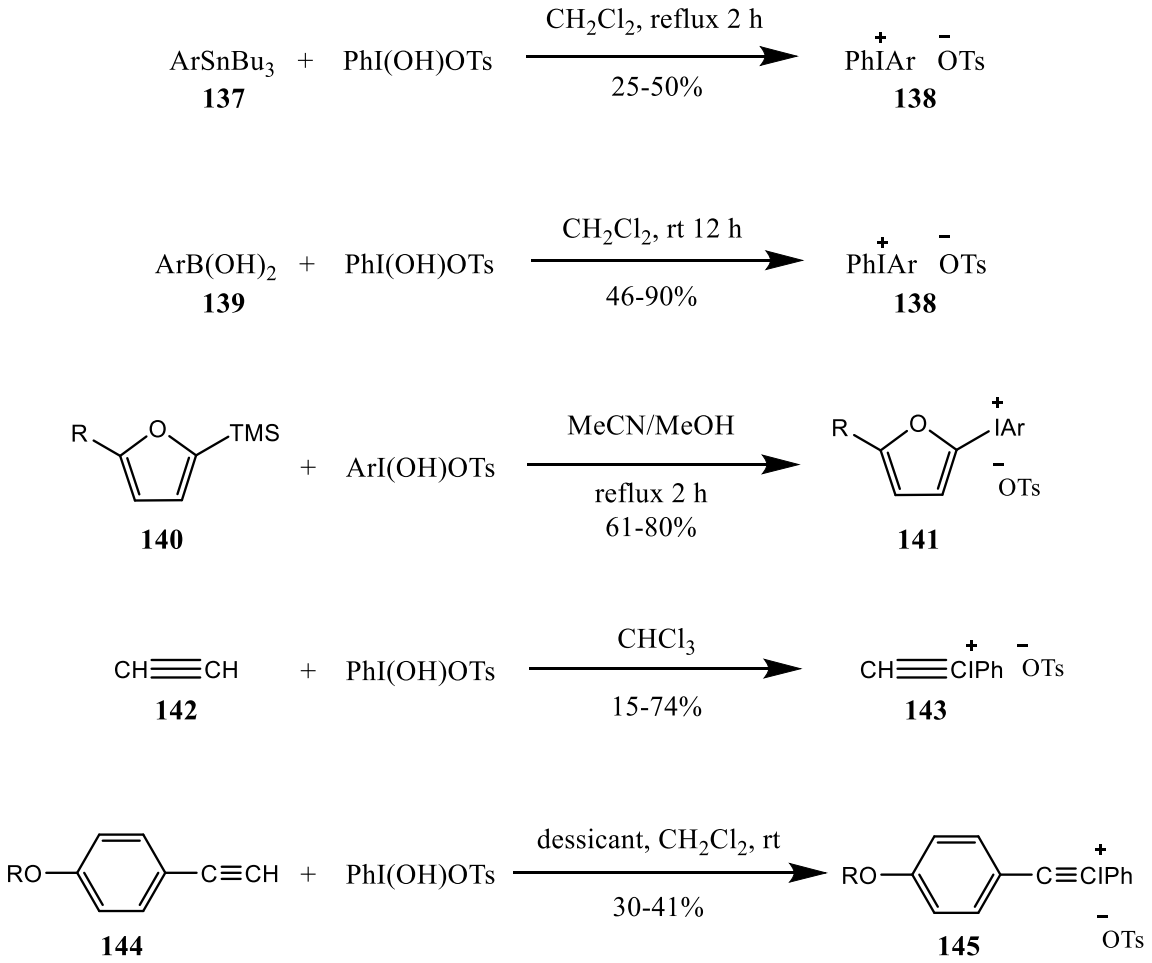
1.6. Formation of Unsymmetrical Iodonium Salts using HTIB

Koser and Wettach in 1980 also explored using HTIB as a reagent for the formation of unsymmetrical iodonium salts using HTIB with aryltrimethylsilanes.[7]



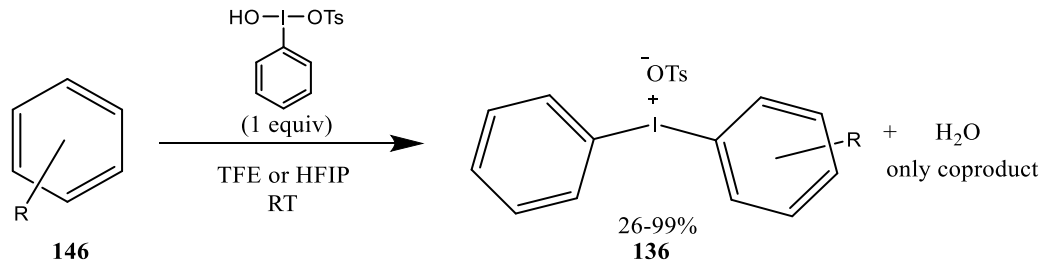
Scheme 28

Similar reactions have been performed to synthesize unsymmetrical iodonium salts from aryltributylstannanes (**137**), boronic acids (**139**), alkynes (**142,144**) or other appropriate aromatic precursors (**140**) as depicted below in Scheme 29.[1]



Scheme 29

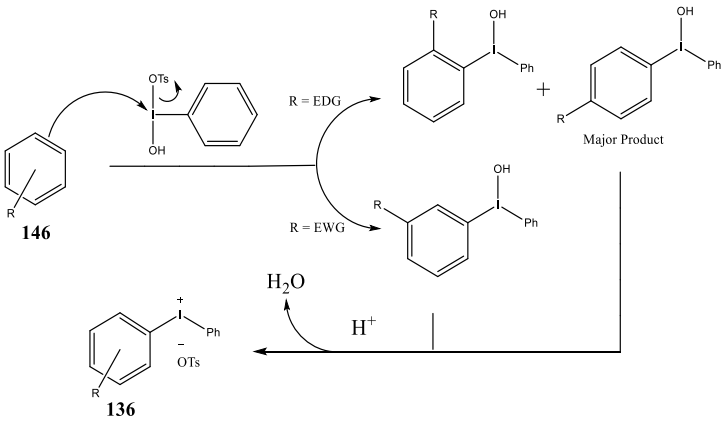
Kita and coworkers in 2010 studied the use of HTIB for the synthesis of diaryliodonium(III) salts (**136**) in fluoroalcohol solutions and the their enhancement for condensation reactions of aromatic compounds and other hypervalent iodine reagents in Scheme 30.[26]



Scheme 30

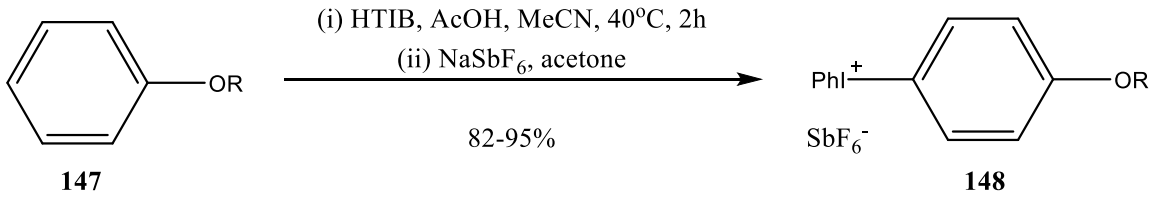
These reactions are versatile and capable of producing a large array of iodonium salts, which have been useful for synthesizing biologically active compounds. These compounds specifically have been found to have antimicrobial, antibacterial, and anthelmintic activity, examples include biological activity against *Staphylococcus aureus, Bacillus Subtilis, Escherichia coli,* and *Streptococcus aureus*.[1] A recent review by Yusubov and coworkers explored various applications of synthesizing diaryliodonium salts for use in Positron Emission Tomography.[3] Diaryl iodonium salts are also used in conjunction with copper or palladium reagents for C-H activation reactions.[25]

The mechanism for a number of these reactions using different arenes is initiated by the electrophilic aromatic substitution (EAS) of the arene with HTIB. Depending on the electron donating (EDG) or withdrawing (EWG) nature of the R group on the arene will influence the products produced from this reaction as depicted below. However, as with many electrophilic aromatic substitutions the presence of an electron withdrawing group decreases the reactivity of the arene to an extent that usually prohibits the reactions from occurring. After the EAS step of the reaction the presence of a acid promotes the removal water from the product to form the diaryl iodonium salt.[27]



Scheme 31

Other applications include using HTIB to form iodonium salts from ethers (**147**) for applications as photoinitiators (**148**).

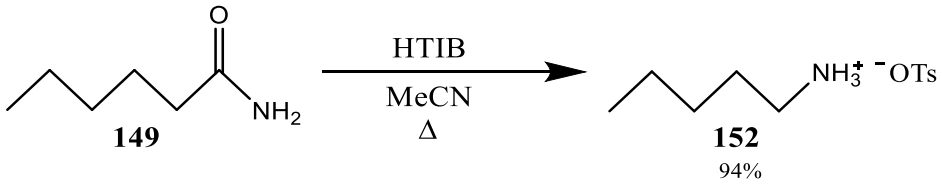


147 **148**

Scheme 32

1.7. Hofmann Rearrangement of Amides using HTIB

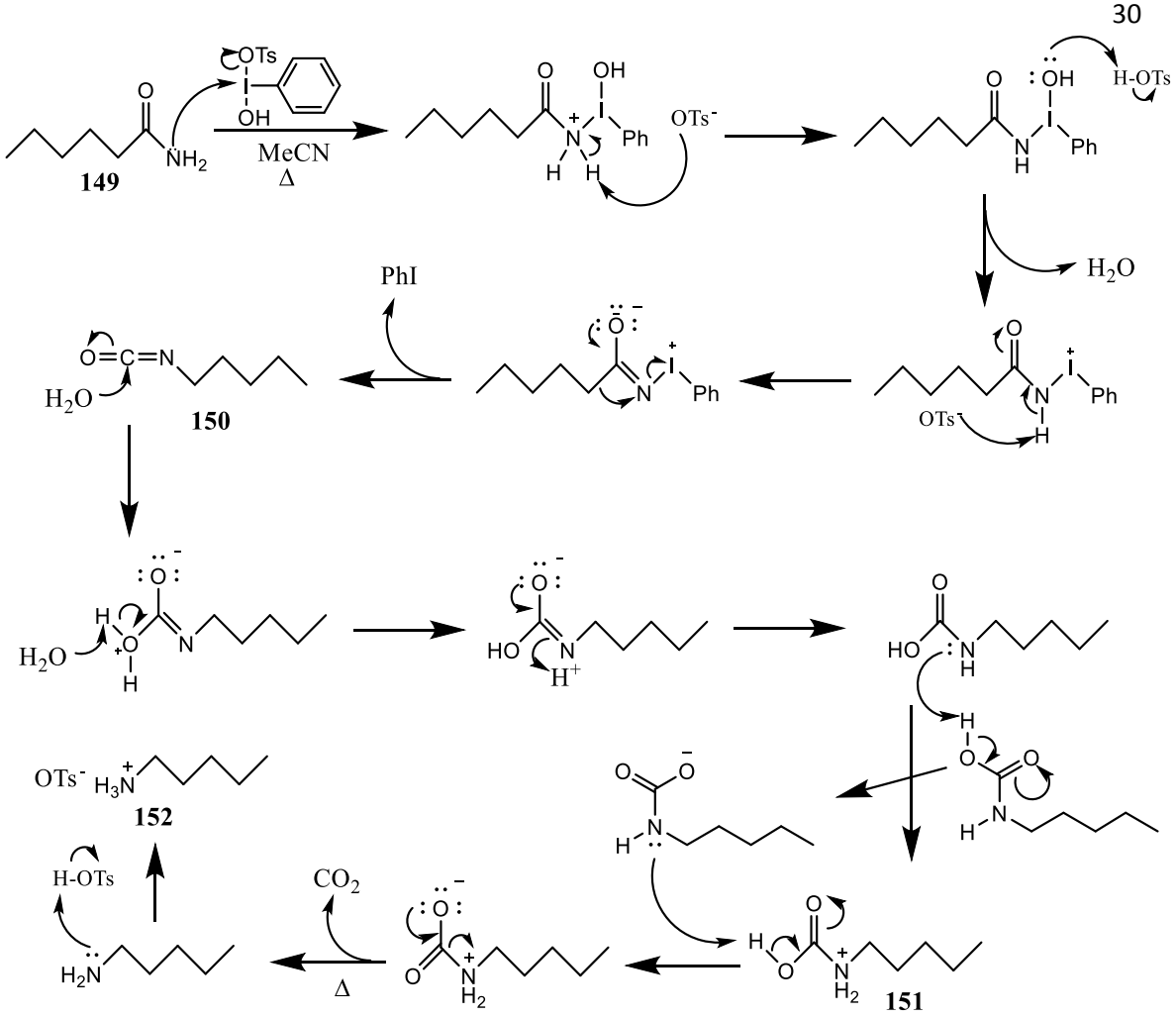
One of most useful applications of HTIB is its ability to directly convert primary and aliphatic amides to alkylammoium tosylates as a Hofmann reagent.



149 **152**
94%

Scheme 33

Due to the low solubility of HITB in acetonitrile these reactions typically utilize a variation of HITB that is more soluble in organic solvent or they are performed under reflux to solubilize HTIB.[12] However, Lazbin and Koser (1986) performed the direct conversion of these amides (**149**) to alkylammonium tosylates (**152**) with yields ranging from 57 - 94% in acetonitrile under reflux.[11]



Scheme 34

The mechanism for Hofmann rearrangements is initiated by nucleophilic attack from the nitrogen of the amide to I(III) of HTIB, which results in hydrolysis to promote the removal of iodobenzene to form the isocyanate intermediate (**150**). The isocyanate intermediate is then susceptible to a nucleophilic attack from water, which results in a rearrangement to produce carbamic acid (**151**) that quickly loses carbon dioxide under reflux and forms an alkylammoium tosylate (**152**).[28] The uniqueness of HTIB for use in Hofmann type rearrangements involves its ability to convert long chain aliphatic amides that are typically unreactive using other Hofmann reagents to their perspective amines as

sulfonate salts. The use of HTIB has even been used as a Hofmann reagent to synthesis structurally unique cubane amine structure.[29]

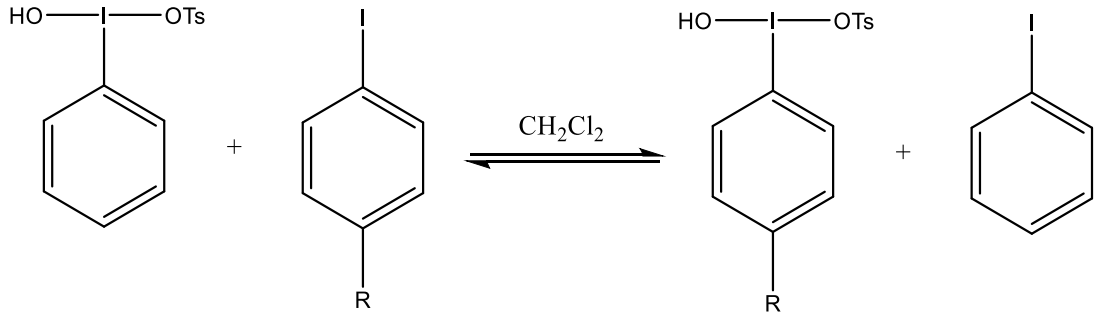
Section 2:

Results and Discussion

2.1. Preparation of New Five-Membered Heterocycles (λ^3-Iodinanes) using ortho-Substituted iodoarenes and HTIB by Transtosylation Reactions

2.1.A. Introduction:

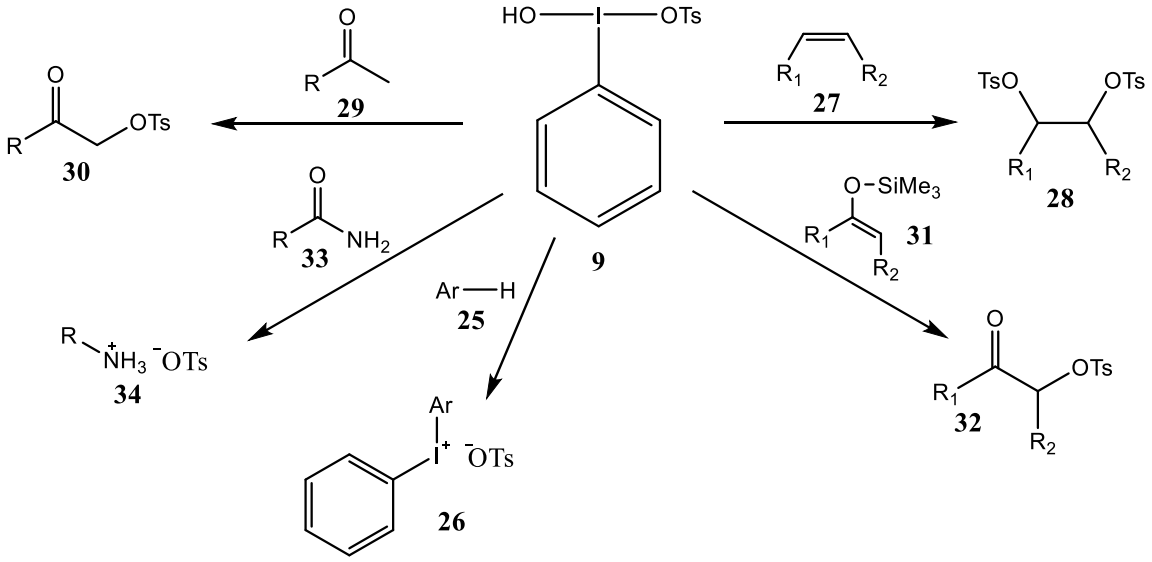
In recent years, organohypervalent iodine compounds have emerged as environmentally friendly and efficient reagents for various synthetically useful oxidative transformations. Hydroxy[(tosyloxy)iodo]benzene has been studied extensively since the 1980's when G. F. Koser discovered a number of new synthetic applications using HTIB and similar analogs.[6] Initially in 1980 Koser studied the mild oxidative nature of HTIB and its ability to undergo ligand exchange through a tosyl-transfer process with other aryl iodides (**22**) in dichloromethane as depicted in Scheme 35. HTIB has found a number of applications in organic synthesis due to the reagent's high reactivity and overall stability.



9 **22** **23** **24**

Scheme 35

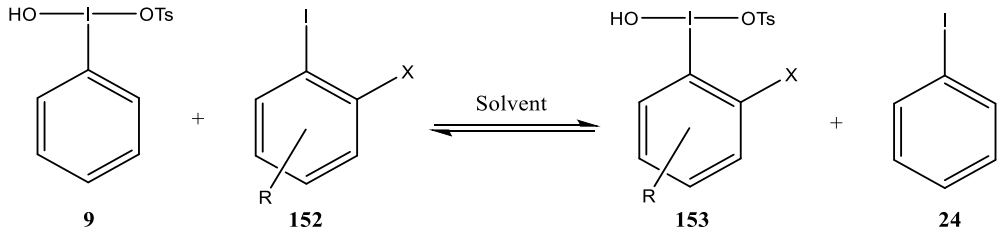
HTIB, which is commonly known as Koser's reagent, is synthesized by the oxidative addition of (diacetoxyiodo)benzene (DIB) (**10)** with *p*-toluenesulfonic acid (**19**).[2] The synthesized HTIB (**9**) is a stable solid with unique properties for different oxidative transformations in comparison to other polyvalent iodine complexes known previously. Koser and coworkers were able to use this reagent to create new derivatives by ligand transfer reactions in order to study their physical properties.[6] The discovery of Koser's reagent led to a number of reactions that could be used for tosyloxylations with alkene and alkynes substrates. Varvoglis describes a number of reactions that involves Koser's reagent special ability to perform different oxidative transformations; some examples are shown in Scheme 36.[5]



Scheme 36

These reactions have been well studied and many researchers have attempted to create similar variations of HTIB (**153**) to enhance their synthetic utility by improving the reagent's green chemistry, solubility, or chemical selectivity. However, variations of HTIB that contain *ortho*-substituents from precursors (**152**), like 2-iodobenzoic acid or 1-

iodo-2-nitrobenzne for example, are less studied and little is known about their stability or chemical selectivity. These compounds, if stable, in theory can be synthesized by a transtosylation reaction by performing a ligand exchange reactions between HTIB and variations of *o*-Iodobenzoic Acid or similar reagents.

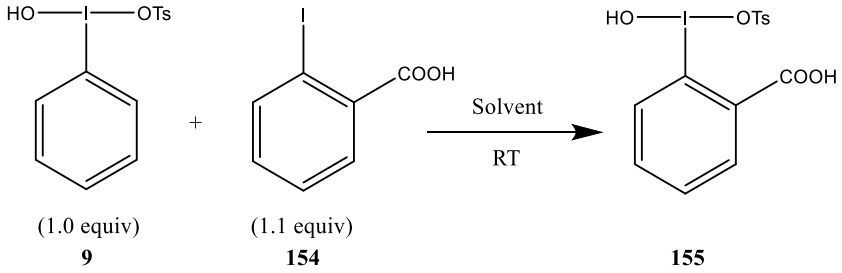


Scheme 37

Since the stability of these reagents is unknown various *ortho*-substituents (X) like nitro, amine, and carboxylic acid groups will be synthesized as well as variations to the R-group substituents to observe the effects of various electron donating or withdrawing groups on overall stability or reactivity.

2.1.B. Results and Discussion:

Various transtosylation reactions were performed using different *ortho*-substituted aryl iodides (**152**) and HTIB (Koser's Reagent). Initial analysis was done by reacting *o*-iodobenzoic acid (**154**) and Koser's reagent (**9**) in various solvent systems at room temperature in order to find optimal solvent systems as depicted in Scheme 38.



(1.0 equiv) **9** (1.1 equiv) **154** **155**

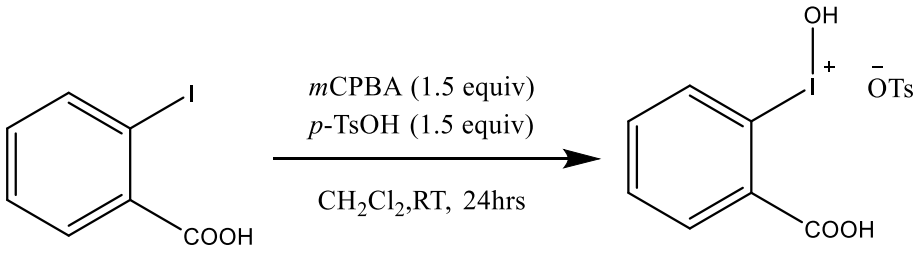
Scheme 38

Table 2: Specific conditions and yields obtained with reactions using 2-Iodobenzoic acid and Koser's reagent.

Entry	**Conditions**	**Solvent**	**Yield**
SCK-001	22hrs, RT	DCM, 2.5mL	98%
SCK-002	24hrs, RT	Acetonitrile, 2.5mL	44%
SCK-003	23hrs, RT	Hexane, 2.5mL	70%
SCK-004	24hrs, RT	Ethyl Acetate, 2.5mL	90%
SCK-005	26hrs, RT	THF, 2.5mL	*
SCK-006	24hrs, RT	Benzene, 2.5mL	79%
SCK-007	24hrs, RT	Diethyl Ether, 2.5mL	0%
SCK-008	2hrs, RT	DCM, 2.5mL	74%
SCK-009	4hrs, RT	DCM, 2.5mL	94%
SCK-010	8hrs, RT	DCM, 2.5mL	98%
SCK-090	24hrs, RT	Acetic Anhydride, 2.5mL	59%
SCK-011	1 hour, Reflux	DCM, 2.5mL	91%

* Product was not easily transferable in order to determine yield and H^1-NMR showed contamination due to polymerization.

Dichloromethane (DCM) was identified as the ideal solvent system to use with these reagents due to the solvents ideal solubility characteristics and ability to not inhibit iodine's reactivity through coordination. Other solvent systems were explored including, tetrahydrofuran (THF), ethyl acetate, hexane, acetic anhydride, acetonitrile, and benzene. However, a 98% yield was obtained after 8hrs using dichloromethane with no decomposition at 22hrs as depicted in Table 2. The reaction in Scheme 38 could also be performed under reflux for 1 hour to isolate a 91% yield of product using dichloromethane. The reaction could also be performed by generating HTIB *in-situ* using *m*CPBA and *p*-toluene sulfonic acid monohydrate (**19**) in dichloromethane at room temperature for 24 hours to isolate an 83% yield of the 2-iodobenzoic acid HTIB derivative (**155**).

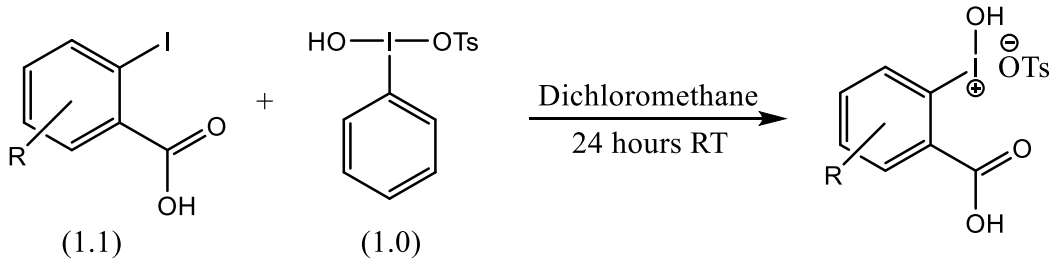


(1.0 Equiv)
154

83% Yield
155

Scheme 39

Further optimization was done after acquiring initial results in order to synthesize other HTIB derivatives and isolate them more effectively. Various starting materials were oxidized using HTIB as a limiting reagent to synthesize these HTIB derivatives with yields ranging from 18-99% as shown in Scheme 40. The halogenated derivatives were observed to be less stable than the other derivatives synthesized attributing to their impurity and lower yields.



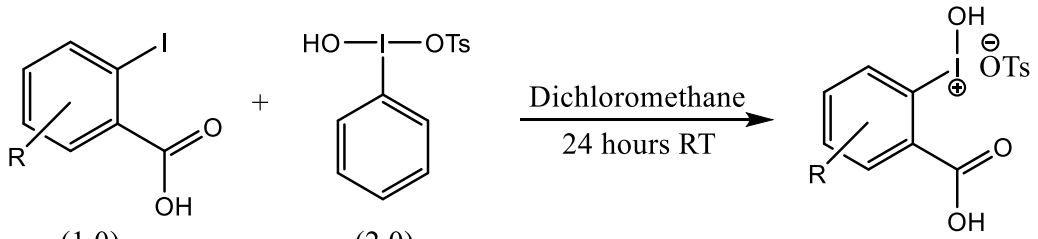
(1.1) (1.0)

156 **9** **157**

R = H(98%), ***p*-Me**(>99%), ***p*-Cl**(77%), ***p*-Br**(79%*), ***p*-I**(18%), ***m*-Me**(75%), ***o*-Me**(43%), ***p*-NO$_2$**(69%), **Naphthoic Acid**(70%), ***m*-F**(53%), ***p*-F**(53%) * indicates impure product

Scheme 40

Reactions were performed using HTIB as the reagent in excess. However, due to the insolubility of HTIB the general workup was not effective in removing the excess HTIB and made obtaining pure products more difficult without any real improvement in yield, which is shown in Scheme 41.



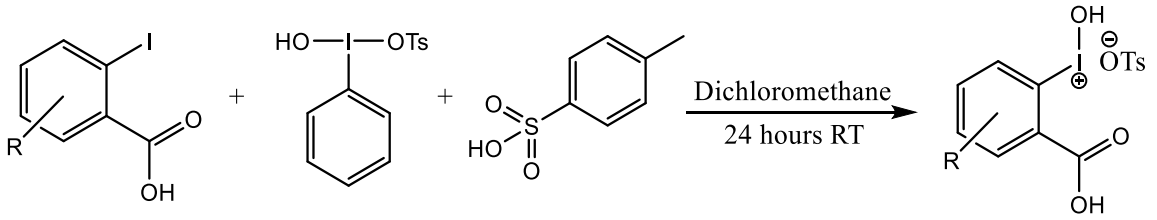
(1.0) (2.0)

156 **9** **157**

R = H(>99%), ***p*-Cl**(Detected)

Scheme 41

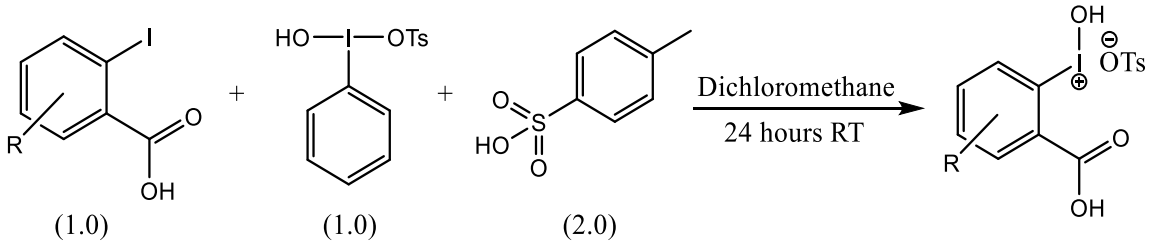
Additional reactions were also performed in order to observe the effect that using varying amounts of *p*-toluene sulfonic acid (**19**) had on yield as shown in Schemes 42 & 43. These reactions were performed using a few representative starting materials with different electron donating or withdrawing properties to observe their effect on the reactivity with HITB. The yields were comparable to the reactions performed with HTIB being the limiting reagent, and the product could be isolated in pure form.



(1.0) **156** (1.0) **9** (1.0) **19** **157**

R = H(93%), ***p*-Me**(99%), ***p*-Cl**(54%)

Scheme 42



(1.0) **156** (1.0) **9** (2.0) **19** **157**

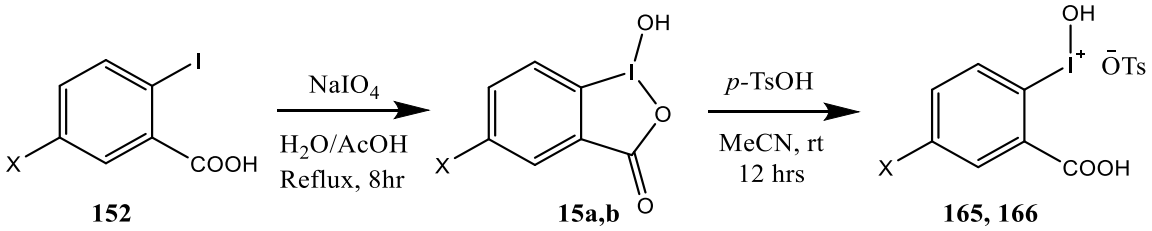
R = H(97%), ***p*-Me**(>99%), (***m*-Me** 56%) **o-Me**(68%), ***p*-Cl**(45%)

Scheme 43

Procedure optimization was done by allowing the reactions to run for 24 hours in dichloromethane at room temperature using HTIB as a limiting or stoichiometric reagent, using data from Schemes 40 through 43. The work up included removing the solvent using a rotovap and stirring the products in 3mL of diethyl ether for 3-12 hours in order to remove all the starting materials like *p*-toluenesulfonic acid (**19**) and the less soluble HTIB (**9**). The resulting suspension was then filtered using a medium frit filter and rinsed with diethyl ether and a small amount of dichloromethane in order to remove any last traces of HTIB or of the unreacted variation of 2-iodobenzoic acid. The final product was then dried for at least 2 hours and analyzed with H^1 NMR in order to observe if the protons, representing the 2-iodobenzoic acid derivatives and the toluene sulfonic acid showed an integration ratio of 1:2 without the presence of other impurities. Many of these products are soluble in deuterated methanol and this was the primary solvent used for

NMR analysis. These products were analyzed using methanol unless the product was insoluble, in which case then deuterated dimethyl sulfoxide (DMSO) was utilized as an alternative NMR solvent. Other variations were introduced to the work up for other HTIB derivatives depending on their level of stability or sensitivity to moisture. Additional examples were performed by reacting different *ortho*-substituted iodobenzene substituents such as 2-nitro-1-iodobenzene and 2-Fluoro-6-iodophenylboronic acid with HTIB. The reaction conditions for these additional chemical reagents included HTIB as the limiting reagent in the same fashion as *o*-iodobenzoic acid.

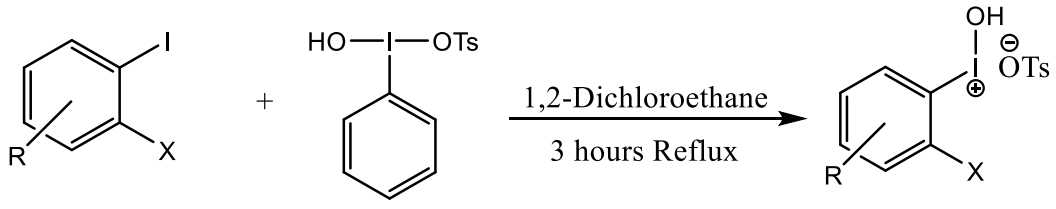
Other variations to the method have been introduced when making halogenated HTIB derivatives by adding an additional step by making IBA type precursors (**15a,15b**) with the starting material before reacting them with HTIB or simply avoiding the use of solvents like diethyl ether, that contain some water to which these derivatives may be sensitive. This IBA precursor method was utilized with the *para*-iodo and *para*-chloro derivatives to produce 43%-60% crude products from **15a** and **15b** to the final products (**165, 166**).



152 **15a,b** **165, 166**

X = **Cl** (43%), **I** (60%)
Yields of second step

Scheme 44

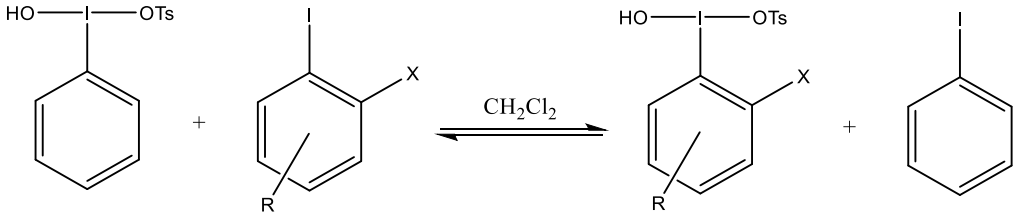


(1.1) **152** (1.0) **9** **153**

R, X = *m*-F, carboxylic acid (81%); ***p*-F, carboxylic acid** (44%); ***o*-F, boronic acid** (detected); **none, nitro** (unobserved)
Scheme 45

Various reactions that produced lower yields were also performed using 1,2-dichloroethane under reflux in an attempt to optimize yields as shown in Scheme 45.

Table 3: Reaction details of new *ortho*-substituted (X) product with secondary group (R).



9 **152** **153** **24**

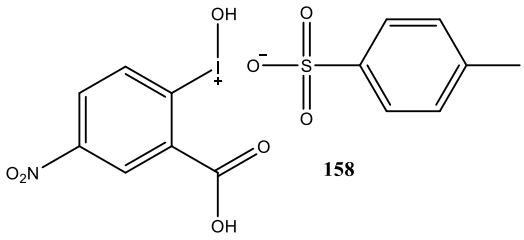
Starting Material	*Ortho*- Group (X)	Secondary Group (R)	Yield	MP (°C)
2-Iodobenzoic Acid	Carboxylic Acid	none	98%	113.0-115.0
2-Iodo-5-Methylbenzoic acid	Carboxylic Acid	*p*- Methyl	99%	128.5-129.0
2-Iodo-4-Methylbenzoic acid	Carboxylic Acid	*m*- Methyl	75%	130.8-133.8
2-Iodo-3-Methylbenzoic acid	Carboxylic Acid	*o*- Methyl	43% (68%)*	139.4-140.1
2-Iodo-5-Nitrobenzoic acid	Carboxylic Acid	*p*- Nitro	69%	204.9-206.1
2-Iodo-5-Bromobenzoic acid	Carboxylic Acid	*p*- Bromo	79%	212.5-213.4
2-Iodo-5-Chlorobenzoic acid	Carboxylic Acid	*p*- Chloro	77%	183.5-185.9
2-Iodo-5-Fluorobenzoic acid	Carboxylic Acid	*p*- Fluoro	53% (44%)**	104.1-106.5
2-Iodo-4-Fluorobenzoic acid	Carboxylic Acid	*m*- Fluoro	53% (81%)**	144.0-145.5
2-Iodonaphthoic acid	Carboxylic Acid	*m,p*- Naphthalene	70%	199.4-201.9
2,5-Diiodobenzoic acid	Carboxylic Acid	*p*- Iodo	18%	209.0-210.1
2-Nitroiodobenzene	Nitro	none	34%	132.6-133.7
2-Fluoro-6-iodophenylboronic acid	Boronic Acid	*m*- Fluoro	35%	143.3-144.8

* indicates reaction condition with two equivalents of *p*-TsOH
** Indicates reaction condition under reflux using 1,2-dichloroethane

Elemental analysis was performed for each new compound in order to determine overall stoichiometry of each structure. Each product was sent for analysis with

theoretical values based on the acyclic benziodoxle like products depicted in Table 4. Obtained elemental analysis values for carbon, hydrogen, iodine, and sulphur are in parenthesize with their potential structure below. The boronic acid structure was determined to have a cyclic structure based on X-ray crystal analysis, which will be expanded upon in the next section.

Table 4: Proposed structures and IUPAC names for new-five membered heterocycles with Elemental Analysis details.



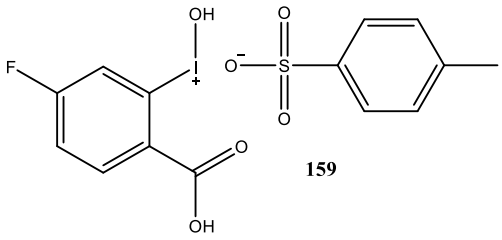
158

(2-carboxy-4-nitrophenyl)(hydroxy)iodonium 4-methylbenzenesulfonate

Chemical Formula: $C_{14}H_{12}INO_8S$

Exact Mass: 480.93

Elemental Analysis: C, 34.94 (34.93); H, 2.51 (2.54); I, 26.37 (26.33); N, 2.91; O, 26.60; S, 6.66 (6.80)



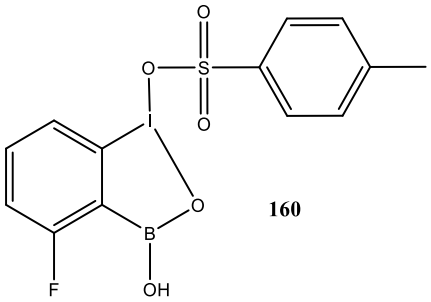
159

(2-carboxy-5-fluorophenyl)(hydroxy)iodonium 4-methylbenzenesulfonate

Chemical Formula: $C_{14}H_{12}FIO_6S$

Exact Mass: 453.94

Elemental Analysis: C, 37.02 (36.53); H, 2.66 (2.60) ; F, 4.18; I, 27.94 (27.16); O, 21.13; S, 7.06 (7.34)



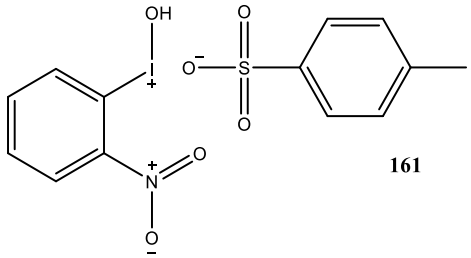
160

4-fluoro-3-hydroxy-1λ^3-benzo[*d*][1,2,3]iodaoxaborol-1(3*H*)-yl 4-methylbenzenesulfonate

Chemical Formula: $C_{13}H_{11}BFIO_5S$

Exact Mass: 435.94

Elemental Analysis: C, 35.81 (35.86); H, 2.54 (2.58); B, 2.48; F, 4.36; I, 29.11 (28.95); O, 18.35; S, 7.35 (7.35)



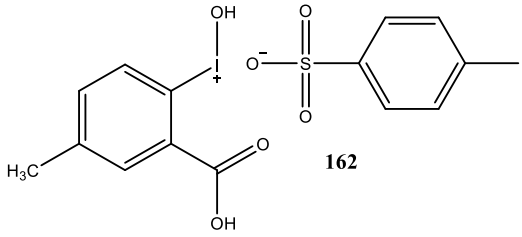
161

hydroxy(2-nitrophenyl)iodonium 4-methylbenzenesulfonate

Chemical Formula: $C_{13}H_{12}INO_6S$

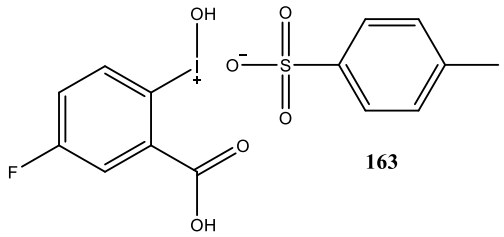
Exact Mass: 436.94

Elemental Analysis: C, 35.71 (39.72); H, 2.77 (3.22); I, 29.03 (32.28); N, 3.20; O, 21.96; S, 7.33 (8.23)



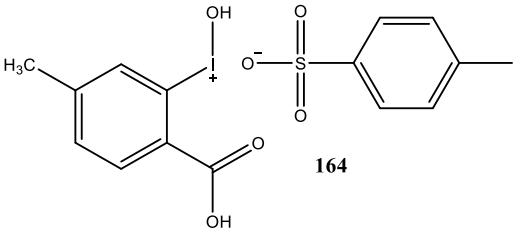
162

(2-carboxy-4-methylphenyl)(hydroxy)iodonium 4-methylbenzenesulfonate
Chemical Formula: $C_{15}H_{15}IO_6S$
Exact Mass: 450.0
Elemental Analysis: C, 40.02 (40.05); H, 3.36 (3.27);
I, 28.19 (28.38); O, 21.32; S, 7.12 (6.97)



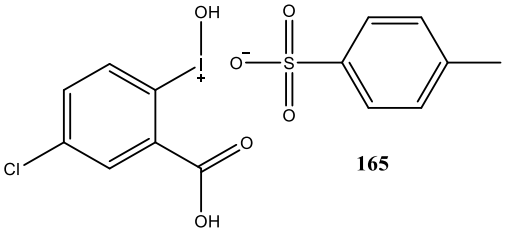
163

(2-carboxy-4-fluorophenyl)(hydroxy)iodonium 4-methylbenzenesulfonate
Chemical Formula: $C_{14}H_{12}FIO_6S$
Exact Mass: 453.9
Elemental Analysis: C, 37.02 (34.30); H, 2.66 (2.62); F, 4.18;
I, 27.94 (29.40); O, 21.13; S, 7.06 (5.66)



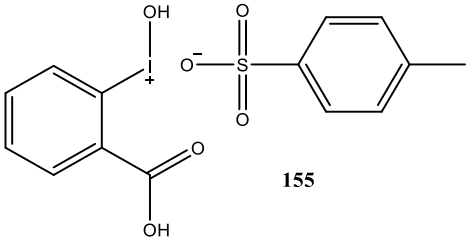
164

(2-carboxy-5-methylphenyl)(hydroxy)iodonium 4-methylbenzenesulfonate
Chemical Formula: $C_{15}H_{15}IO_6S$
Exact Mass: 450.0
Elemental Analysis: C, 40.02 (38.78); H, 3.36 (3.70);
I, 28.19 (26.85); O, 21.32; S, 7.12 (7.05)



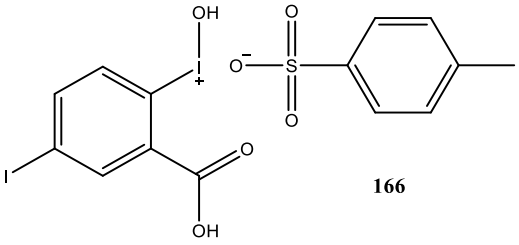
165

(2-carboxy-4-chlorophenyl)(hydroxy)iodonium 4-methylbenzenesulfonate
Chemical Formula: $C_{14}H_{12}ClIO_6S$
Exact Mass: 469.9
Elemental Analysis: C, 35.73 (34.18); H, 2.57 (2.35); Cl, 7.53;
I, 26.96 (31.83); O, 20.40; S, 6.81 (5.00)



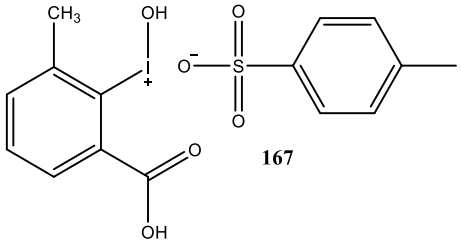
155

(2-carboxyphenyl)(hydroxy)iodonium 4-methylbenzenesulfonate
Chemical Formula: $C_{14}H_{13}IO_6S$
Exact Mass: 435.9
Elemental Analysis: C, 38.55 (38.58); H, 3.00 (3.14);
I, 29.09 (28.90); O, 22.01; S, 7.35 (7.40)



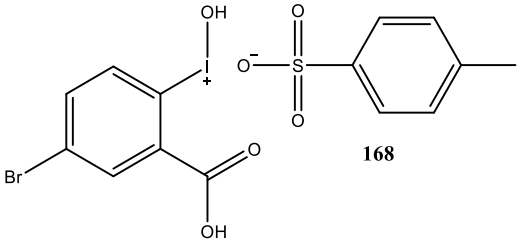
166

(2-carboxy-4-iodophenyl)(hydroxy)iodonium 4-methylbenzenesulfonate
Chemical Formula: $C_{14}H_{12}I_2O_6S$
Exact Mass: 561.8
Elemental Analysis: C, 29.91 (24.23); H, 2.15 (1.54);
I, 45.15 (57.97); O, 17.08; S, 5.70 (2.47)



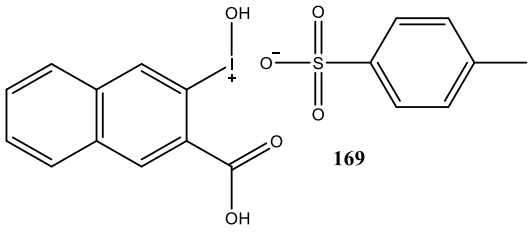
167

(2-carboxy-6-methylphenyl)(hydroxy)iodonium 4-methylbenzenesulfonate
Chemical Formula: $C_{15}H_{15}IO_6S$
Exact Mass: 450.0
Elemental Analysis: C, 40.02 (40.11); H, 3.36 (3.24); I, 28.19 (28.21); O, 21.32; S, 7.12 (7.19)



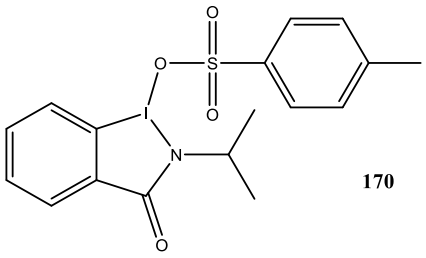
168

(4-bromo-2-carboxyphenyl)(hydroxy)iodonium 4-methylbenzenesulfonate
Chemical Formula: $C_{14}H_{12}BrIO_6S$
Exact Mass: 513.9
Elemental Analysis: C, 32.64 (25.26); H, 2.35 (1.38); Br, 15.51; I, 24.64 (33.90); O, 18.64; S, 6.22 (1.00)



169

(3-carboxynaphthalen-2-yl)(hydroxy)iodonium 4-methylbenzenesulfonate
Chemical Formula: $C_{18}H_{15}IO_6S$
Exact Mass: 485.96
Elemental Analysis: C, 44.46 (42.89); H, 3.11 (3.47); I, 26.10 (25.29); O, 19.74; S, 6.59 (6.31)



170

2-isopropyl-3-oxo-2,3-dihydro-1*H*-1λ^3-benzo[*d*][1,2]iodazol-1-yl 4-methylbenzenesulfonate
Chemical Formula: $C_{17}H_{18}INO_4S$
Exact Mass: 459.00
Elemental Analysis: C, 44.46; H, 3.95; I, 27.63; N, 3.05; O, 13.93; S, 6.98

Additional details on the preparation of these compounds are available, including the general workup procedures, in Section 3.3, along with H^1 & C^{13} NMR spectra in the appendix. Compound **170** will be discussed further in Section 2.4.

2.1.C. Summary:

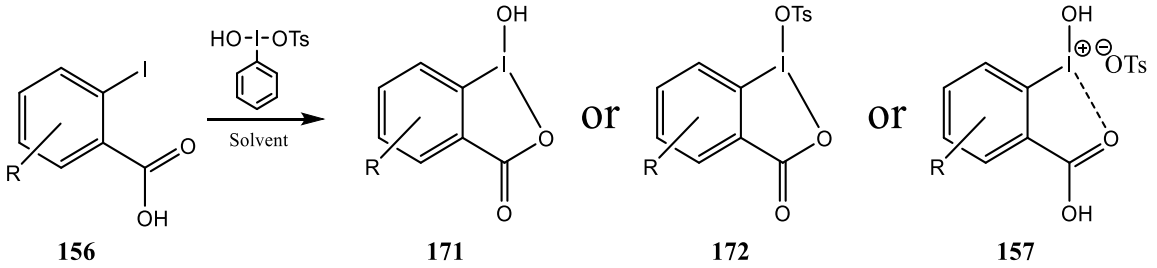
The reactions between *ortho*-substituted iodoarenes and HTIB was successfully performed in order to synthesize new Koser reagent derivatives most in moderate to high yields. Method optimization has been done in order to easily acquire clean products for use in future applications. Preliminary research has observed that the *para*-halogenated derivatives synthesized are to some degree unstable, have moderate to low yields, and

appear to degrade over time unlike the methyl substituted products, which could be a result of the electron withdrawing nature of halogens. The extremely low yields associated with the *p*-iodo product **166** is most likely due to the second iodine's sensitivity to HTIB that was previously mentioned creating a lack of chemoselctivity and mixture of products. However, the electron withdrawing nature of the secondary group does not explain the exceptional stability that 5-nitro-2-iodobenzoic acid derivative exhibits which is observed by the compounds stability over time by H^1 & C^{13} NMR.

2.2. Structural Characterization and Analysis of New Five-Membered Heterocycles

2.2.A. Introduction:

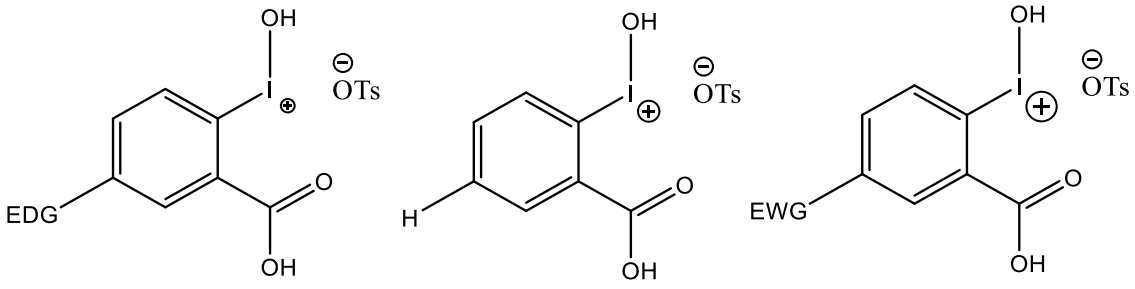
The use of hypervalent iodine compounds for selective oxidations of various substrates have been studied rigorously over the past 40 years especially for HTIB due to its unique reactivity.[1] However, little is known about the structural characteristics of these new five-membered heterocycles or benziodoxle like compounds derived from HTIB. The stability of these new reagents with various nitro, amine, boronic acid and carboxylic acid *ortho*-substituents is determined using NMR spectroscopy. It is of interest to gain a better understanding of structural configuration of these new compounds and could be of use for predicting each compounds reactivity for selective oxidations. The structural position of the *ortho* substituent to the iodine can either form a ring to form a cyclic 5-membered heterocycle like IBA or the structure could be coordinated in an acyclic fashion, which is commonly unstable. Some examples of the possible structural rearrangements are depicted in Scheme 46.



156 **171** **172** **157**

Scheme 46

In order to study the structure of these HTIB derivatives it is important to consider the cationic nature of the iodine that is created from its two electrons that exist in their non-bonding orbital. Thus different variations of these Koser reagents will be created in order to observe structural differences or changes in reactivity from the attachment of electron donating or electron withdrawing substituents. A theoretical depiction of the effect that *p*-oriented electron donating or withdrawing groups might have on the hypervalent iodine is shown in Scheme 47.



174 **155** **173**

Scheme 47

The purpose of this research will be to create a number of different Koser reagent derivatives with different electronic configurations along with a synthetic method to obtain crystal structures in order to confirm their geometry, compare them to the crystal

structure geometry of HTIB, and finally utilize them for reactions that can be used in simple but selective oxidation reactions.[16]

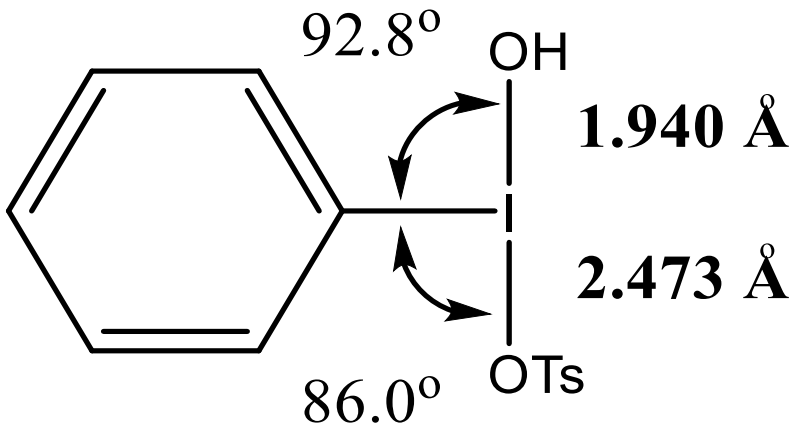


Figure 8: Structure of HTIB based on X-ray analysis.

2.2.B. Results and Discussion:

The structural analysis of the synthesized HTIB derivatives was initially performed by NMR and Elemental Analysis. The synthesized compounds were then used to saturate various solvents, which were allowed to slowly evaporate in order to grow crystals for single crystal X-Ray analysis. Crystals were grown in ethyl acetate, methanol, and acetonitrile, and some samples were prepared by adding 300 μL of one of the previously mentioned saturated solvent systems with 300 μL of hexanes carefully added above that with the purpose of testing solubility's of these new compounds and determining an effective solvent for growth of single crystals. As crystals developed and were analyzed by X-ray crystallography, acetonitrile was determined to be the most effective solvent system. Single crystals were successfully produced using methanol and ethyl acetate, however, the crystal structures did not contain tosylate groups which were previously confirmed by NMR and elemental analysis.

Two crystals structures were produced in acetonitrile by single crystal X-Ray crystallography of new five-membered heterocycles **160** and **167** (Figure 9)**.**

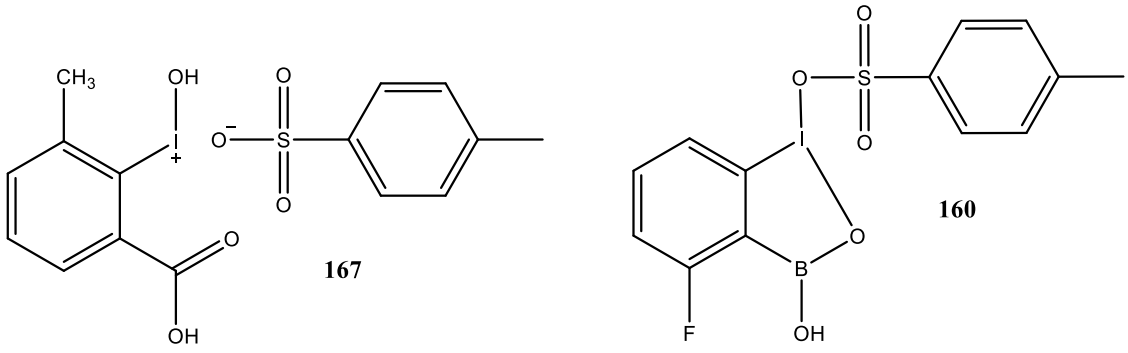


Figure 9: Structure of two compounds analyzed by X-ray crystallography.

Compound **160** is a boronic acid HTIB derivative as depicted in Figure 10. The bond length of 1.991Å between I-O bond is important in this structure since 1.99Å is the sum of the covalent radii of iodine and oxygen.[16] The structure of the *ortho*-iodoarene substituent (boronic acid) is interesting since iodine is unable to bind itself to the oxygen of boronic acid as tightly as a hydroxyl group is with HTIB. This in turn may allow electron density between the two axial ligands to be shared more evenly due to the lack of hyper-conjugation from boron's empty p-orbitals in comparison to other elements. The bond angles associated with the hypervalent iodine atom are 85.14^{o} (C-I-OTs) and 84.96^{o} (C-I-OBOH) both of which are smaller in comparison to HTIB. The crystal structure with key bond lengths and angels are in Figure 10. In regards to the packing of the crystal structure for compound (**160**) there are only two short contacts of 2.318Å and 2.696Å between each molecule as shown in Figure 12.

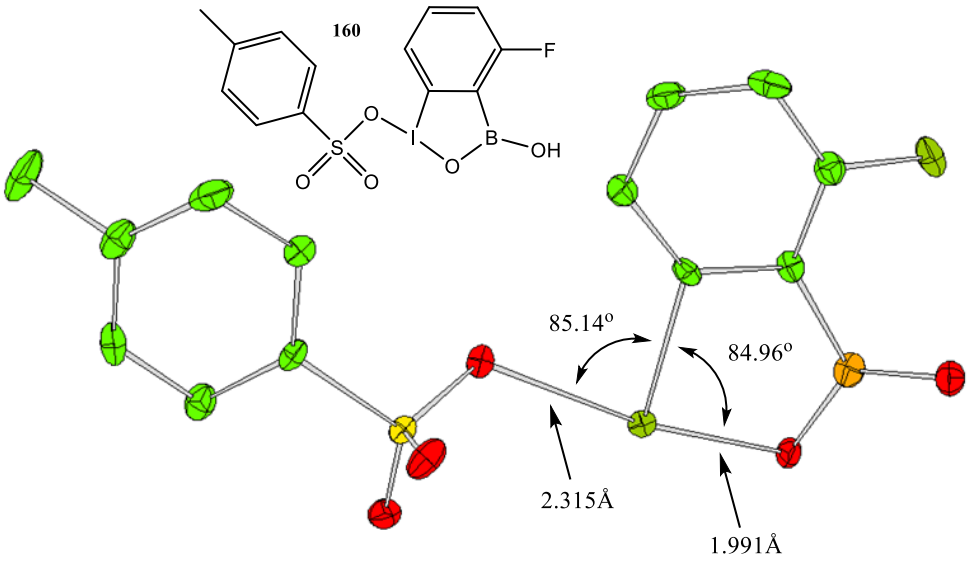


Figure 10: Crystal structure of compound **160** with key bond lengths and angles.

The other crystal structure analyzed was for compound **167**, which is (2-carboxy-6-methylphenyl)(hydroxy)iodonium 4-methylbenzenesulfonate, which is shown in Figure 13. In comparison of compound **167** to HTIB (**9**) it is apparent that the bond lengths around the hypervalent iodine(III) are similar. The I(III) to OTs interaction has a length of 2.945Å suggesting that the interaction is ionic in nature as depicted in Figure 15. The acyclic nature of compound **167** is confirmed by the 2.360Å bond between I(III) and the adjacent oxygen of the carboxylic acid while the 1.937Å bond between I(III) and the hydroxyl group is smaller than the sum of the covalent I-O radii suggesting some hyper conjugation from the hydroxyl group as observed with HTIB.

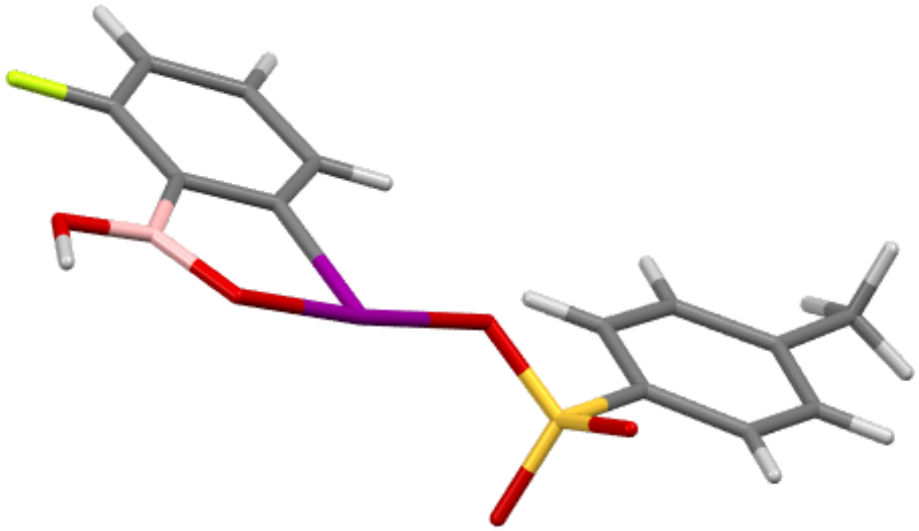


Figure 11: Alternative view of compound **160** based on X-ray analysis.

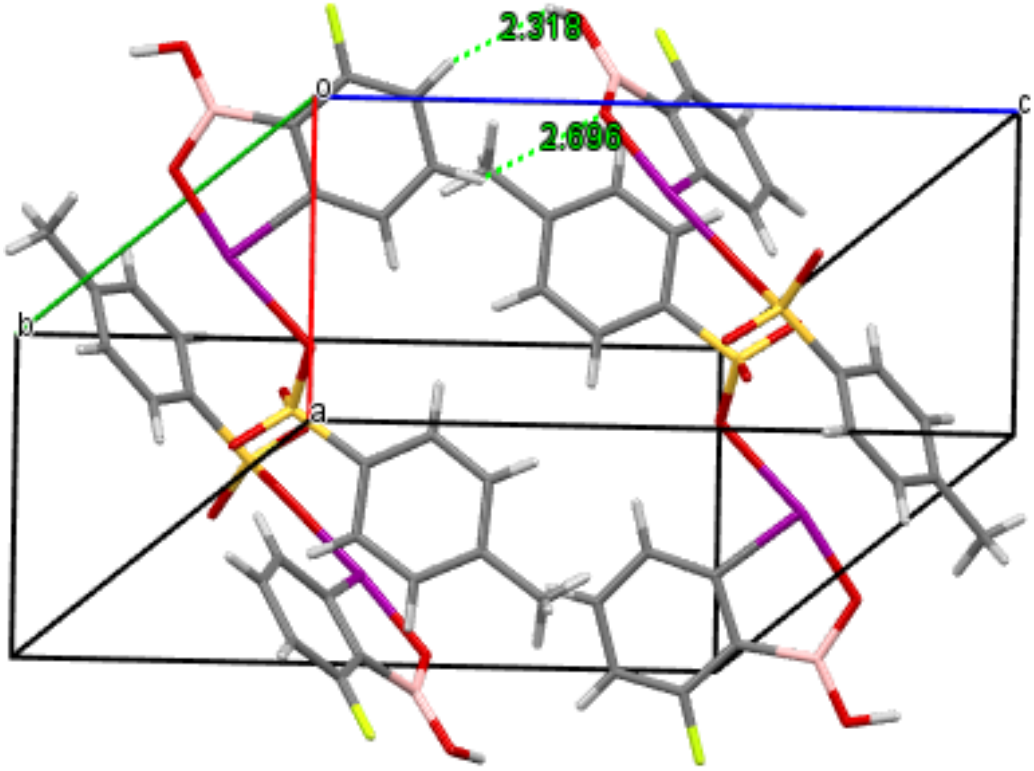


Figure 12: Unit-cell of compound **160** showing short contacts present.

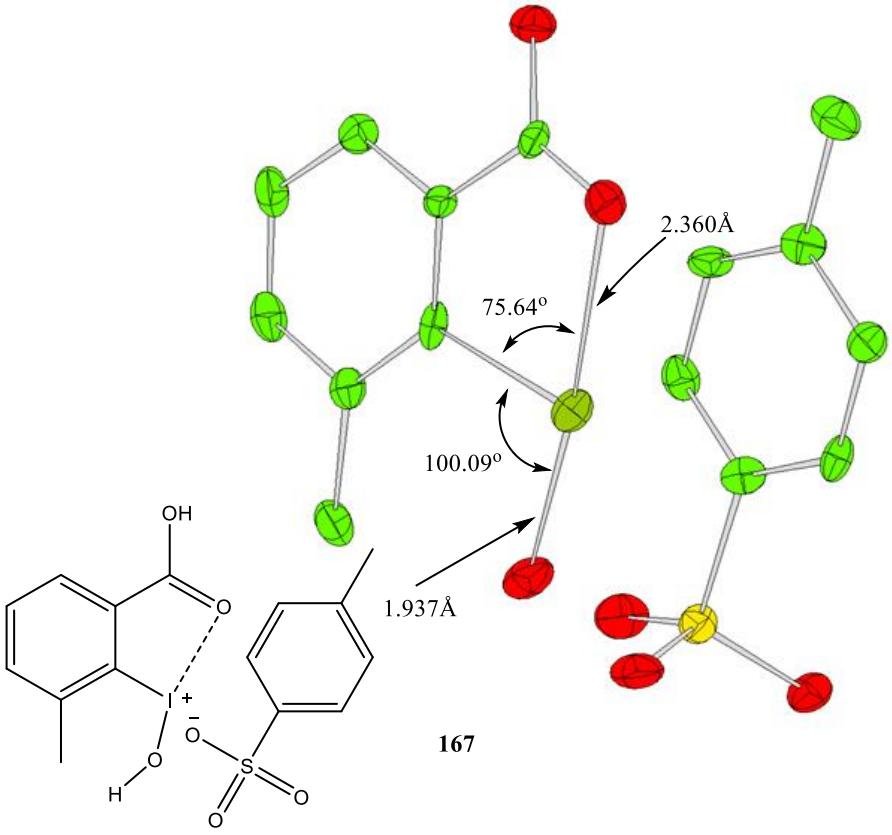


Figure 13: Crystal structure of compound **167** with key bond lengths and angles.

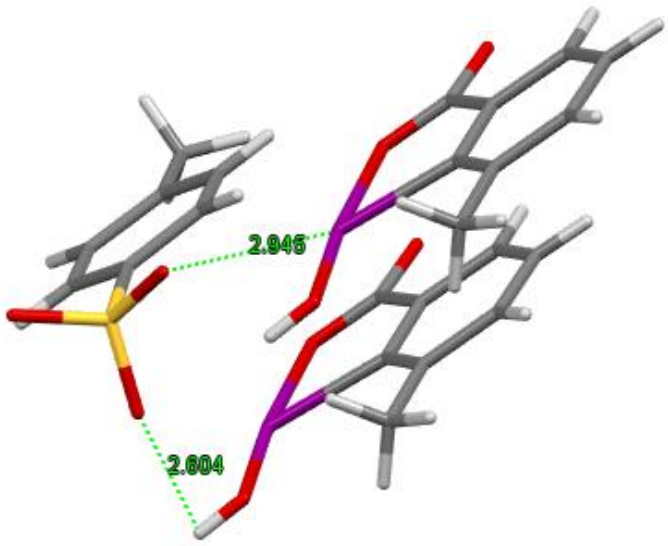


Figure 14: Alternative view of compound **167** showing short contacts present.

The bond angles between associated with the hypervalent iodine are 100.09° (C-I-OH) and 75.64° (C-I-OCOH). The orientation of the tosylate group is depicted in Figure 14 showing its short contact with neighboring molecules.

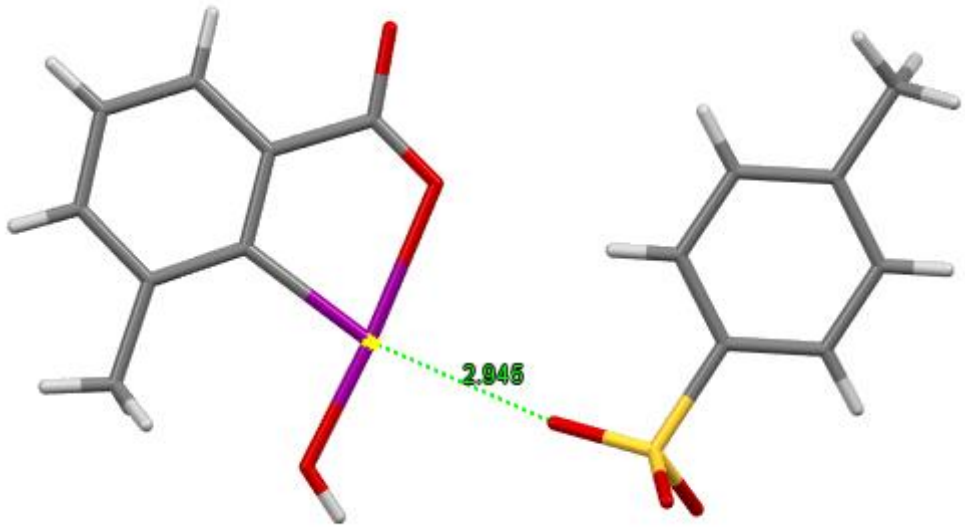


Figure 15: Alternative view of compound **167** showing distance of key anionic contact.

2.2.C. Summary:

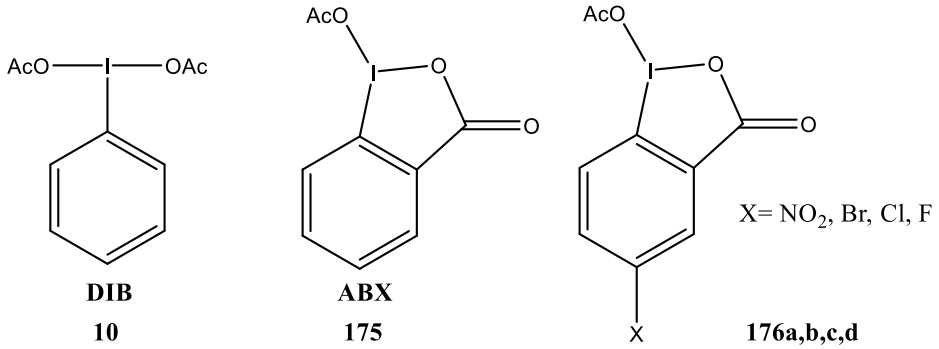
The structural features for a cyclic (**160**) and acyclic (**167**) HTIB derivative show key characteristics that are expected in comparison to HITB (**9**). Key bond lengths and angles were shown with a 2.315Å bond for compound **160** between I(III) and the tosylate group, demonstrating more covalent interactions in comparison to the 2.945Å short contact between I(III) and the tosylate group for compound **167**. While these crystal structures are useful, it is important to acquire additional examples in order to gain a better understanding of the structure of these new five-membered heterocycles. New

crystal strucutres would also be in order to observe if the structure or the electron density of the arene itself has any effect on the overall structure of the HTIB derivative.

2.3. Synthetic Applications of using New Five-Membered Heterocycles for Tosyl Transfer Reactions

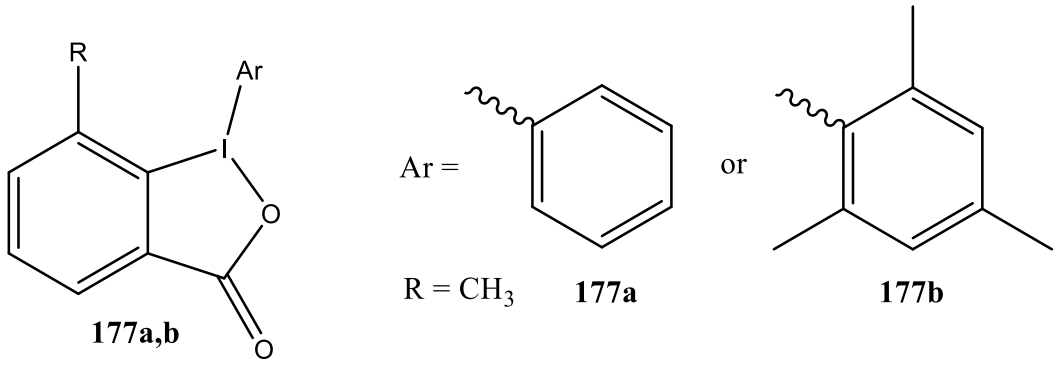
2.3.A. Introduction:

The benign character of organohypervalent iodine compounds make them excellent candidates as versatile oxidants. The purpose of this study is to explore the reactivity of new five-membered heterocycles derived from HTIB that are reffered to by the collective name of benziodoxoles for various tosyl transfer, α-functionalization, and diaryl iodonium salt reactions. The general reactivity of hypervalent iodine complexes is typically influenced by the electron density surronding the hypervalent iodine atom. For example a recent study by Iinuma explored using 1-acetoxy-1,2-benziodoxle-3(1*H*)-one (ABX) in order to create derivatives of DIB (**10**) that have additional electron withdrawing groups on the benzene ring. The electron withdrawing substituents decrease the amount of electron density around the hypervalent iodine atom and make it more susceptible to being attacked by weaker nucleophiles.[30,31]



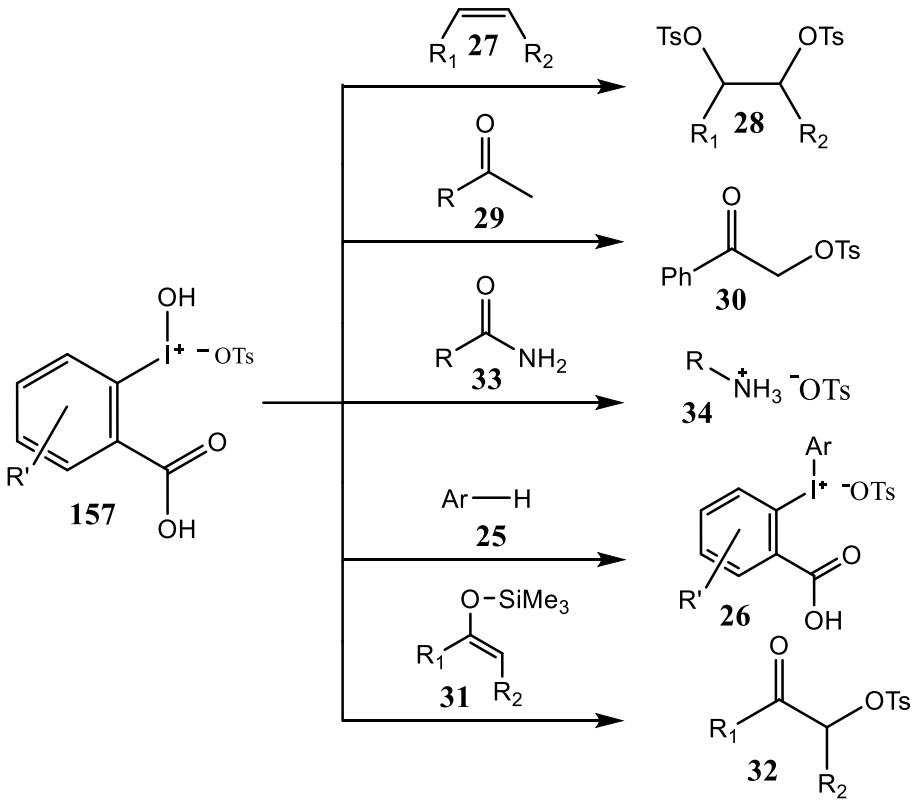
Scheme 48

Yusubov and co-workers have also explored using 1-arylbenziodoxole as new reagents for ligand transfer reactions and found that 1-aryl-7-methylbenziodoxolones had an enhanced reactivity towards nucleophiles in comparison to their unsubstituted counterparts, which suggested that some steric interaction of the nearby methyl group contributed to the reagents enhanced reactivity.



Scheme 49

These new five-membered heterocycles discussed previosuly will be utilized for a number of different reactions similar to those that are typically performed using HTIB in order to observe the chemical reactivity of these new reagents and see if they produce products similar to that of HTIB (Scheme 50) or if new reactivity is observed.[5]

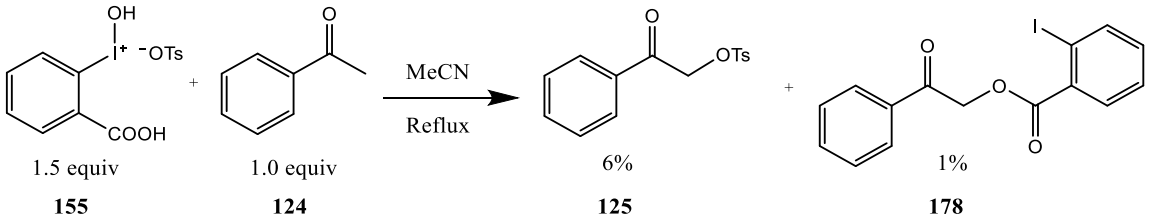


Scheme 50

2.3.B. Results and Discussion:

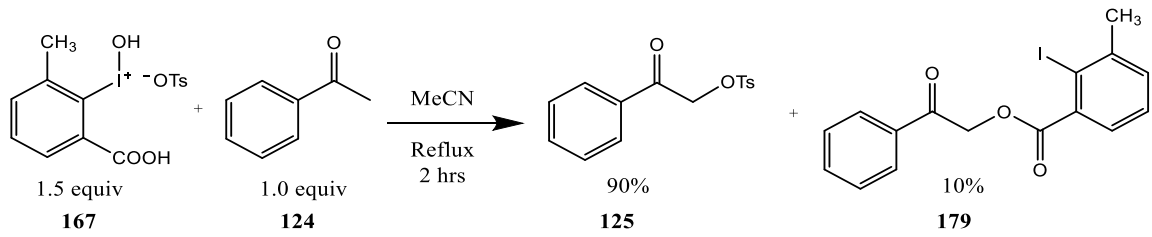
Reactions were performed with the new five-membered heterocycles in order to observe the electronic or steric effect that an R group can have in influencing reactivity or selectivity in products. A common application of HTIB is for the α−functionalization (**30**) of acetophenone (**29**). Thus a series of reactions can be performed in order to observe the electronic and steric effects that a methyl group on an iodoarene has the reactivity of these new five-membered heterocycles. The first representative reaction involves using the new five-membered heterocycle (2-carboxyphenyl)(hydroxyl) iodonium 4-methylbenzenesulfonate (**155**) in excess and acetophenone under reflux for 2

hours in acetonitrile as depicted in Scheme 51.



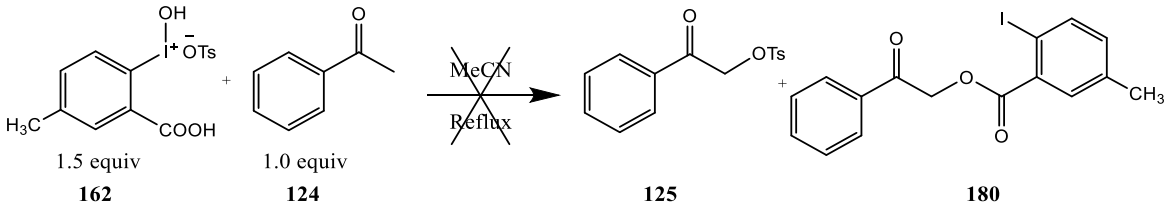
Scheme 51

The reaction proceeded with low yields of two α–functionalized products one being the α–tosylated product (6% yield) and the other being the esterification of acetophenone incorporating the carboxylic acid portion of the new heterocycle. (2-carboxy-6-methylphenyl)(hydroxy)iodonium 4-methylbenzenesulfonate (**167**) was observed under the same conditions and produced a 90% yield of the α–tosylated product and 10% of the minor α–ester product shown in Scheme 52.



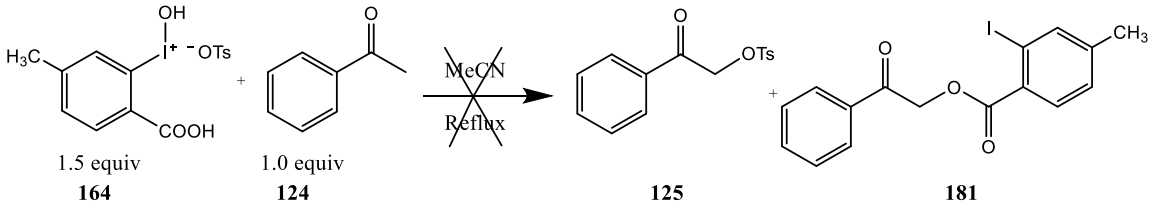
Scheme 52

However, the electron donating contributions by methyl group appear to have no effect on the reactivity of this reaction due to the reaction not proceeding in the presence of (2-carboxy-4-methylphenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate (**162**) as depicted in Scheme 53.



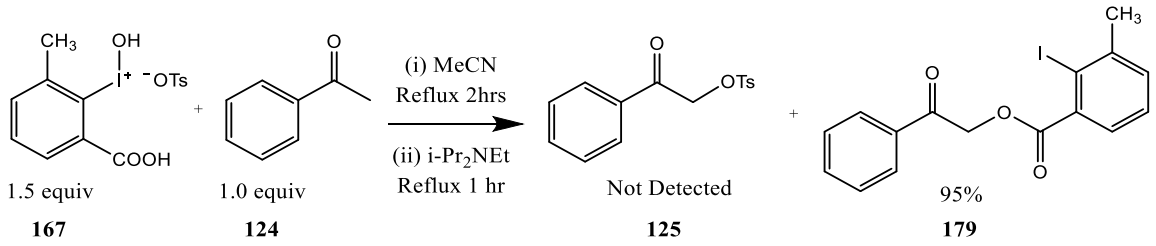
Scheme 53

The reactivity for (2-carboxy-5-methylpheny)(hydroxyl)iodonium 4-methylbenzenesulfonate (**164**) also did not proceed to create the α–tosylated product or the α–ester product based on NMR or GC-MS analysis shown in Scheme 54.



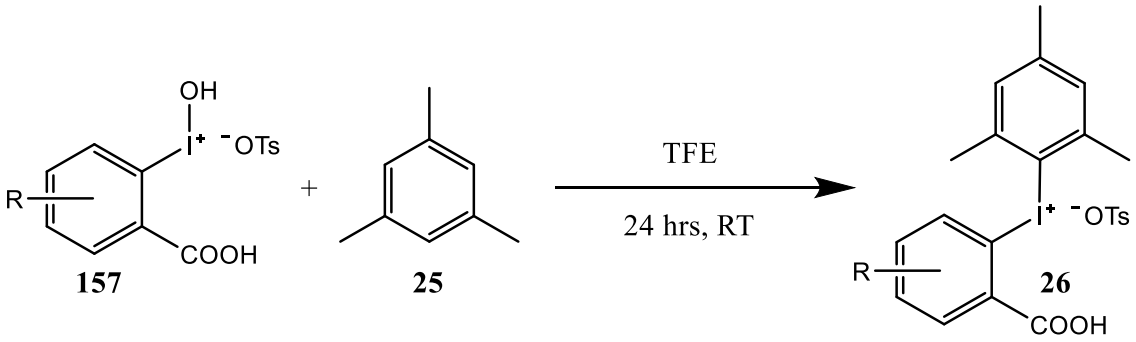
Scheme 54

The reactive (2-carboxy-6-methylphenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate (**167**) heterocycle was used again but in the presence of a Hunig base (*N*,*N*-Diisopropylethylamine) in order to deprotonate the carboxylic acid. The reaction under reflux for 2 hours in acetonitrile and then for an additional hour in the presence of a Hunig base was very selective and produced a 95% yield of the lone α–ester product as shown in Scheme 55.



Scheme 55

Another reaction that was explored involved the synthesis of unsymmetrical diaryl iodonium salts (**26**) using these new five-membered heterocycles and arenes (**25**) capable of performing electrophilic aromatic substitutions like mesitylene. Different variations of these new five-membered heterocycles have been tested in order to observe their reactivity towards arenes and the overall stability of the iodonium slats formed. As discussed previously many of the *p*-halogenated derivatives have been observed to be less stable and were utilized as reagents for the synthesis of different iodonium salts (three examples **186-189**). Compounds **182-190** were successfully synthesized as different variations of compound **26** with moderate to high yields using the method described in Scheme 56.

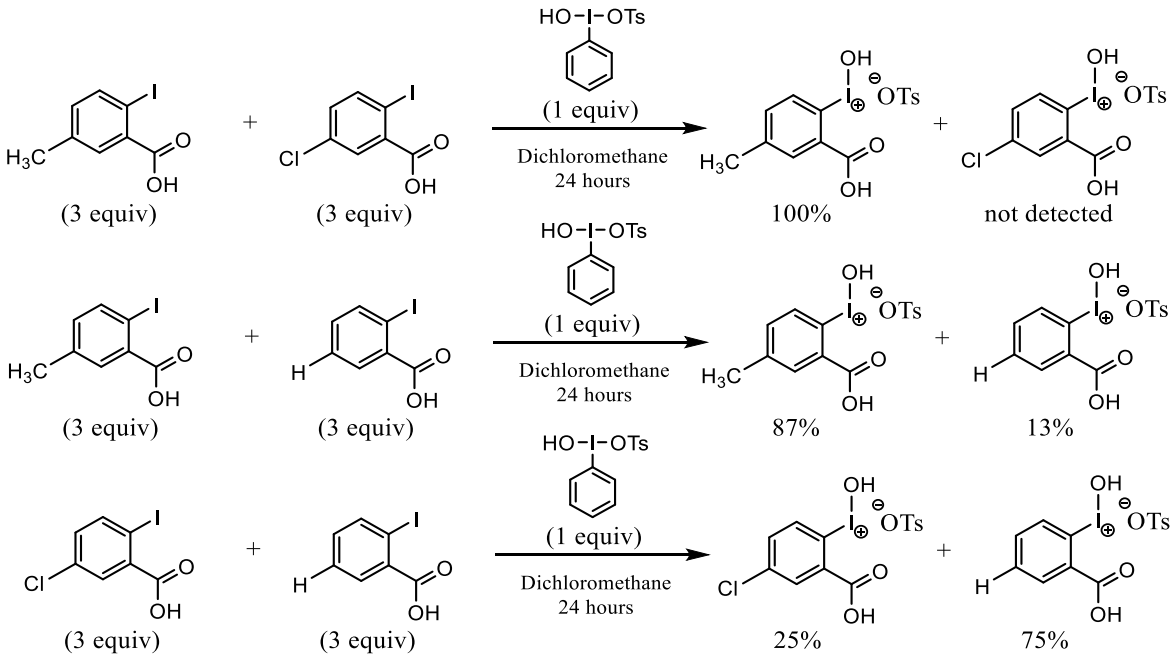


R = H (91%), ***o*-Me** (89%), ***m*-Me** (79%), ***p*-Me** (60%), ***m*-F** (47%), ***p*-F** (68%), ***p*-Cl** (68%), ***p*-Br** (79%), **Naphthoic Acid** (55%)

Scheme 56

Basic kinetic studies were performed by competitively reacting different excess starting materials with various electronic donating or withdrawing characteristics with a limited amount of HTIB. Scheme 57 describes three different combinations using products **155, 162** & **165** in order to observe the ratio of products, which can be determined using H^1 NMR in conjunction with an internal standard. The observed results from these three kinetic studies show that the electron donation from the methyl group

appears to have a significant effect on yield. The electron donating effect in the *para*-position of the iodoarene starting material, 5-methyl-2-iodobenzoic acid, appears to make it much more reactive towards HTIB. The increased reactivity of 5-methyl-2-iodobenzoic acid could be occurring due to the electron rich nature of the starting materials giving it the ability to participate in the oxidation step more quickly in comparison to electron deficient starting materials, like 5-chloro-2-iodobenzoic acid. Overall, electron deficient starting materials appear to be less reactive towards HTIB when placed in a competitive environment with comparable electron rich starting materials based on results in Scheme 57.



Scheme 57

2.3.C Summary:

To summarize the use of new five-member HTIB derived heterocycles were used to synthesize new products for synthetic applications including α–functionalization

reactions and for the synthesis of new unsymmetrical iodonium salts. The steric interaction of (2-carboxy-6-methylphenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate (**167**) greatly enhanced its reactivity for the α–tosyloxylation of acetophenone or for producing an α–ester product in the presence of Hunig base both in 90+% yields.

The synthesis of various iodonium salts including *para*-halogenated derivatives were successfully synthesized in moderate to high yields. However, further work should be done to improve yields and develop *in-situ* applications in order to improve their use as reagents for diaryliodonium salt synthesis as well as to find other applications for these new five-membered HTIB derived heterocycles.

The kinetic studies show that there is a correlation between the reactivity of the iodine and electronic influences in the *para*-position of the iodoarene. The study does suggest that more electron deficient starting materials are less likely to react with HTIB when in competition with similar electron rich starting materials.

2.4. Conclusions and Future Directions

To conclude as a result of this research the discovery of 13 new examples of five-membered HTIB derived heterocycles have been synthesized, 7 of which are fully characterized by H^1 and C^{13} NMR, elemental analysis, and 2 of which have been analyzed X-ray crystal analysis. The instability of the halogenated derivatives are still being explored and more work needs to be done to isolate these product in pure form for characterization either by elemental analysis, ESI-MS, or X-ray crystallography.

The two crystal structures obtained consisted of both a cyclic and acyclic example in regards to structure of these new five-membered HTIB derived heterocycles. The structures showed a 0.63A difference in the anionic interaction between the tosylate group and the hypervalent iodine, which could be useful in predicting trends for the reactivity of these compounds in relation to structure if more crystal structures are obtained.

These new five-membered HTIB derive heterocycles have successfully been used for various α–functionalization reactions and for the synthesis of new unsymmetrical iodonium salts in moderate to high yields. Future studies should include method optimization of starting HTIB derivatives, including more *in-situ* methods, for potential products using these reagents in order to demonstrate the synthetic utility of these reagents. Additional kinetic studies using *m*-iodobenzoic acid and *p*-iodobenzoic acid derived HTIB variations would be useful for analyzing the effect that the carboxylic acid group has on the reactivity of these reagents for transtosylation reactions. Other directions include creating other HTIB derivatives that utilize *o*-iodobenzylamides (**170**) starting materials and observing the effect that other *o*-iodoarene substituents have on the synthetic utility of these reagents.

Section 3:

Experimental Design

3.1. General Methods

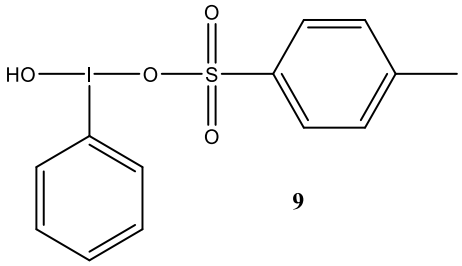
All melting points were determined in an open capillary tube with a Mel-temp II® melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian UNITY INOVA 500 MHz NMR spectrometer at 500 MHz (H^1 NMR), and 125 MHz (C^{13} NMR); chemical shifts are reported in parts per million (ppm) with H^1 and C^{13} chemical shifts referenced to the corresponding solvent. Elemental Analysis samples were prepared and performed by Atlantic Microlab Inc. in Norcross, Georgia for analysis of carbon, hydrogen, sulfur, and iodine content. GC-MS analysis was carried out with an Agilent 7890A gas chromatography system using a 5975C Series mass selective detector.

3.2. Materials

All commercial reagents were ACS reagent grade and used without further purification. All silica gel columns were constructed using 63-200μm, 60Å silica gel from Dynamic Adsorbents, Inc.

3.3 Synthesis of Compounds

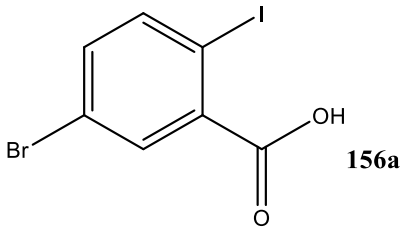
Hydroxy[(tosyloxy)iodo]benzene (HTIB or Koser's Reagent)



9

The most common method for preparing HTIB uses DIB and *p*-toluene sulfonic acid monohydrate in acetonitrile as described in Scheme 1. Product (**9**) was prepared by adding 5000mg (15.5mmol) of diacetoxyiodobenzene and 3090mg (16.2mmol) of *p*-toluene sulfonic acid monohydrate in 20.0mL of acetonitrile, which was allowed to react under reflux for 1 hour while stirring. After refluxing, the reaction mixture was allowed to cool to room temperature and stir overnight before being filtered and washed with acetonitrile to obtain the final product. H^1 NMR (500MHz, DMSO-d6): δ 8.21 (d, 2H), 7.70 (t, 1H), 7.62 (t, 2H), 7.46 (d, 2H), 7.10 (d, 2H)

5-Bromo-2-iodobenzoic acid

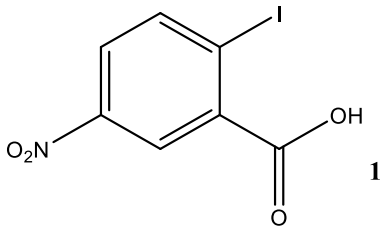


156a

5-bromo-2-iodobenzoic acid (**156a**) was synthesized according to literature by Valois-Escamilla *et al.*[32] A 1240mg (5.0mmol) sample of 2-Iodobenzoic acid was added to 10.0mL of concentrated sulfuric acid, which then was stirred and heated to 60°C until the starting material dissolves to form a pale yellow solution. While maintaining constant temperature, 1068mg of *N*-bromosuccinamide (NBS) (1.2mmol) was added to the reaction mixture in 3 equal portions 15 minutes apart and the reaction continued for a total of 90 minutes. **Note: If the reaction cools to 50°C to desired product will precipitate and cause the reaction to cease affecting yield. Heating the reaction to an excess over 70°C will cause the removal of iodine from the starting material and the**

desired product as is noticed by the formation of crystalline iodine. The precipitated product is washed with ice water and filtered. The filtered product is then dissolved in ethyl acetate and washed with an aqueous brine in a seperatory funnel. The organic layer is collected, dried using sodium sulfate, reduced in a rotovap, and vacuum dried. The dried solid was then dissolved using acetone and precipitated using 35-60^{o} petroleum ether, filtered, and recrystallized with 95% ethanol. A 53% yield was obtained with a melting point range of 160-161^{o}C. H^{1} NMR (500MHz, DMSO-d6): δ 7.88 (d, 1H), 7.83 (s, 1H), 7.42 (d, 1H)

5-Nitro-2-iodobenzoic acid

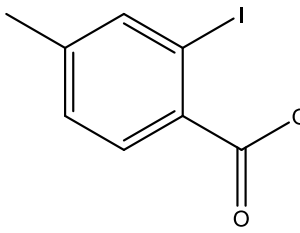


156b

5-nitro-2-iodobenzoic acid (**156b**) was synthesized in reference to literature by Uyanik *et al.*[33] The following product was synthesized by adding 1000mg (5.49mmol) of 2-amino-5-nitrobenzoic acid to 10.0mL of 0.5M sodium hydroxide solution. The mixture was stirred and heated until the orange solid dissolved and formed a yellow solution. Slowly, 2.0mL of 12M HCl was added to form a light yellow suspension and was placed on ice. While the mixture was being stirred on ice 379mg (5.49mmol) of sodium nitrite, dissolved in 5mL of distilled water, was added to the suspension in order to form the diazonium salt. After 30 minutes of stirring 1820mg of crushed potassium iodide briquettes, dissolved in 5.0mL of distilled water, was stirred for additional hour on ice

while gas evolved and the product turned dark orange and stirred overnight at room temperature. The product was then filtered and washed with water to obtain a crude orange solid. Recrystallization was performed with ethyl acetate to acquire a pale orange solid that was vacuum dried. A total of 353mg (34% yield) of clean product was isolated. H^1 NMR (500MHz, MeOH-d4): δ 8.57 (s, 1H), 8.31 (d, 1H), 8.03 (d, 1H)

4-Methyl-2-iodobenzoic acid

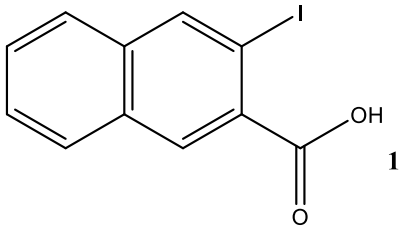


156c

4-methyl-2-iodobenzoic acid (**156c**) was synthesized in reference to literature by Vaidyanthan *et al.*[34] 4-methyl-2-iodobenzoic acid was synthesized using 1512mg (10.0mmol) of starting material 2-amino-4-methylbenzoic acid. The solid starting material was placed in a flask with 12 grams of ice and then a solution, made up of 18.0mL of water and 2.0mL of concentrated sulfuric acid, was added to the flask. The mixture was stirred on ice (2-3^{o}C) and a creamlike suspension formed. Over a 10 minute period 747mg (10.8mmol) of sodium nitrite, dissolved in 6.0mL of distilled water, was added to the mixture and an orange suspension was formed. The mixture was stirred for 2 hours in order for the diazonium salt to form and then 2280mg (10.8mmol) of potassium iodide briquettes, ground up and dissolved in 5.0mL of distilled water, was slowly added over the course of 15 minutes on ice and the mixture turned dark instantly upon the first drop. Potassium iodide was then added to the mixture and heated to 60^{o}C for 1 hour, which caused the mixture solidify and then dissolve as a red solution. The product was

then extracted using ethyl acetate. The organic layer was collected and washed using saturated sodium thiosulfate twice and then dried using an aqueous brine. The dried organic layer was reduced on the rotovap, separated on a silica column with a 70:30:0.01 ethyl acetate, hexane, and acetic acid gradient, and dried under vacuum for 6 hours to obtain 1716mg of orange solid. **Note: The column suggested by Vaidyanthan *et al.* was not effective in separating the two components observed with TLC and would skip using the silica column and purify using recrystallization.** The orange solid was then recrystallized using acetonitrile, filtered, and rinsed with additional cold acetonitrile to isolate a light brown product. H^1 NMR (500MHz, MeOH-d4): δ 7.87 (s, 1H), 7.73 (d, 1H), 7.26 (d, 1H), 2.34 (s, 3H)

3-Iodo-2-naphthonic acid

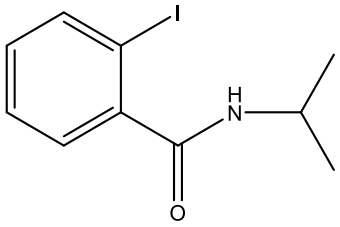


156d

3-iodo-2-naphtoic acid (**156d**) was synthesized in reference to literature by Uyanik *et al.*[33] The desired product (**156d**) was derived from 3-amino-2-naphtonic acid via a sandmeyer type reaction using 1000mg (4.27mmol) of starting material with 10.0mL of distilled water and 5g of ice to produce a yellow suspension. The mixture was placed on ice. Then 6.0mL of concentrated hydrochloric acid was added slowly to the mixture to produce a brown solution. 345mg (5.0mmol) of sodium nitrite was slowly added to the mixture and was allowed to react for 30 minutes while being stirred on ice. A solution of

potassium iodide made using 1035mg (8.0mmol) of potassium iodide and 5.0mL of distilled water was added over the course of 5 minutes to the mixture to form a dark red solution. The mixture was then removed from the ice bath and heated in a boiling water bath (90-100^{o}C) for 30 minutes to form a black suspension. The desired product was then extracted using ethyl acetate four times and washed with concentrated sodium thiosulfate twice. The red organic layer was dried using sodium sulfate and reduced using a rotovap to produce a crude red solid. The solid was then ran through a silica column with a 10:1:0.01 hexane, ethyl acetate, acetic acid gradient to produce a brown solid after reducing the solution and drying the isolated product under vacuum to acquire 456mg (36%) of solid. H^1 NMR (500MHz, DMSO-d6): δ 13.30 (s, 1H), 8.57 (d, 1H), 8.30 (d, 1H), 7.93 (t, 2H), 7.56 (d, 2H)

2-iodo-*N*-isoproylbenzamide

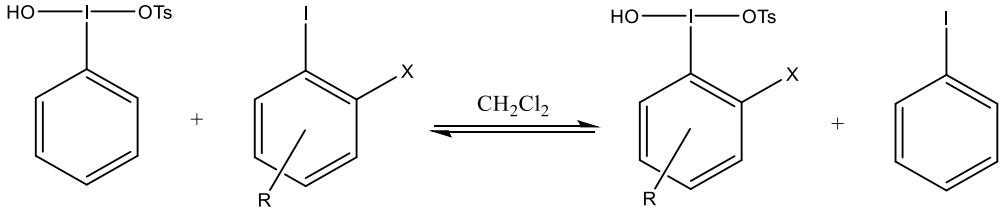


156e

2-iodo-*N*-isopropylbenzamide (**156e**) was synthesized in reference to literature by Dev & Maurya.[35] The following product (**156e**) was synthesized by added 533mg (2.00mmol) of 2-iodobenzoyl chloride to 10.0mL of dichloromethane along with 0.187mL (2.20mmol) of isopropyl amine and 0.610mL (4.40mmol) of triethyl amine. The solution was stirred for 6 hours at room temperature, quenched with water, and extracted with 2 additional 10.0mL portions of dichloromethane. The combined organic layers were then washed

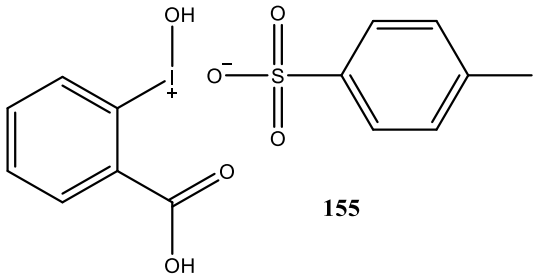
with 3M HCl followed by a washing with distilled water, saturated sodium bicarbonate, saturated aqueous brine, and finally dried over anhydrous sodium sulfate. The product was then dried under vacuum to acquire crude product.

General Reaction Workup for Synthesized HTIB derivatives



The synthesis of HTIB derivatives **155, 158-169** were produced using the following method. Each reaction used 2.5mL of dichloromethane along with 0.55mmol of an *ortho*-substituted iodoarene (**152**) with 196mg (0.50mmol) HTIB (**9**). The reaction mixture was then stirred for 24 hours, quench by reducing the dichloromethane in a rotovap, and stirred in diethyl ether for 3-12 hours to dissolve and remove starting materials. Optimized procedures for products **163, 165, 166, 168** have modified washing procedures to avoid decomposition of products. Optimized procedure for product **167** is performed using excess *p*-toluene sulfonic acid in solution. After washing, the suspension is then filtered through a medium frit filter and the product is vacuum dried for at least 2 hours to remove residual solvents and isolate final products that is then analyzed using H^1 & C^{13} NMR and Elemental Analysis.

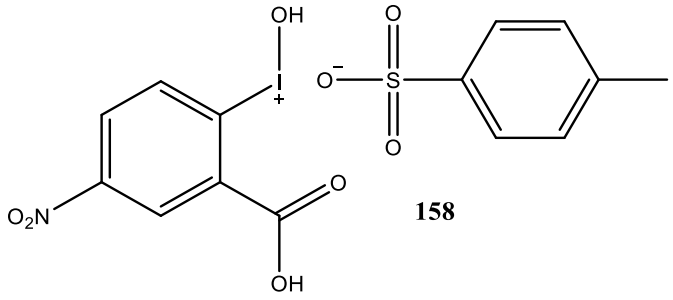
(2-carboxy-6-methylphenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate



155

Reaction with 2-iodobenzic acid (136mg, 0.55mmol) according to general procedure afforded 205mg (98%) of desired product **155**, isolated as a white solid: mp 113.0-115.0 ^{o}C; ^{1}H NMR (500MHz, MeOH-d4): δ 8.19 (d, 1H), 8.02 (t, 1H), 7.89 (d, 1H), 7.78 (t, 1H), 7.71 (d, 2H), 7.24 (d, 2H), 2.37 (s, 3H); ^{1}H NMR (500MHz, DMSO-d6): δ 8.00 (d, 1H), 7.95 (t, 1H), 7.83 (t, 1H), 7.49 (d, 2H), 7.48 (d, 1H), 7.13 (d, 2H), 2.28 (s, 3H); ^{13}C NMR (125MHz, DMSO-d6): d 168.2, 145.6, 138.5, 134.8, 131.8, 131.5, 130.8, 128.8, 128.6, 126.0, 120.9, 21.3. Analysis Calculated for $C_{14}H_{13}IO_6S$: C, 38.55; H, 3.00; I, 29.09; O, 22.01; S, 7.35. Found: C, 38.58; H, 3.14; I, 28.90; S, 7.40

(2-carboxy-4-nitrophenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate

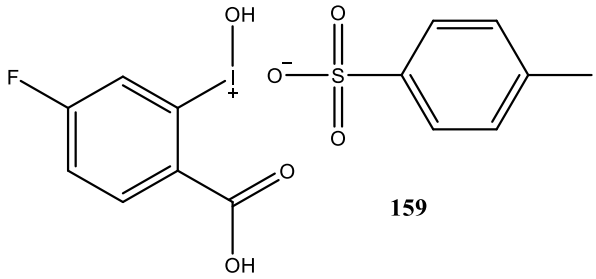


158

Reaction with 5-nitro-2-iodobenzic acid (161mg, 0.55mmol) according to general procedure afforded 166mg (69%) of desired product **158**, isolated as a light brown solid:

mp 204.9-206.1 °C; ^{1}H NMR (500MHz, DMSO-d6): δ 8.71 (d, 1H), 8.56 (s, 1H), 8.09 (d, 1H), 7.46 (d, 2H), 7.10 (d, 2H), 2.275 (s, 3H); ^{13}C NMR (125MHz, DMSO-d6): δ 166.3, 150.1, 147.9, 145.8, 143.4, 138.2, 133.9, 129.2, 128.8, 126.0, 125.3, 21.7. Analysis Calculated for $C_{14}H_{12}INO_8S$: C, 34.94; H, 2.51; I, 26.37; N, 2.91; O, 26.60; S, 6.66. Found: C, 34.93; H, 2.54; I, 26.33; S, 6.80

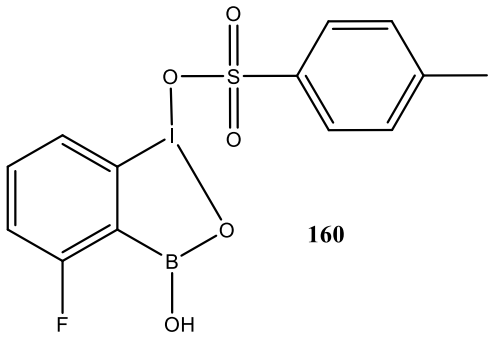
(2-carboxy-5-fluorophenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate



159

Reaction with 4-fluoro-2-iodobenzic acid (146mg, 0.55mmol) according to general procedure except that the reaction was performed using 1,2-dichloroethane under reflux for 3 hours, which afforded 183mg (81%) of desired product **159**, isolated as a white solid: mp 144.0-145.5 °C; ^{1}H NMR (500MHz, MeOH-d4): δ 8.16 (d, 1H), 7.71 (d, 2H), 7.61 (d, 1H), 7.52 (d, 2H), 2.37 (s, 3H); ^{13}C NMR (125MHz, MeOH-d4): δ 167.0, 141.8, 140.5, 134.7, 133.7, 128.5, 125.6, 118.3, 118.5, 114.1, 113.8, 19.9. Analysis Calculated for $C_{14}H_{12}FIO_6S$: C, 37.02; H, 2.66; F, 4.18; I, 27.94; O, 21.13; S, 7.06. Found: C, 36.53; H, 2.60; I, 27.16; S, 7.34

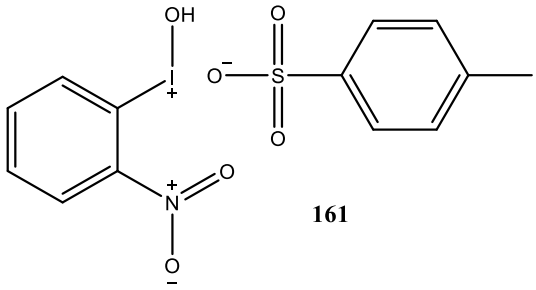
4-fluoro-3-hydroxy-1λ^3-benzo[*d*][1,2,3]iodoxaborol-1(3*H*)-yl 4-methyl benzene sulfonate



160

Reaction with 2-Fluoro-6-iodophenyl boronic acid (143mg, 0.55mmol) according to general procedure afforded 76mg (35%) of desired product **160**, isolated as a white solid: mp 143.4-144.8 ^{o}C; ^{1}H NMR (500MHz, $CDCl_3$): δ 7.84-7.68 (m, 4H), 7.38-7.28 (m, 3H), 6.81 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 170.9, 168.4, 142.0, 139.6, 137.3, 133.7, 130.4, 127.6, 125.9, 45.2, 21.3. Analysis Calculated for $C_{13}H_{11}BFIO_5S$: C, 35.81; H, 2.54; B, 2.48; F, 4.36; I, 29.11; O, 18.35; S, 7.35. Found: C, 35.86; H, 2.58; I, 28.95; S, 7.35

Hydroxy(2-nitrophenyl)iodonium 4-methylbenzenesulfonate

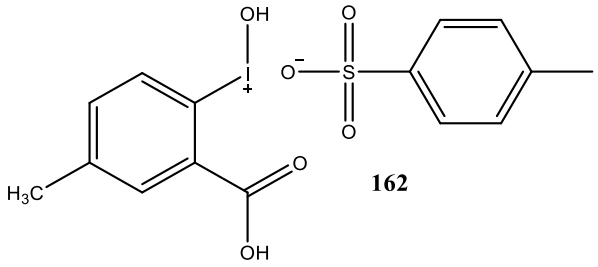


161

Reaction with 2-nitroiodobenzene (137mg, 0.55mmol) according to general procedure afforded 75mg (34%) of desired product **161**, isolated as a white solid: mp 132.6-133.7

^{o}C; ^{1}H NMR (500MHz, DMSO-d6): δ 8.36 (d, 2H), 8.85 (t, 1H), 7.73-7.68 (m, 3H), 7.23 (d, 2H), 2.37 (s, 3H); ^{13}C NMR (125MHz, DMSO-d6): δ 140.5, 135.8, 135.6, 133.8, 133.5, 131.9, 131.3, 128.8, 128.1, 125.7, 120.6, 26.0. Analysis Calculated for $C_{13}H_{12}INO_6S$: C, 35.71; H, 2.77; I, 29.03; N, 3.20; O, 21.96; S, 7.33. Found: C, 39.72; H, 3.22; I, 32.28; S, 8.23

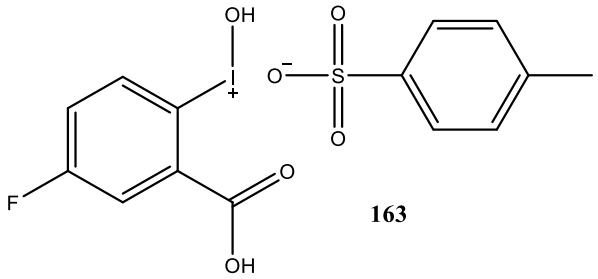
(2-carboxy-4-methylphenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate



162

Reaction with 2-iodo-5-methylbenzoic acid (144mg, 0.55mmol) according to general procedure afforded 210mg (99%) of desired product **162**, isolated as a white solid: mp 128.5-129.0 ^{o}C; ^{1}H NMR (500MHz, MeOH-d4): δ 7.84 (s, 1H), 7.69 (d, 1H), 7.55 (m, 3H), 7.08 (d, 2H), 2.39 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (125MHz, MeOH-d4): δ 141.9, 140.5, 136.4, 133.2, 132.3, 128.6, 126.2, 125.7, 115.5, 19.9, 19.3. Analysis Calculated for $C_{15}H_{15}IO_6S$: C, 40.02; H, 3.36; I, 28.19; O, 21.32; S, 7.12. Found: C, 40.05; H, 3.27; I, 28.38; S, 6.97

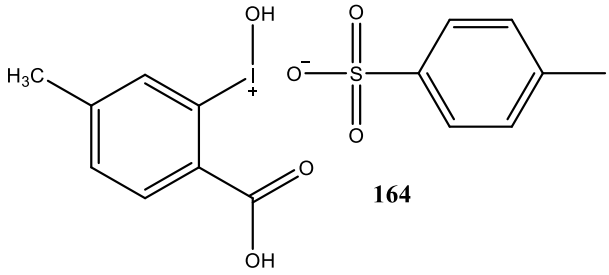
(2-carboxy-4-fluorophenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate



163

Reaction with 5-fluoro-2-iodobenzoic acid (146mg, 0.55mmol) according to general procedure afforded 121mg (53%) of desired product **163**, isolated as a white solid: mp 104.1-106.5 ^{o}C; ^{1}H NMR (500MHz, MeOH-d4): δ 8.16 (d, 1H), 7.71 (d, 2H), 7.61 (d, 1H), 7.53 (s, 1H), 7.24 (d, 2H), 2.37 (s, 3H); ^{13}C NMR (125MHz, MeOH-d4): δ 168.8, 165.9, 163.9, 133.2, 128.3, 128.2, 122.4, 122.2, 118.2, 118.1, 112.4, 37.4. Analysis Calculated for $C_{14}H_{12}FIO_6S$: C, 37.02; H, 2.66; F, 4.18; I, 27.94; O, 21.13; S, 7.06. Found: C, 34.30; H, 2.62; I, 29.40; S, 5.66

(2-carboxy-5-methylphenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate

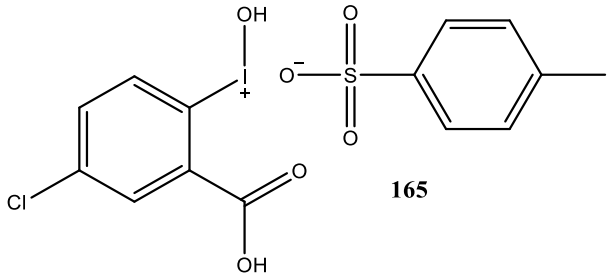


164

Reaction with 4-methyl-2-iodobenzic acid (144mg, 0.55mmol) according to general procedure, with 24 hours of stirring in diethyl ether after initial reaction, afforded 157mg (75%) of desired product **164**, isolated as a light brown solid: mp 130.3-133.8 ^{o}C; ^{1}H NMR (500MHz, MeOH-d4): δ 8.03 (s, 1H), 7.62-7.73 (m, 3H), 7.56 (s, 1H), 7.23 (d,

2H), 2.37 (s, 3H); ^{13}C NMR (125MHz, MeOH-d4): δ 171.2, 151.0, 147.5, 141.8, 140.3, 132.3, 132.4, 131.3, 128.5, 126.3, 125.8, 132.4, 20.6, 19.9. Analysis Calculated for $C_{15}H_{15}IO_6S$: C, 40.02; H, 3.36; I, 28.19; O, 21.32; S, 7.12. Found: C, 38.78; H, 3.70; I, 26.85; S, 7.05

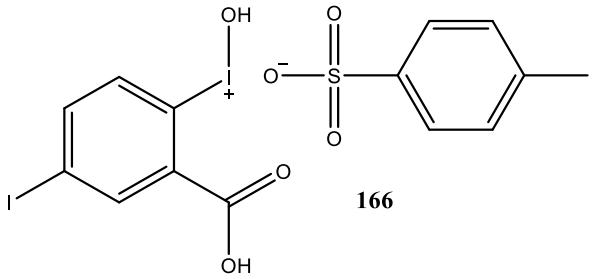
(2-carboxy-4-chlorophenyl)(hydroxy)iodonium-4-methylbenzenesulfonate



165

Reaction with 5-chloro-2-iodobenzic acid (155mg, 0.55mmol) according to general procedure, except for being washed with diethyl ether only during the filtration step skipping the 3-12hrs stirring in diethyl ether, afforded 181mg (77%) of desired product **165**, isolated as a white solid: mp 183.5-185.9 ^{o}C; ^{1}H NMR (500MHz, MeOH-d4): δ 8.11 (s, 1H), 7.99 (d, 1H), 7.83 (d, 1H), 7.71 (d, 2H), 7.24 (d, 2H), 2.33 (s, 3H); ^{1}H NMR (500MHz, DMSO-d6): δ 8.02 (d, 1H), 7.93 (s, 1H), 7.79 (d, 1H), 7.46 (d, 2H), 7.10 (d, 2H), 2.28 (s, 3H); ^{13}C NMR (125MHz, DMSO-d6): δ 166.8, 146.1, 138.1, 136.4 134.1, 130.8, 128.6, 128.5, 125.9, 125.7, 119.2, 21.2. Analysis Calculated for $C_{14}H_{12}ClIO_6S$: C, 35.73; H, 2.57; Cl, 7.53; I, 26.96; O, 20.40; S, 6.81. Found: C, 34.18; H, 2.35; I, 31.83; S, 5.00

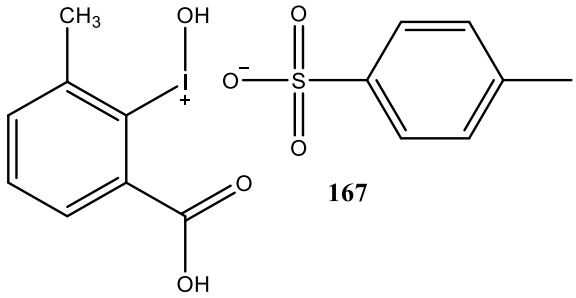
(2-carboxy-4-iodophenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate



166

Reaction with 2,5-diiodobenzic acid (206mg, 0.55mmol) according to general procedure, except for being washed with diethyl ether for 24 hours, afforded 42mg (18%) of desired product **168**, isolated as a white solid; mp: 209.0-210.1; ^{1}H NMR (500MHz, MeOH-d4): δ 8.44 (s, 1H), 8.23 (d, 1H), 7.71 (d, 2H), 7.61 (d, 1H) 2.24 (d, 2H), 2.37 (s, 3H); ^{13}C NMR (125MHz, DMSO-d6): δ 166.8, 143.2, 139.9, 138.0, 134.2, 134.1, 128.9, 128.5, 125.9, 121.0, 97.9, 21.2. Analysis Calculated for $C_{14}H_{12}I_2O_6S$: C, 29.91; H, 2.15; I, 45.15; O, 17.08; S, 5.70. Found: C, 24.23; H, 1.54; I, 57.97; S, 2.47

(2-carboxy-6-methylphenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate

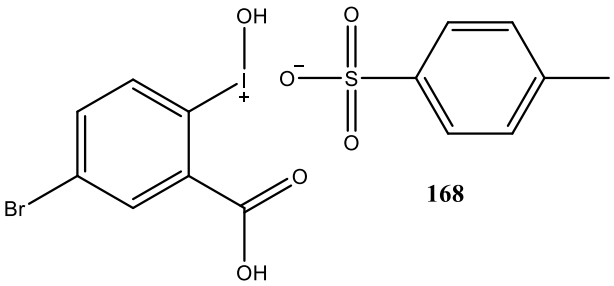


167

Reaction with 3-methyl-2-iodobenzic acid (131mg, 0.50mmol) according to general procedure with 0.50mmol of HTIB, except that an additional 190mg (1.00mmol) of *p*-toluene sulfonic acid monohydrate was added at the beginning of the reaction, affording

143mg (68%) of desired product **167**, isolated as a white solid: mp 139.4-140.1 °C; ^{1}H NMR (500MHz, MeOH-d4): δ 7.95 (d, 1H), 7.30-7.84 (m, 3H), 7.64 (t, 1H), 7.35 (d, 2H) 2.59 (s, 3H), 2.41 (s, 3H); ^{1}H NMR (500MHz, DMSO-d6): δ 7.85 (d, 1H), 7.40-7.66 (m, 4H), 7.12 (d, 2H), 2.64 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125MHz, DMSO-d6): δ 168.5, 145.4, 141.6, 139.3, 138.6, 133.1, 130.8, 130.5, 128.7, 126.0, 119.3, 21.3, 21.0. Analysis Calculated for $C_{15}H_{15}IO_6S$: C, 40.02; H, 3.36; I, 28.19; O, 21.32; S, 7.12. Found: C, 40.11; H, 3.24; I, 28.21; S, 7.19

(4-bromo-2-carboxyphenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate

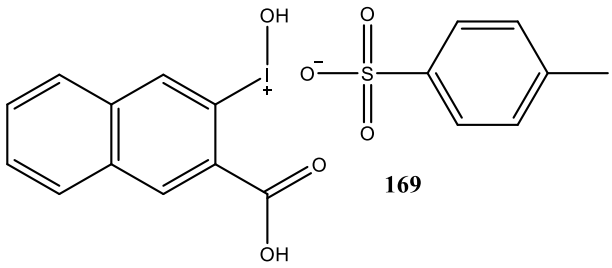


168

Reaction with 5-bromo-2-iodobenzic acid (180mg, 0.55mmol) according to general procedure, except for being washed with diethyl ether 3 times and extracting ether layer using a pipette skipping the 3-12hrs stirring in diethyl ether, afforded 203mg (79%) of desired product **168**, isolated as a white solid: mp 212.5-213.4 °C; ^{1}H NMR (500MHz, MeOH-d4): δ 8.26 (s, 1H), 8.12 (d, 1H), 7.76 (d, 2H), 7.71 (d, 2H), 7.23 (d, 2H), 2.37 (s, 3H); ^{1}H NMR (500MHz, DMSO-d6): δ 8.13 (d, 1H), 8.05 (s, 1H), 7.72 (d, 1H), 7.46 (d, 2H), 7.09 (d, 2H), 2.37 (s, 3H); ^{13}C NMR (125MHz, DMSO-d6): δ 166.8, 138.1, 137.4, 134.3, 133.8, 129.9, 125.5, 128.2, 125.9, 124.8, 120.0, 21.2. Analysis Calculated for

$C_{14}H_{12}BrIO_6S$: C, 32.64; H, 2.15; Br, 15.51; I, 24.64; O, 18.64; S, 6.22. Found: C, 25.26; H, 1.38; I, 33.90; S, 1.00

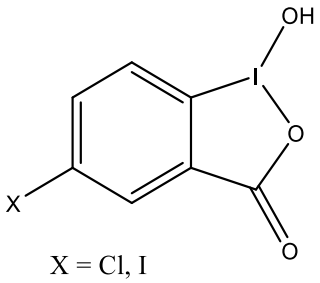
(3-carboxynaphthalen-2-yl)(hydroxyl)iodonium 4-methylbenzenesulfonate



169

Reaction with 2-iodonaphthioc acid (163mg, 0.55mmol) according to general procedure afforded 170mg (70%) of desired product **169**, isolated as a light brown solid: mp 199.4-201.9 ^{o}C; ^{1}H NMR (500MHz, DMSO-d6): δ 8.64 (d, 1H), 8.37 (d, 1H), 8.28 (d, 1H), 8.19 (d, 1H), 8.03 (d, 1H), 7.92 (d, 1H), 7.72 (m, 1H), 7.63 (m, 1H), 7.46 (d, 2H), 7.10 (d, 2H), 2.28 (s, 3H); ^{13}C NMR (125MHz, DMSO-d6): δ 206.9, 136.4, 133.3, 132.2, 129.8, 129.4, 128.6, 128.5, 128.4, 126.9, 125.9, 116.4, 105.0, 65.4, 45.0, 31.1, 21.2, 15.6. Analysis Calculated for $C_{15}H_{15}IO_6S$: C, 40.02; H, 3.36; I, 28.19; O, 21.32; S, 7.12. Found: C, 38.78; H, 3.70; I, 26.85; S, 7.05. Analysis Calculated for $C_{18}H_{15}IO_6S$: C, 44.46; H, 3.11; I, 26.10; O, 19.74; S, 6.59. Found: C, 42.89; H ,3.47 ; I, 25.29; S, 6.31

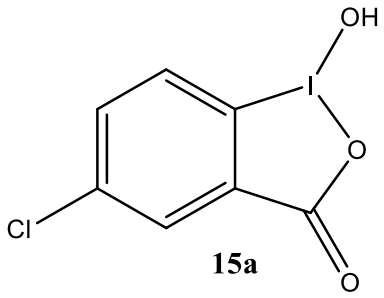
General Reaction Workup of HITB derivatives using IBA type precursors



X = Cl, I

A solution containing 6.5mL of glacial acetic acid and 11.0mL of distilled water was prepared and 2.00mmol of the appropriate 2-iodo-5-chloro or 2,5-diiodobenzoic acid was combined with 2.10mmol (449mg) of sodium periodate. The reaction mixture was heated and allowed to react under reflux for 8 hours to form a significant amount of precipitate. The reaction was then allowed to cool and was placed in the fridge to promote precipitation, which was then filtered, rinsed with cold water, and dried under vacuum. The isolated product was checked using H^1 NMR and then 0.50mmol of the IBA type product was added to 2.5mL of acetonitrile and 1.0mmol of *p*-toluene sulfonic acid monohydrate and allowed to stir for 12 hours at room temperature, which was then reduced and dried under vacuum. Isolated products were labeled as crude yields due to low integration values for toluene sulfonic acid peaks.

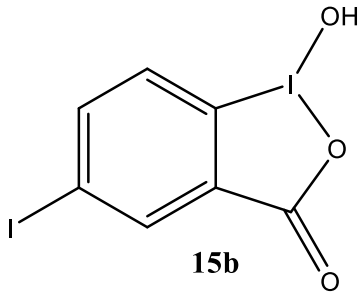
5-chloro-1-hydroxy-1l3-benzo[d][1,2]iodaoxol-3(1H)-one



15a

Reaction with 2-iodo-5-chlorobenzoic acid (566mg, 2.00mmol) according to general procedure afforded 475mg (80%) of desired product **15a**, isolated as a white solid.

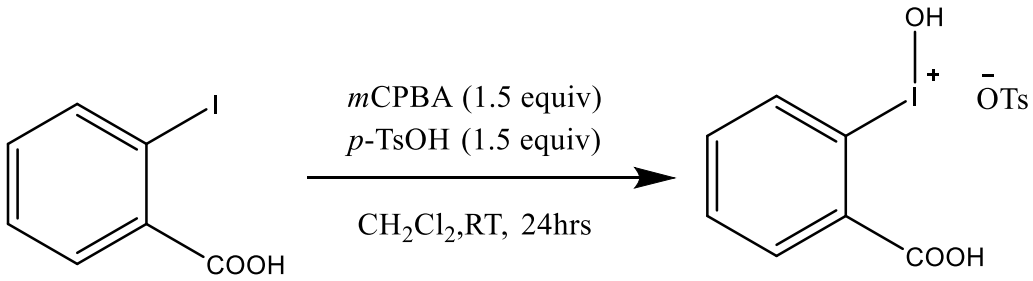
5-iodo-1-hydroxy-1l3-benzo[d][1,2]iodaoxol-3(1H)-one



15b

Reaction with 2,5-diiodobenzoic acid (770mg, 2.00mmol) according to general procedure afforded 556mg (71%) of desired product **15b**, isolated as a white solid.

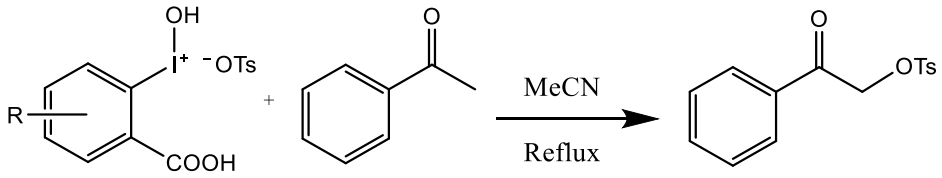
General Reaction Workup of *in-situ* generated HTIB with 2-Iodobenzic acid



(1.0 Equiv) 83% Yield

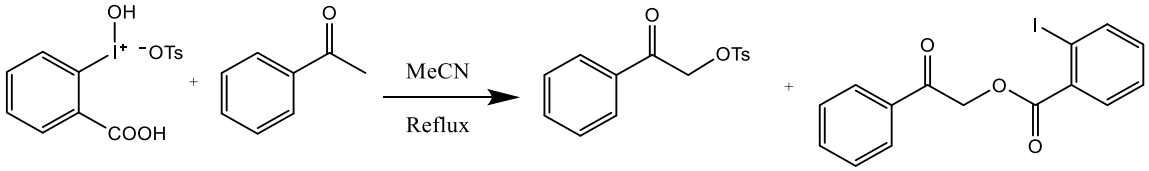
The following reaction was performed by added 124mg (0.50mmol) of 2-iodobenzoic acid to 2.5mL of dichloromethane followed by the addition of *m*CPBA (0.75mmol, 129mg) and *p*-TsOH monohydrate (0.75mmol, 142mg). The reaction mixture was then stirred at room temperature for 24 hours. The mixture was quenched, reduced, and washed using diethyl ether during filtration. The isolated solid was then vacuum dried to acquire a yield of 83%. Refer to spectra details for compound **155** in General workup.

Reaction Workup for α-tosyloxylation of acetophenone using HTIB derivatives



The following reaction was performed by taking 0.15mmol of the appropriate HTIB derivative and adding 1.5mL of acetonitrile and 12μL of acetophenone (0.10mmol). The mixture was then allowed to react under reflux for 2 hours and then cool to room temperature for 1 hour before quenching with 1.5mL of 5% sodium thiosulfate solution. The work up involved washing the solution with saturated sodium bicarbonate and extracting with 3 portions of dichloromethane, which was then dried over anhydrous sodium sulfate. After reducing the dried organic layer, the product was analyzed using proton NMR and GC-MS in methanol with 0.019mmol of 1,1,2,2-tetrachloroethane as an internal standard to quantify yield.

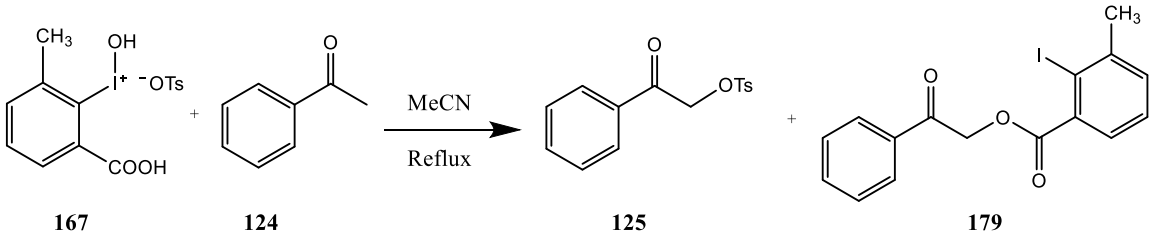
α-tosyloxylation using (2-carboxyphenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate



155 **124** **125** **178**

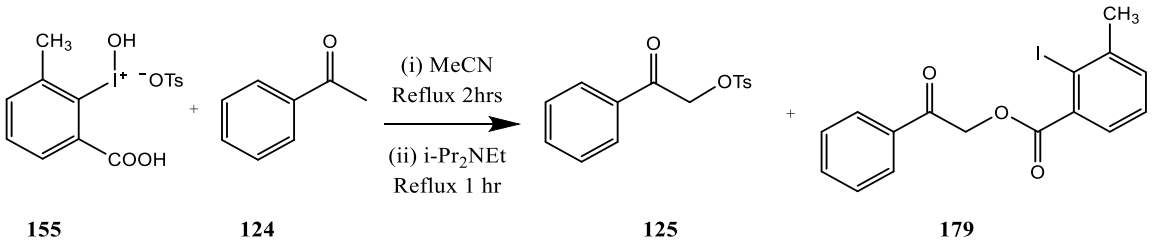
Reaction with **155** (65mg, 0.15mmol) according to general procedure afforded 16% of product **125** and 1% of product **178** as determined by H^1 NMR using internal standard.

α-tosyloxylation using (2-carboxy-6-methylphenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate



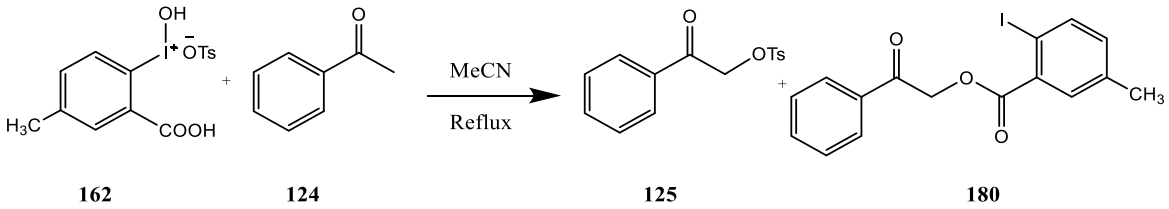
Reaction with **167** (68mg, 0.15mmol) according to general procedure afforded 90% of product **125** and 10% of product **178** as determined by H^1 NMR using internal standard.

α-tosyloxylation using (2-carboxy-6-methylphenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate and Hunig base



Reaction with **167** (68mg, 0.15mmol) according to general procedure, except with an additional step that involved adding 35μL (0.20mmol) of *N*,*N*-Diisopropylethylamine after the 2 hour reflux and allowed to react under reflux for an additional hour to afforded 95% of product **178** as determined by H^1 NMR using internal standard. Product **125** was not observed.

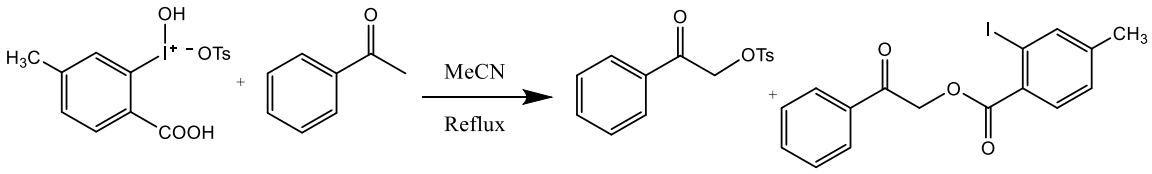
α-tosyloxylation using (2-carboxy-5-methylphenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate



162 **124** **125** **180**

Reaction with **164** (68mg, 0.15mmol) according to general procedure, except for running reaction under reflux for 4 hours afforded no observable products with only the presence of starting materials observed by GC-MS.

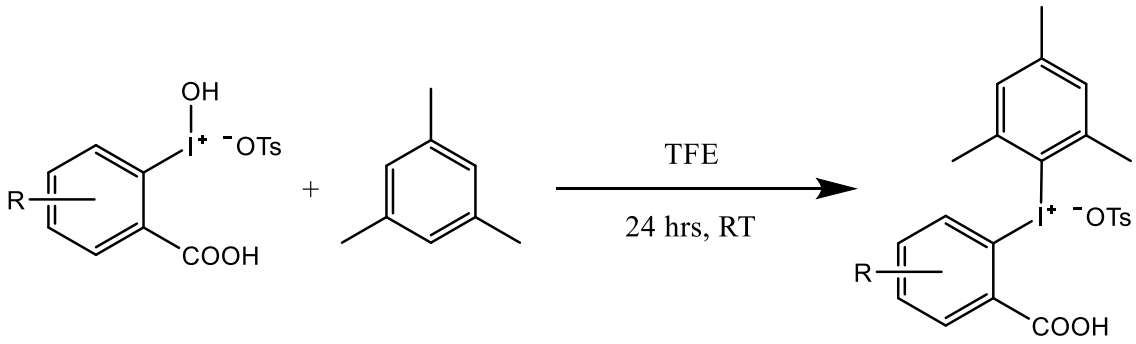
α-tosyloxylation using (2-carboxy-4-methylphenyl)(hydroxyl)iodonium 4-methylbenzenesulfonate



164 **124** **125** **181**

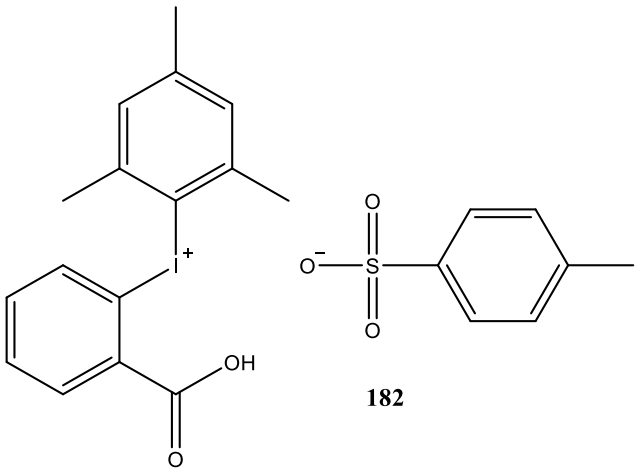
Reaction with **162** (68mg, 0.15mmol) according to general procedure, except for running reaction under reflux for 4 hours afforded no observable products with only the presence of starting materials observed by GC-MS.

Reaction Workup for iodonium salts using HTIB derivatives and mesitylene



The synthesis of iodonium salts using HTIB derivatives and mesitylene as the reactive arene. The reaction was performed using 0.20mmol of the appropriate HTIB derivative and 28μL of mesitylene (0.20mmol) in 1.0mL of 2,2,2-trifluoroehtanol. The reaction mixture was allowed to react with stirring for 24 hours before being quenched with dichloromethane, reduced using a rotovap, and washed using diethyl ether before being vacuum dried to acquire the isolated unsymmetrical iodonium salt.

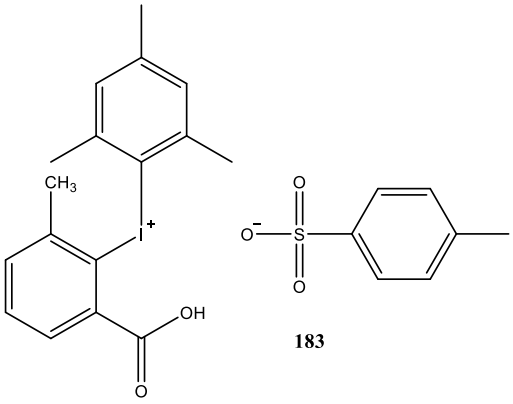
(2-carboxyphenyl)(mesityl)iodonium 4-methylbenzenesulfonate



182

Reaction with **155** (87mg, 0.20mmol) according to general procedure, with the addition of diethyl ether to the resulting oil produced from drying under vacuum and again vacuum dried to afforded 98mg (91%) of desired product **182**, isolated as a white solid.

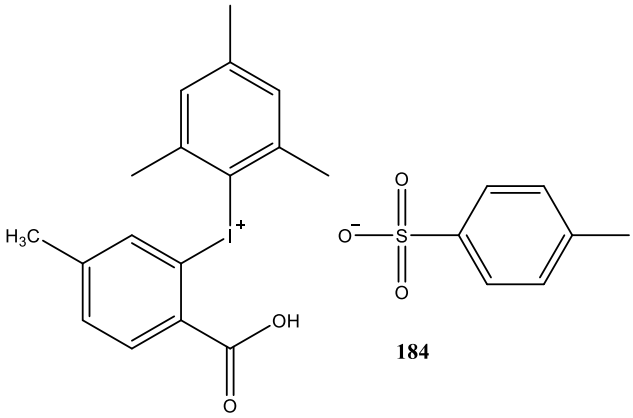
(2-carboxy-6-methylphenyl)(mesityl)iodonium 4-methylbenzenesulfonate



183

Reaction with **167** (90mg, 0.20mmol) according to general procedure, with the addition of diethyl ether to the resulting oil produced from drying under vacuum and again vacuum dried to afforded 98mg (89%) of desired product **183**, isolated as a white solid. ^{1}H NMR (500MHz, $CDCl_3$): δ 8.18-8.11 (m, 1H), 7.74-7.63 (m, 4H), 7.26-7.16 (m, 4H), 2.48 (s, 6H), 2.37 (s, 3H), 2.21 (s, 3H)

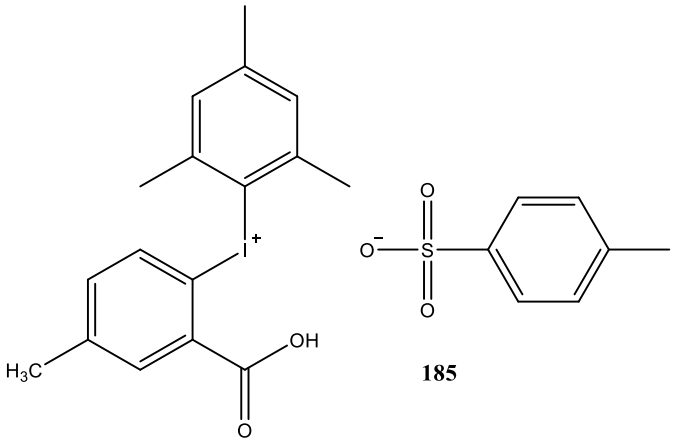
(2-carboxy-5-methylphenyl)(mesityl)iodonium 4-methylbenzenesulfonate



184

Reaction with **164** (90mg, 0.20mmol) according to general procedure, afforded 87mg (79%) of desired product **184**, isolated as a brown solid: mp 159.0-161.7 ^{1}H NMR (500MHz, $CDCl_3$): δ 8.25 (d, 1H), 7.46 (d, 2H), 7.37 (d, 1H), 7.26 (s, 1H), 7.04 (m, 4H), 6.47 (s, 1H), 2.23 (s, 3H), 2.50 (s, 6H), 2.37 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 169.1, 147.4, 144.0, 143.7, 141.7, 139.6, 133.5, 133.4, 130.1, 128.0, 128.7, 126.4, 125.8, 125.5, 113.4, 45.0, 27.2, 26.9, 20.9

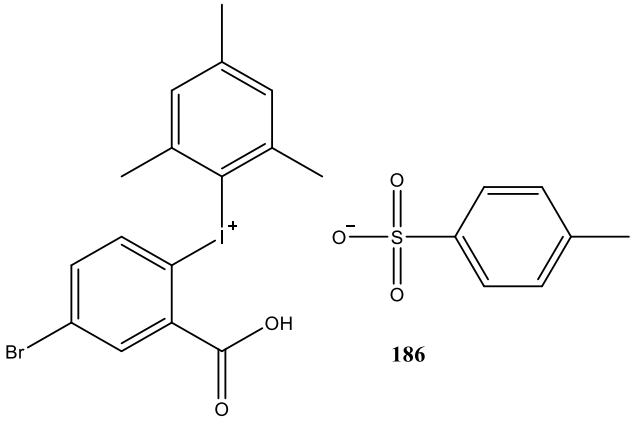
(2-carboxy-4-methylphenyl)(mesityl)iodonium 4-methylbenzenesulfonate



185

Reaction with **162** (90mg, 0.20mmol) according to general procedure, with the addition of diethyl ether to the resulting oil produced from drying under vacuum and again vacuum dried to afforded 66mg (60%) of desired product **185**, isolated as a white solid: mp 178.7-180.3 ^{o}C; ^{1}H NMR (500MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.47 (d, 2H), 7.26 (d, 1H), 7.04 (d, 2H), 7.04 (s, 2H), 6.58 (d, 2H), 2.45 (s, 6H), 2.39 (s, 3H), 2.37 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 169.1, 144.1, 143.7, 141.4, 139.8, 136.9, 134.4, 129.8, 127.4, 126.9, 126.0, 118.2, 109.1, 26.7, 21.3, 21.7, 20.6

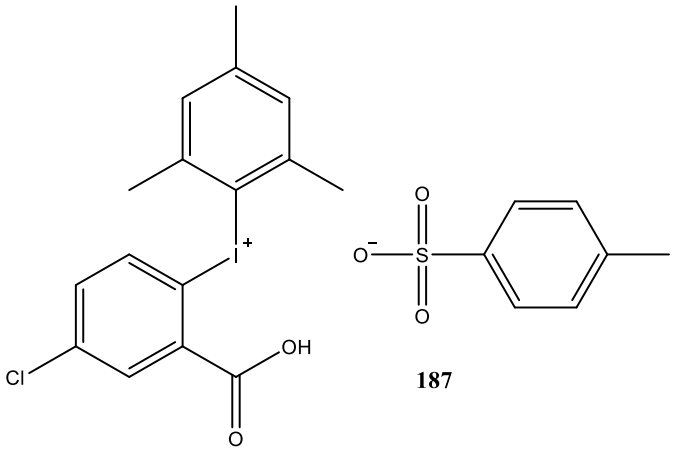
(2-carboxy-4-bromophenyl)(mesityl)iodonium 4-methylbenzenesulfonate



186

Reaction with **168** (103mg, 0.20mmol) according to general procedure afforded 97mg (79%) of desired product **186**, isolated as a white solid: mp 193.4-194.2 ^{o}C; ^{1}H NMR (500MHz, $CDCl_3$): δ 8.50 (s, 1H), 7.53 (d, 1H), 7.40 (d, 2H), 7.03 (m, 4H), 6.55 (d, 1H), 2.50 (s, 6H), 2.37 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 167.9, 144.2, 132.7, 131.4, 139.8, 138.5, 136.5, 131.0, 129.8, 129.1, 128.4, 125.9, 125.6, 118.8, 111.7, 26.8, 21.4, 21.3

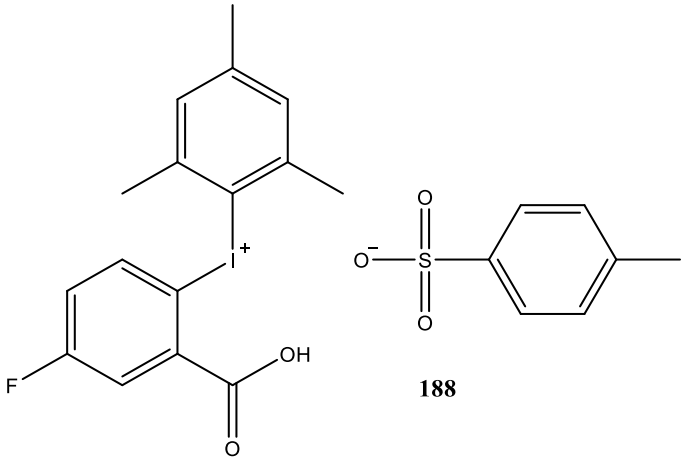
(2-carboxy-4-chlorophenyl)(mesityl)iodonium 4-methylbenzenesulfonate



187

Reaction with **165** (93mg, 0.20mmol) according to general procedure afforded 77mg (68%) of desired product **187**, isolated as a white solid: mp 190.0-191.3 ^{o}C; ^{1}H NMR (500MHz, $CDCl_3$): δ 8.36 (s, 1H), 7.39 (m, 3H), 7.04 (m, 4H), 6.63 (d, 1H), 2.50 (s, 6H), 2.37 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 167.8, 144.2, 143.7, 141.3, 139.8, 137.8, 135.6, 133.6, 130.8, 129.8, 128.9, 128.4, 126.0, 118.9, 110.7, 26.8, 21.3, 21.3

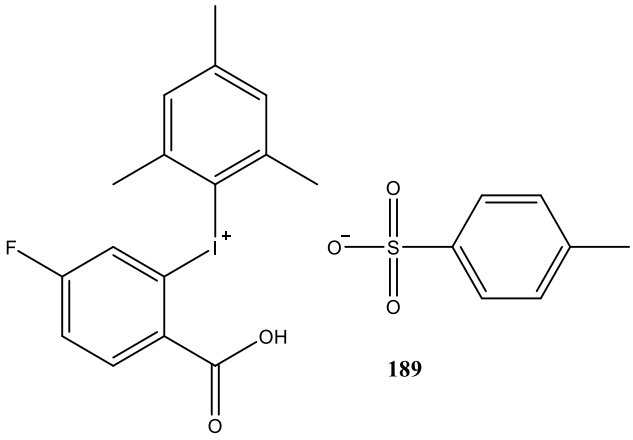
(2-carboxy-4-fluorophenyl)(mesityl)iodonium 4-methylbenzenesulfonate



188

Reaction with **155** (91mg, 0.20mmol) according to general procedure afforded 76mg (68%) of desired product **188**, isolated as a white solid: mp 179.1- 180.5°C; ^{1}H NMR (500MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.41, (d, 2H), 7.16 (m, 1H), 7.04, (m, 4H), 6.68 (m, 1H), 2.51 (s, 6H), 2.37 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 168.0, 165.1, 163.1, 143.7, 141.2, 139.9, 129.8, 128.5, 126.0, 123.1, 120.8, 118.7, 116.9, 106.5, 105.0, 26.8, 21.3, 21.3

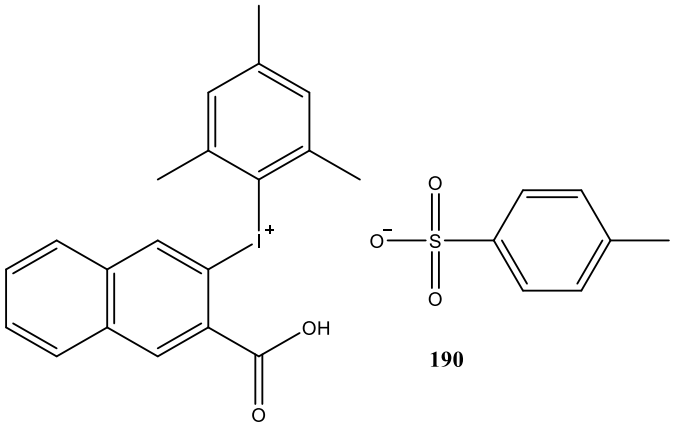
(2-carboxy-4-fluorophenyl)(mesityl)iodonium 4-methylbenzenesulfonate



189

Reaction with **159** (91mg, 0.20mmol) according to general procedure, with the addition of dichloromethane to the resulting oil produced from drying under vacuum and again vacuum dried to afforded 52mg (47%) of desired product **189**, isolated as a white solid: mp 70.5-71.6 °C; ^{1}H NMR (500MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.44 (d. 2H), 7.26-7.29 (d, 1H*), 7.04-7.05 (m, 4H), 6.40 (d, 1H), 2.51 (s, 6H), 2.38 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 168.6, 144.8, 143.7, 141.6, 140.0, 135.1, 135.0, 130.2, 128.6, 126.0, 125.7, 118.2, 118.0, 115.7, 105.0, 45.1, 26.0, 21.4

(3-carboxynaphthalen-2-yl)(mesityl)iodonium 4-methylbenzenesulfonate



190

Reaction with **169** (60mg, 0.12mmol) modified to general procedure by using 18μL of mesitylene in 1.0mL of 2,2,2-trifluoroethanol, with the addition of dichloromethane to the resulting oil produced from drying under vacuum and again vacuum dried to afforded 39mg (55%) of desired product **190**, isolated as a brown solid: mp 123.0-126.0 ^{o}C ^{1}H NMR (500MHz, $CDCl_3$): δ 9.00 (s, 1H), 8.02 (d, 1H), 7.67-7.60 (m, 2H), 7.53 (m, 3H), 7.29-7.10 (m, 4H), 7.06-7.13 (m, 2H), 2.56 (s, 6H), 2.43 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (125MHz, $CDCl_3$): δ 169.6, 144.5, 144.0, 139.9, 139.7, 136.7, 135.0, 132.9, 130.0, 129.6, 128.9, 128.6, 127.9, 126.0, 124.5, 117.8, 117.7, 108.2, 45.0, 27.3, 26.7, 21.4

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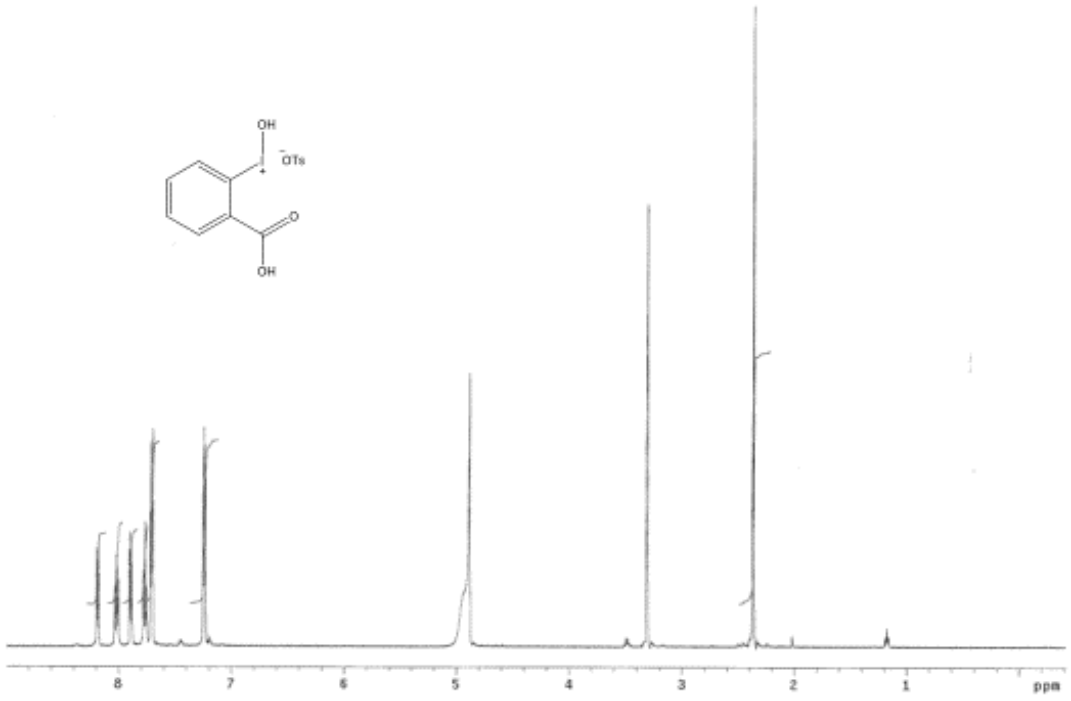
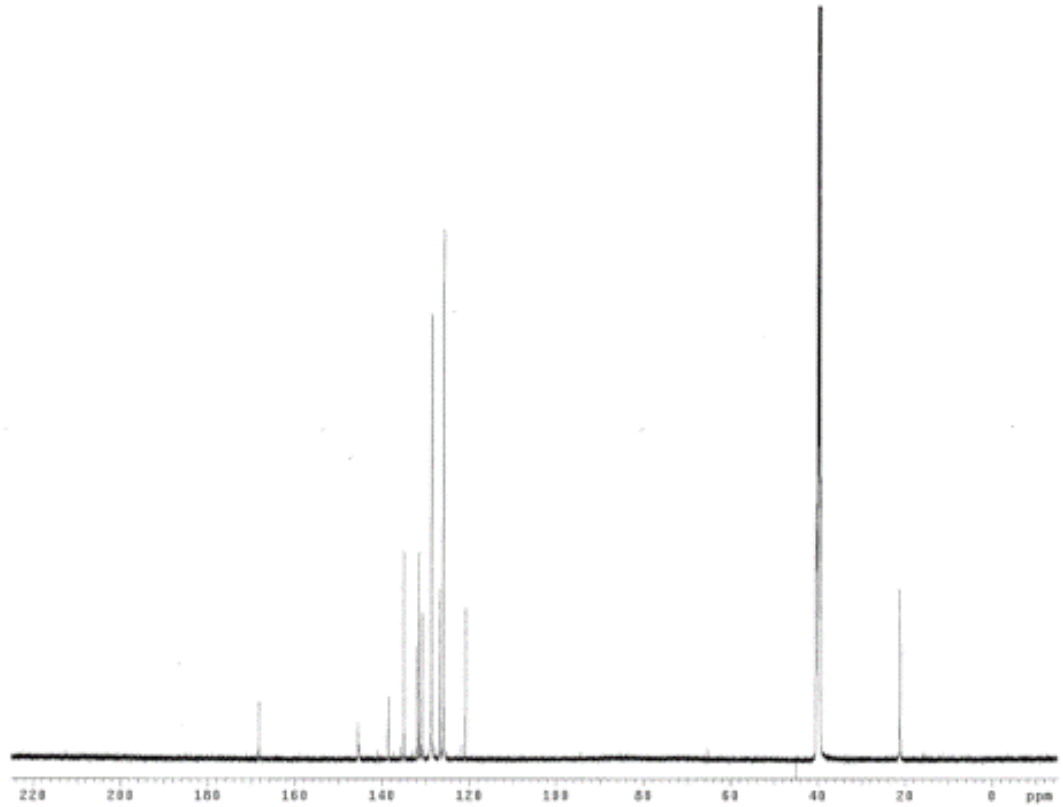
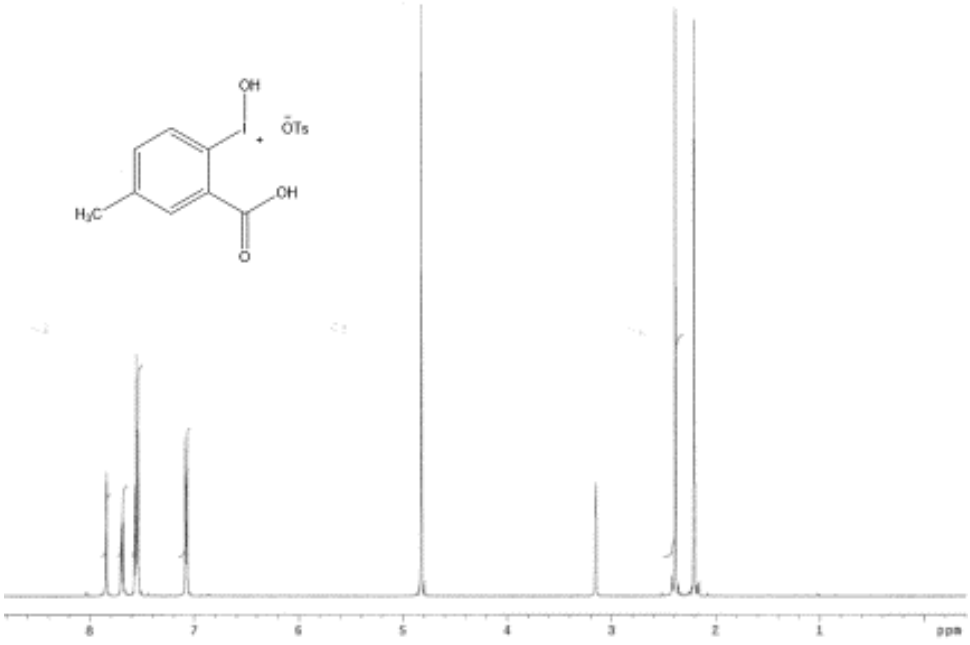
Appendix (Spectra):



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H3C
O
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6
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2
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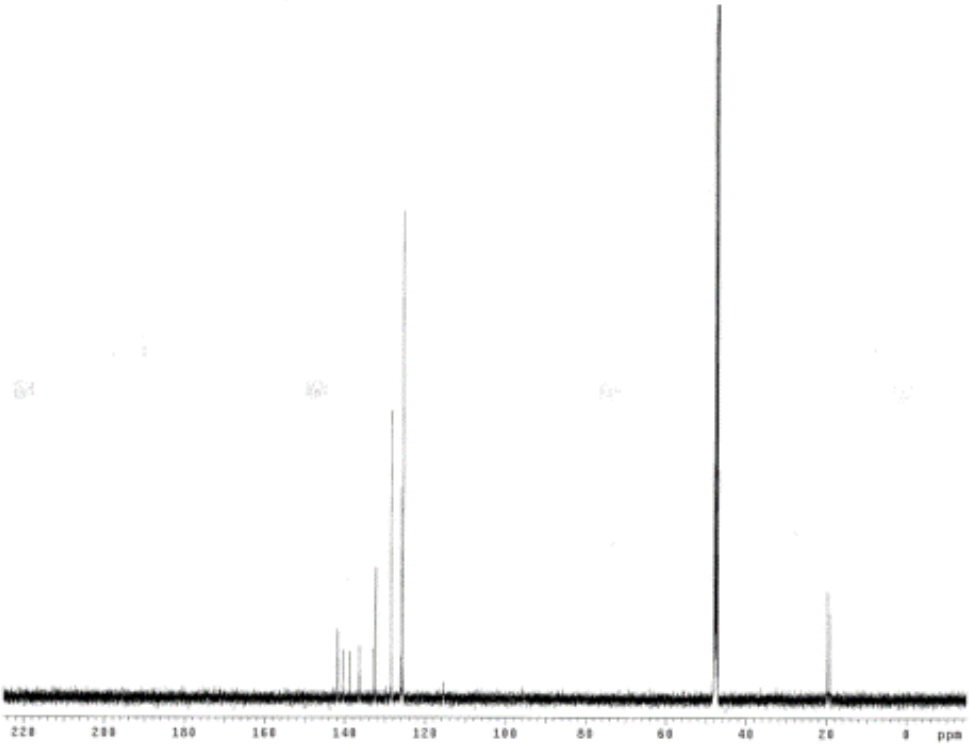
ppm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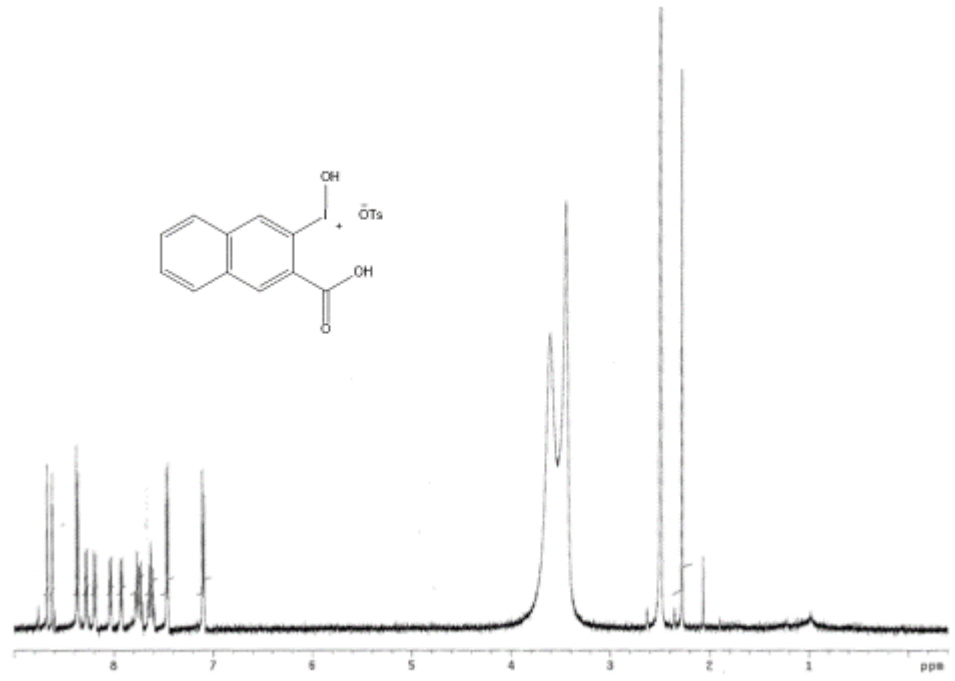
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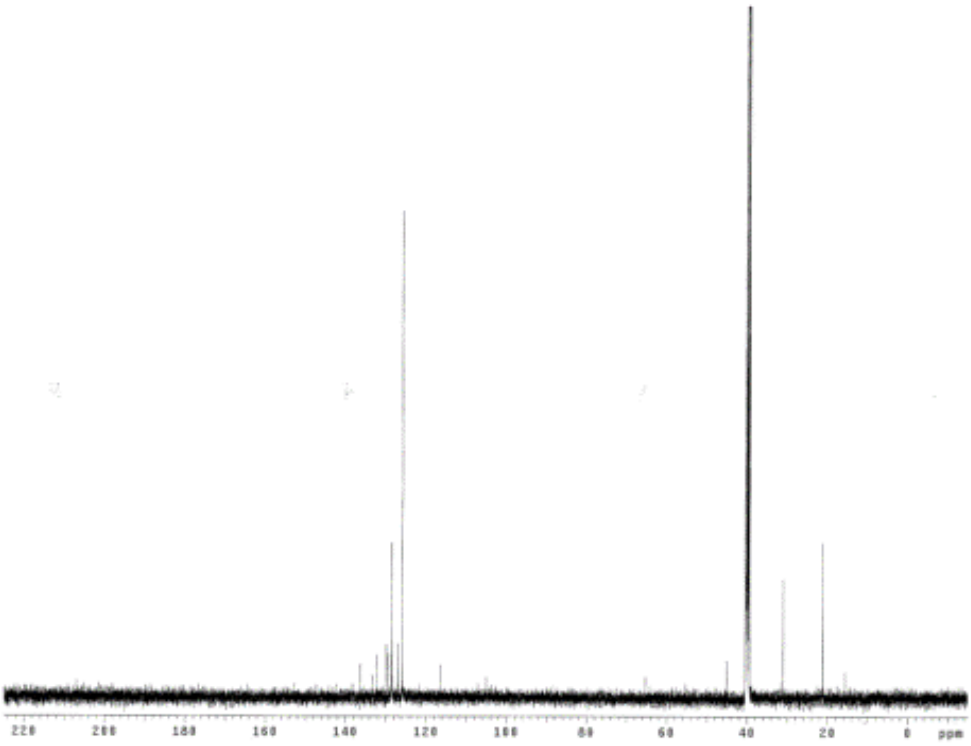
ppm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200
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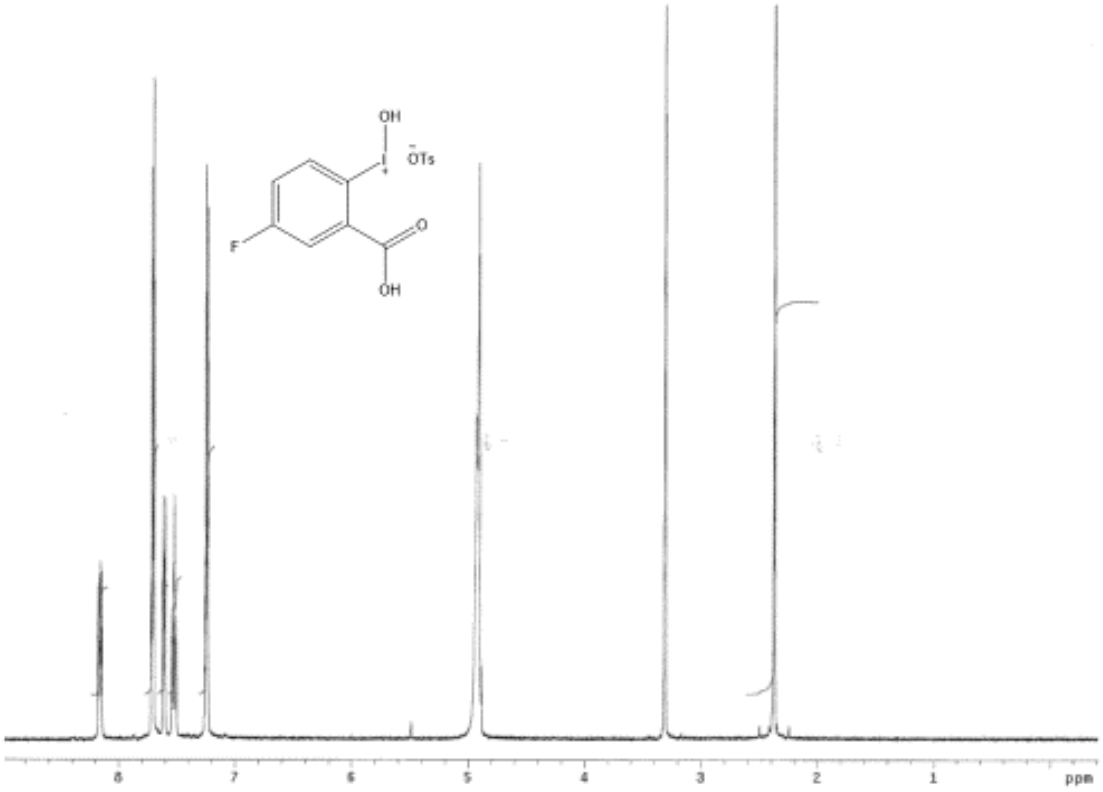
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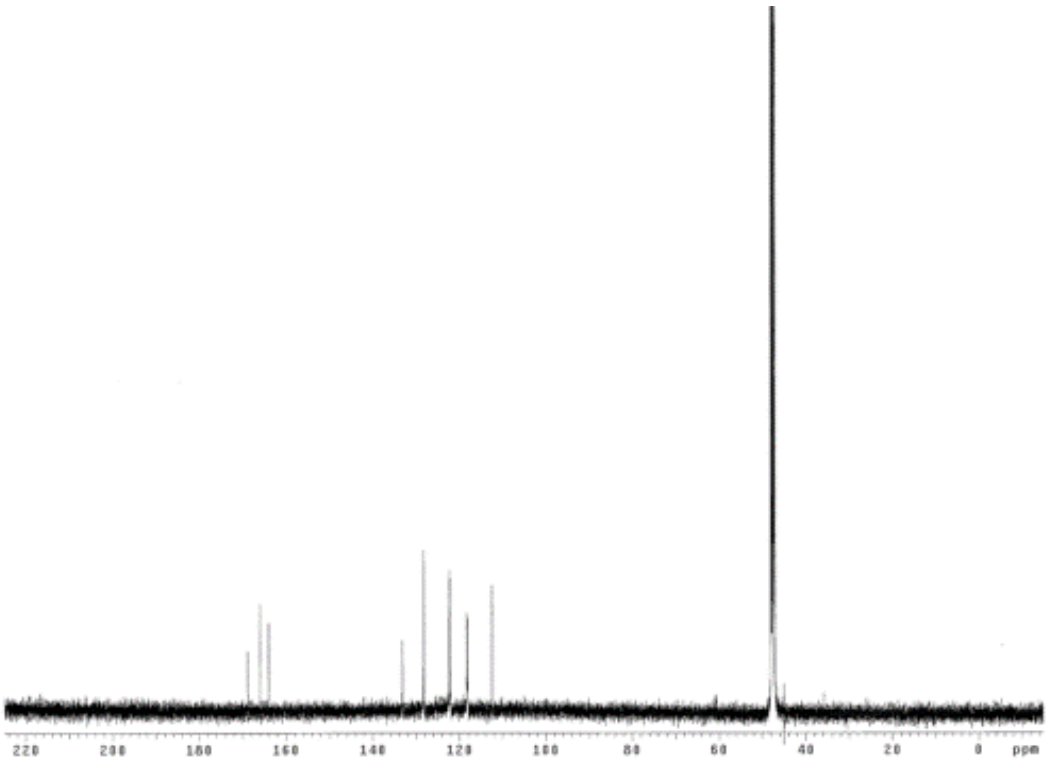
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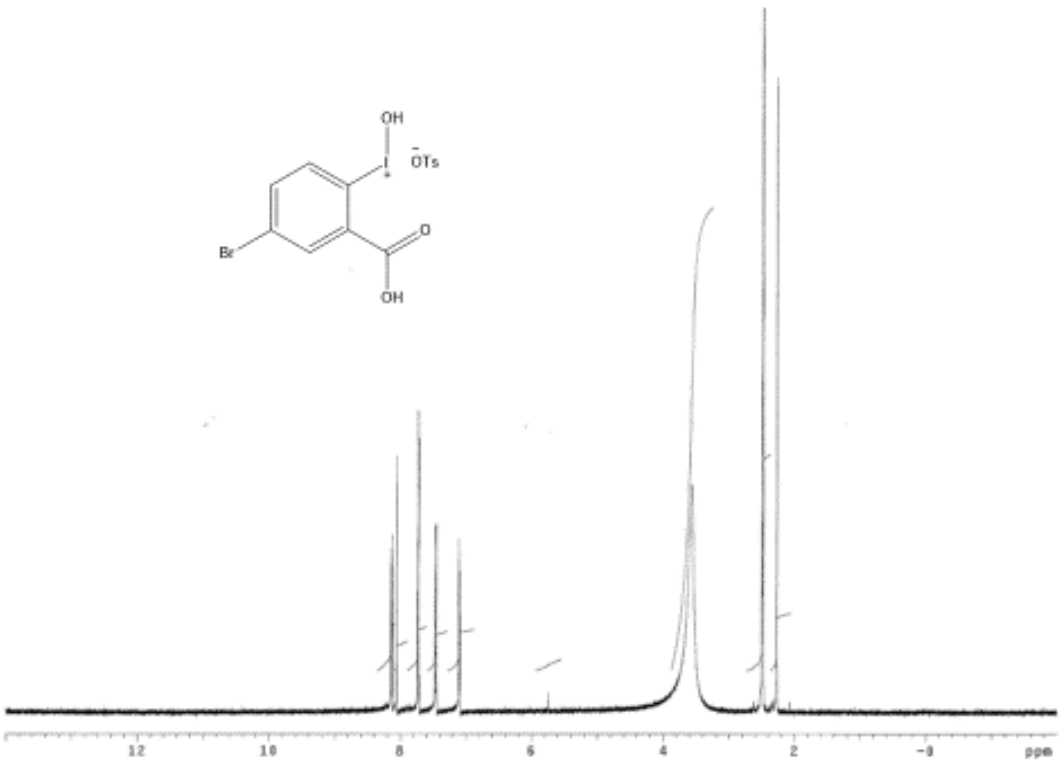
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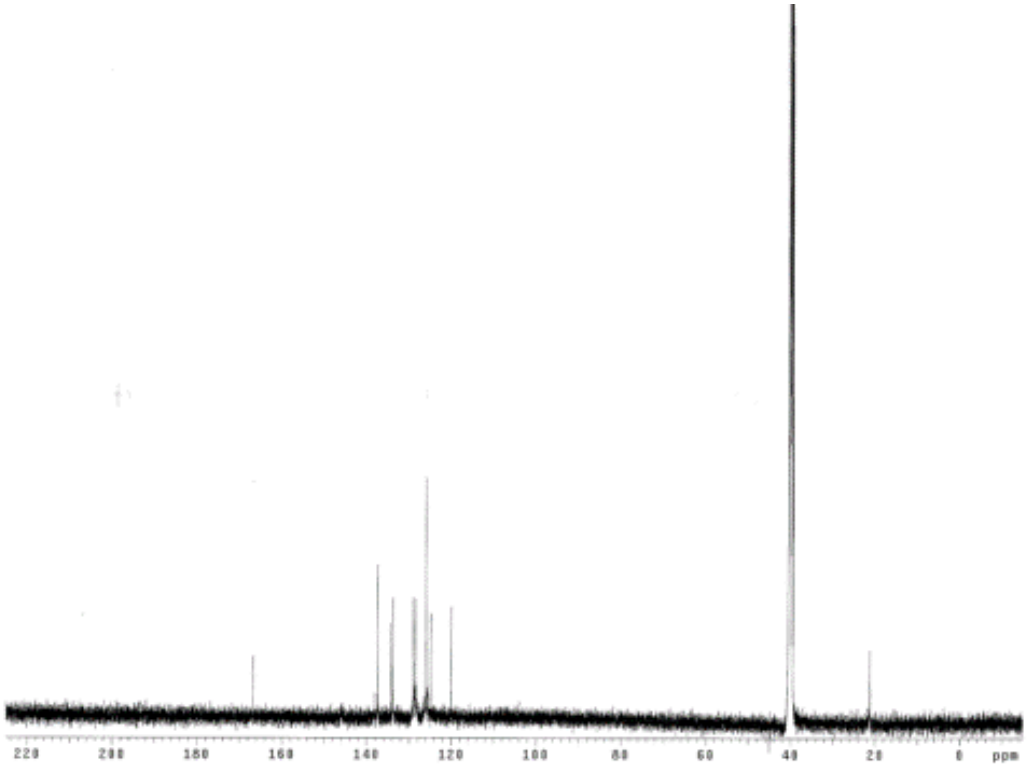
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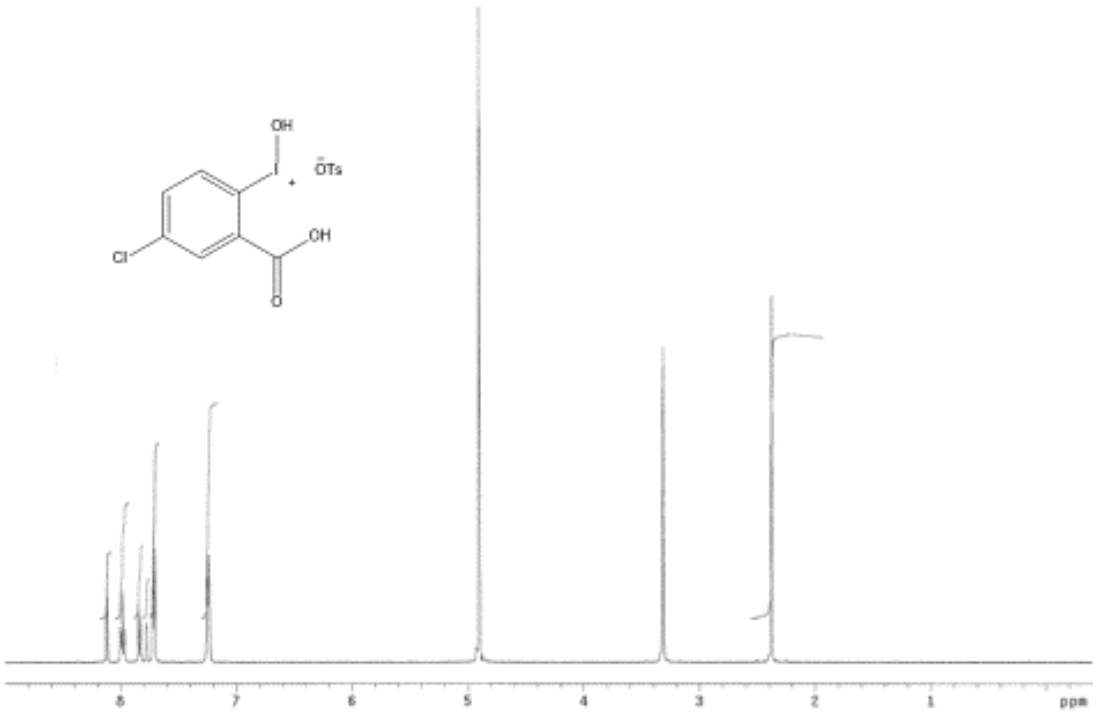
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OTs
Cl
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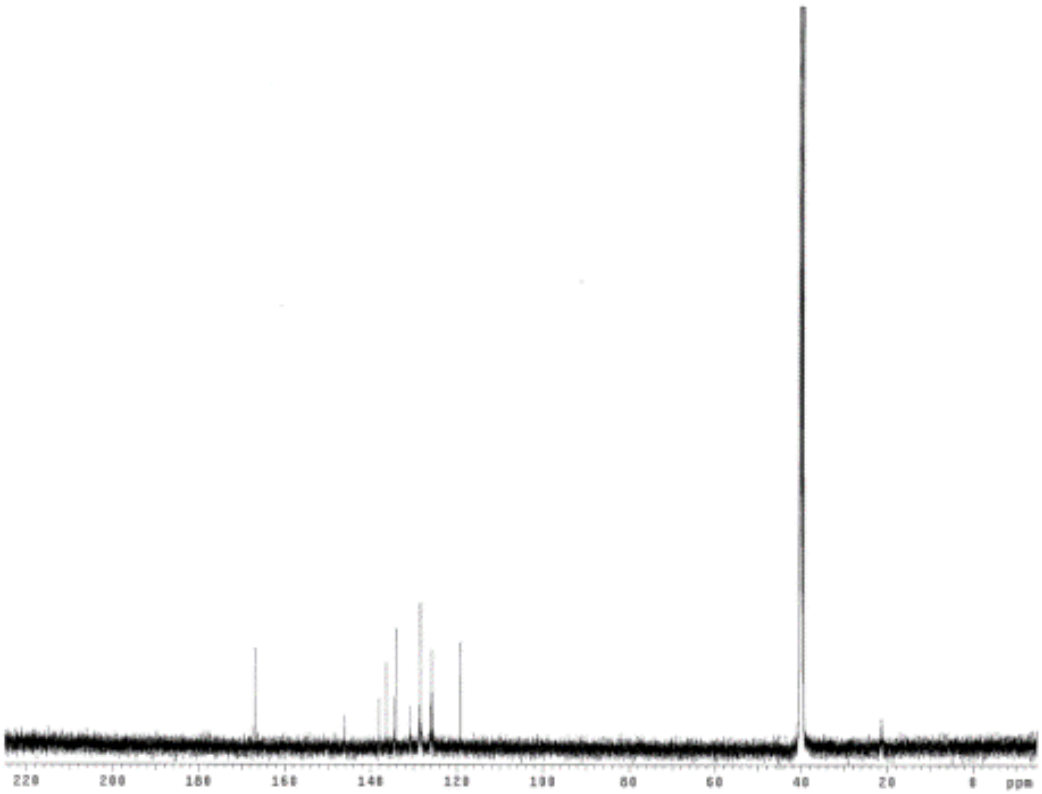
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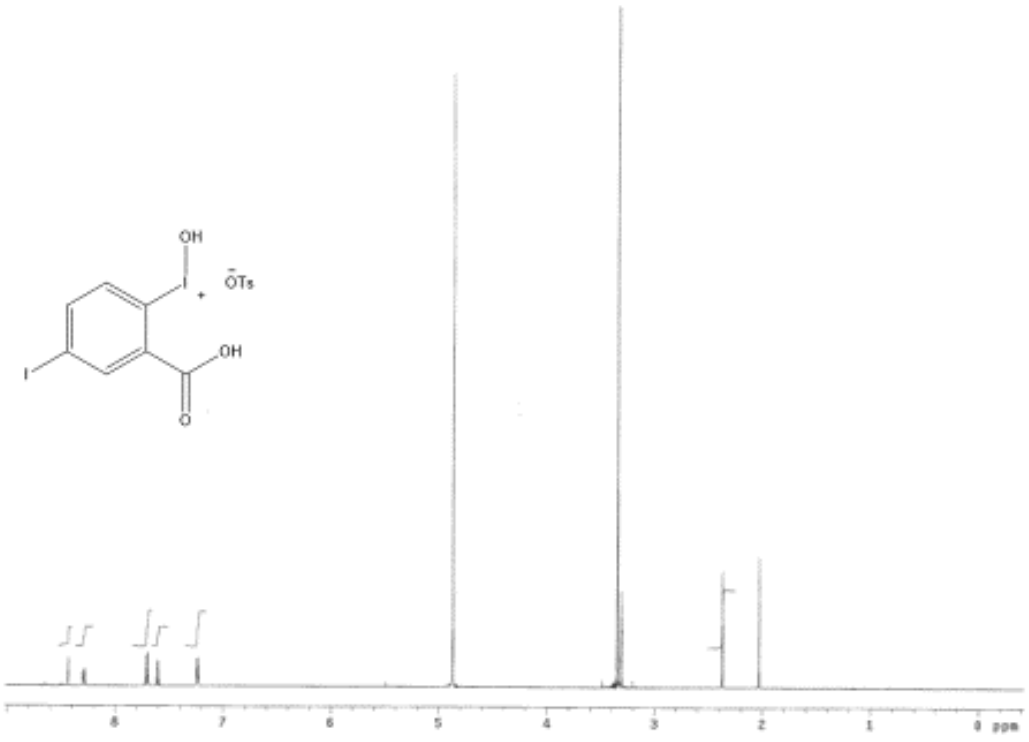
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+
OTs
OH
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O
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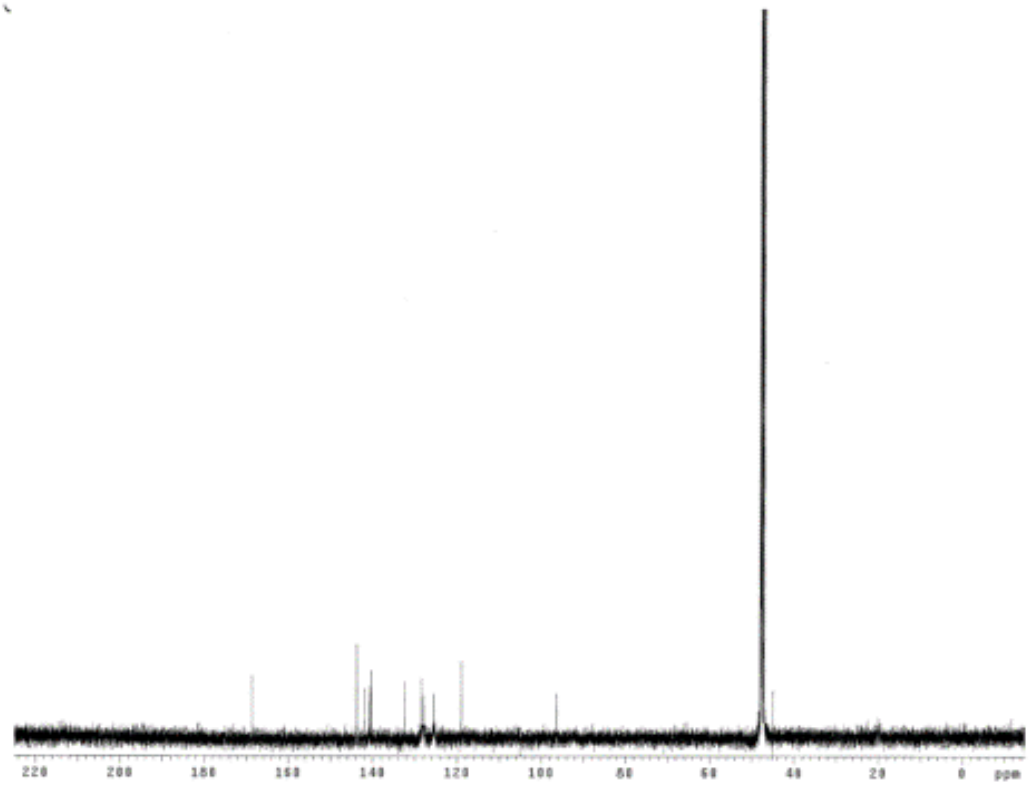
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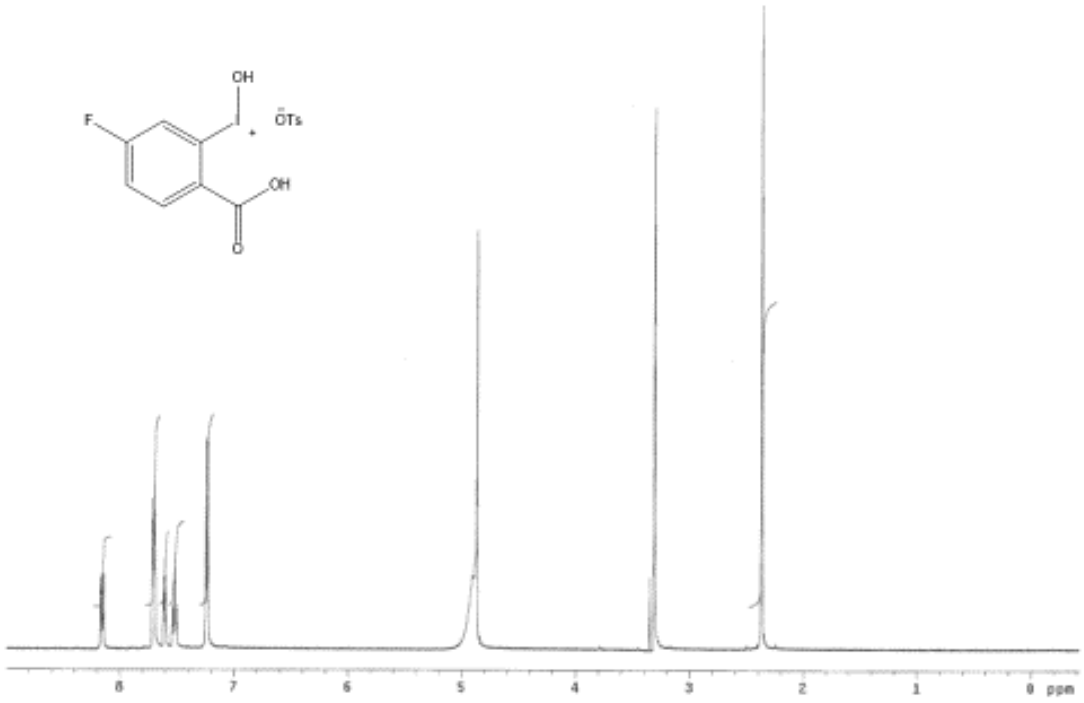
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OTs
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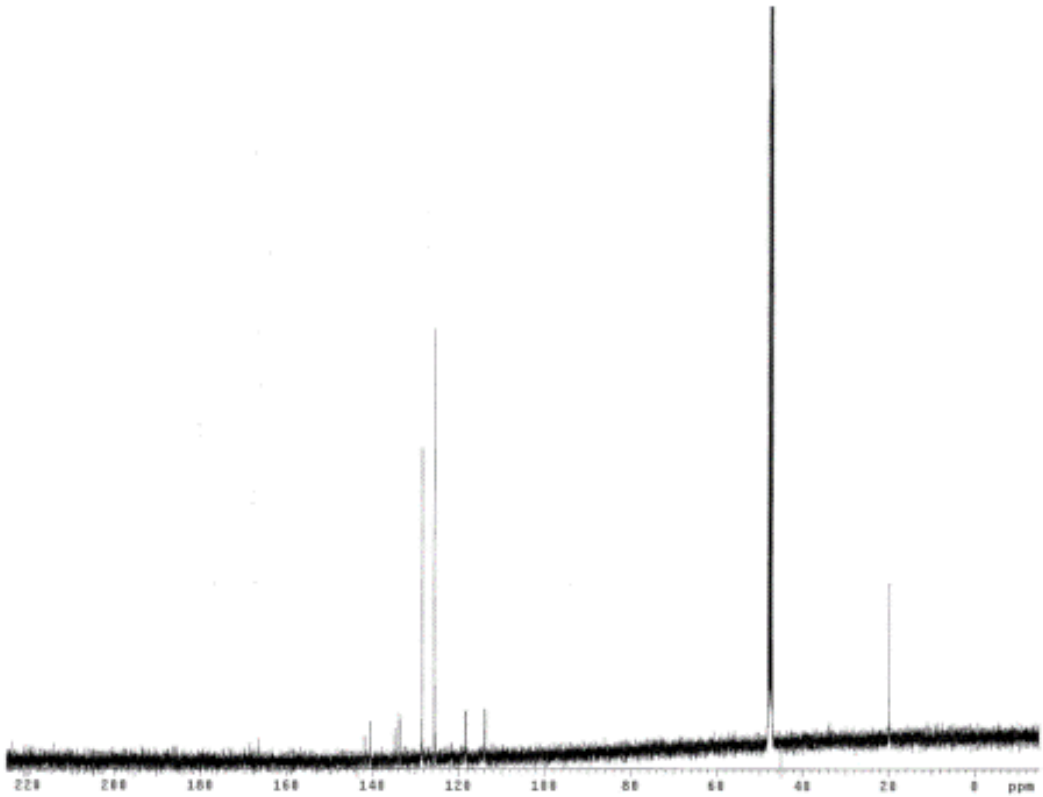
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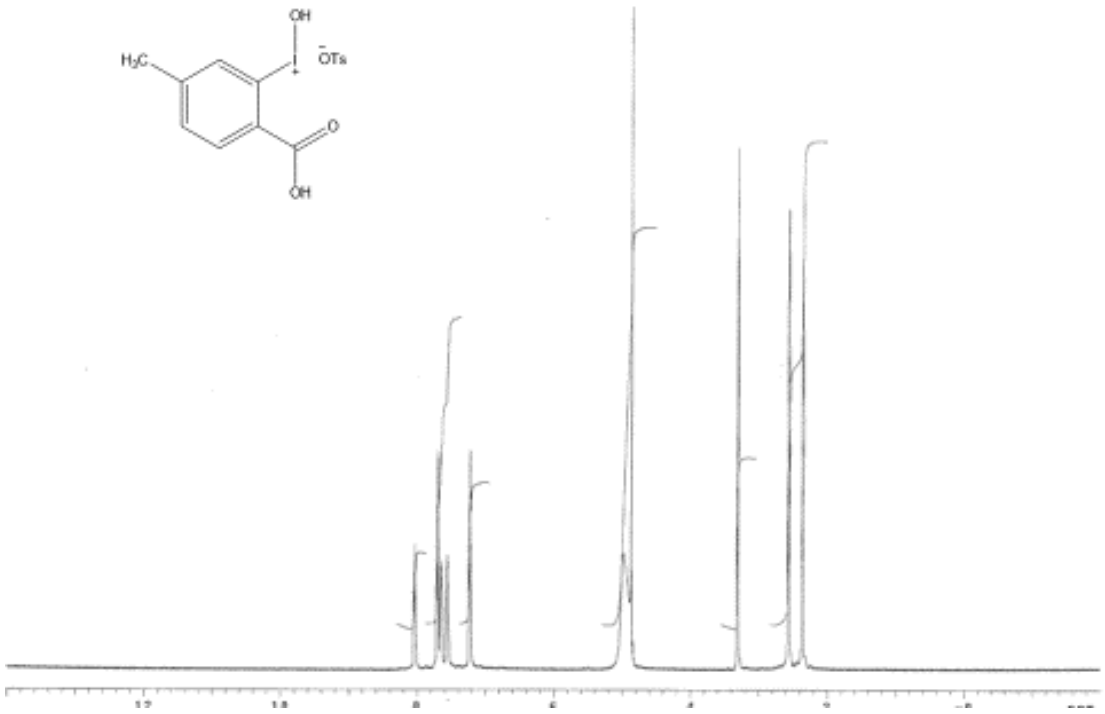
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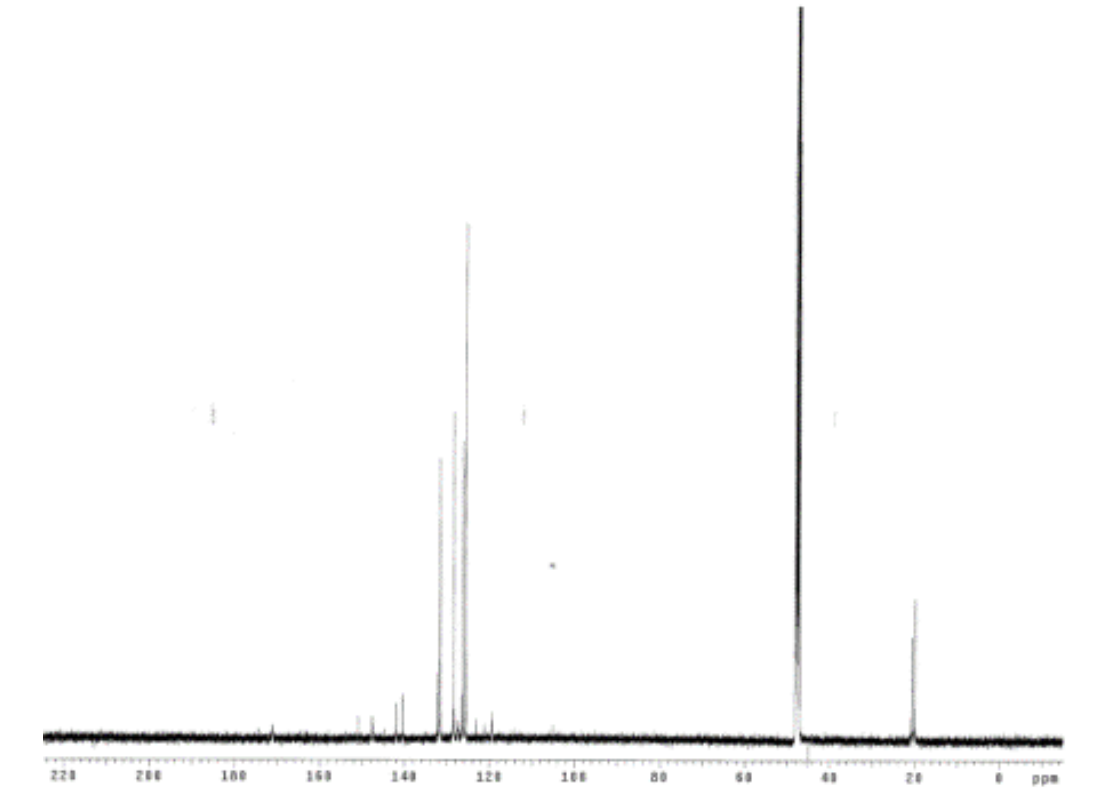
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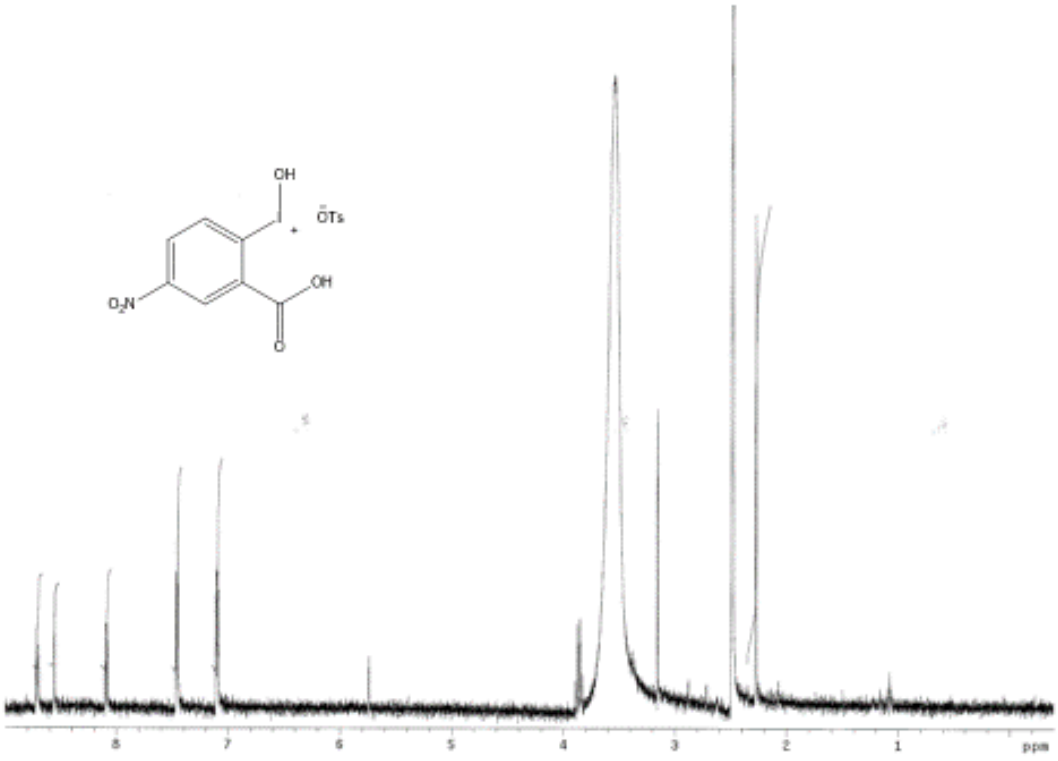
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3
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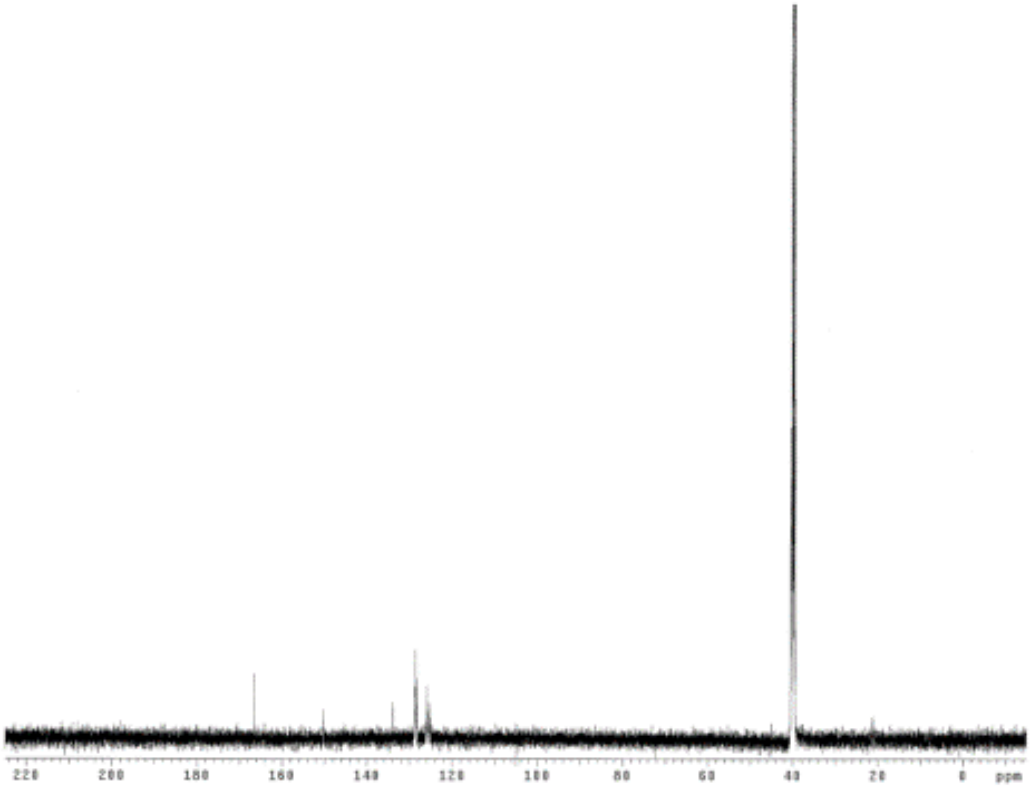
ppm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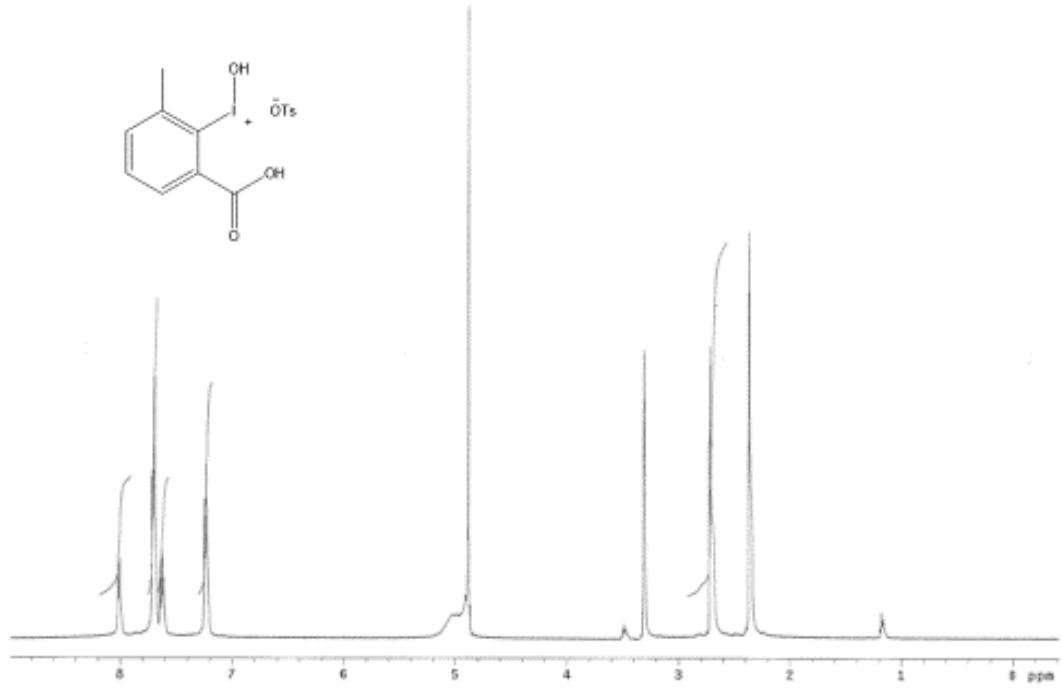
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OTs
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O
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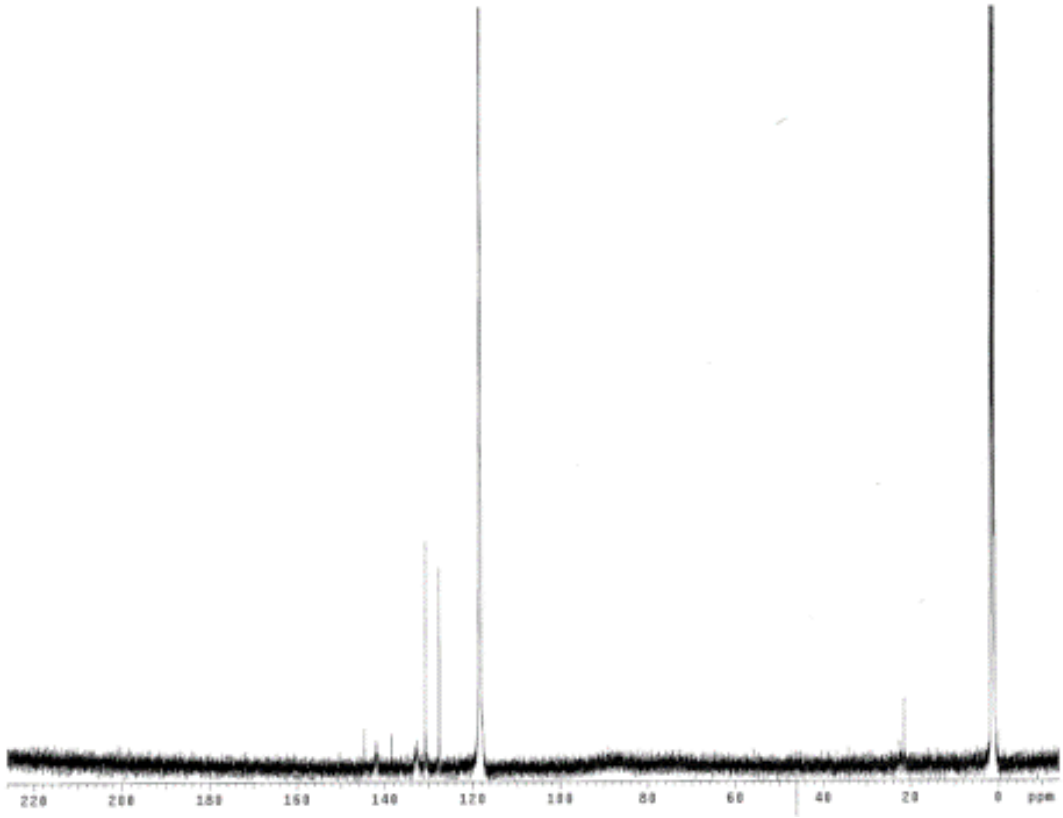
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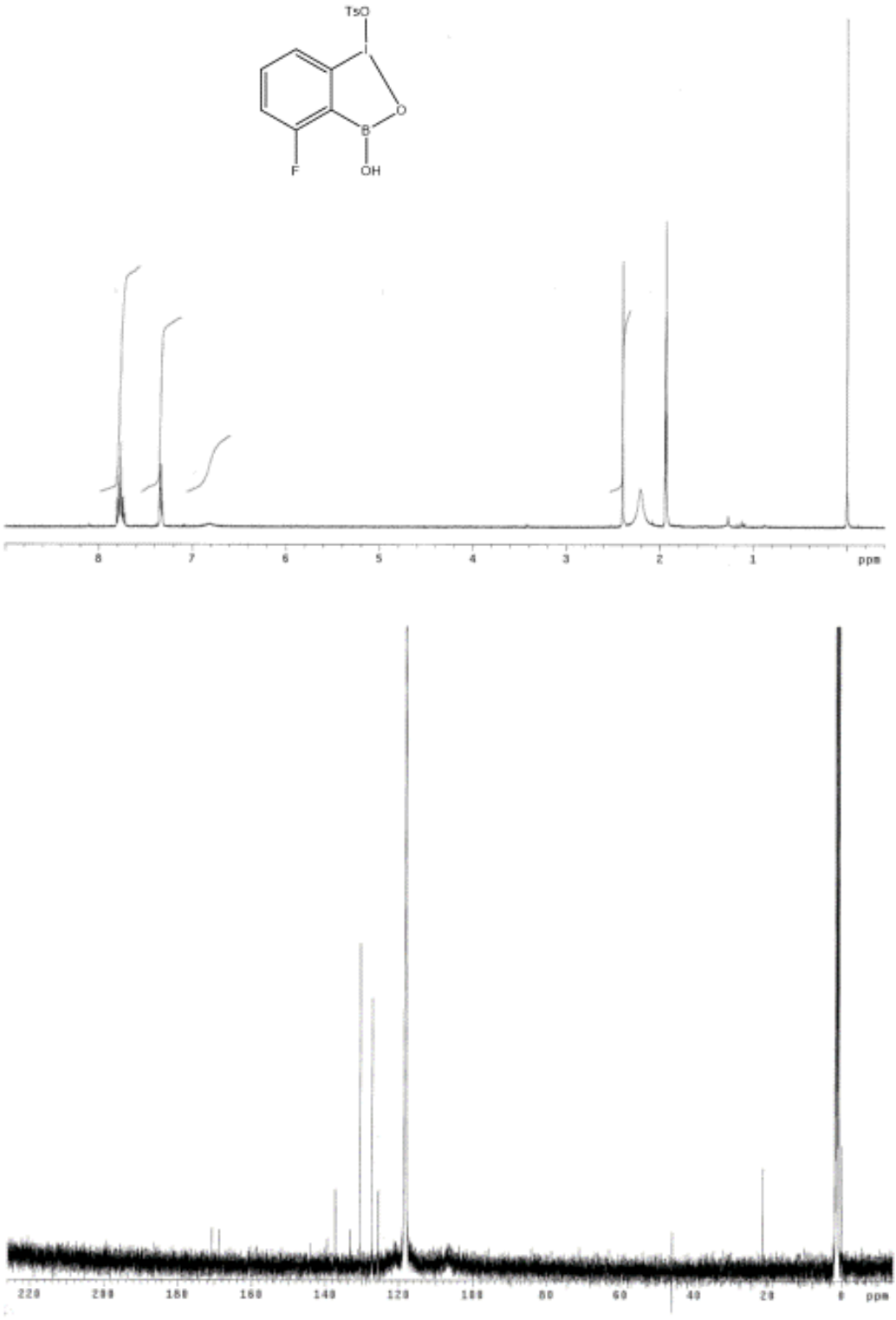
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OH
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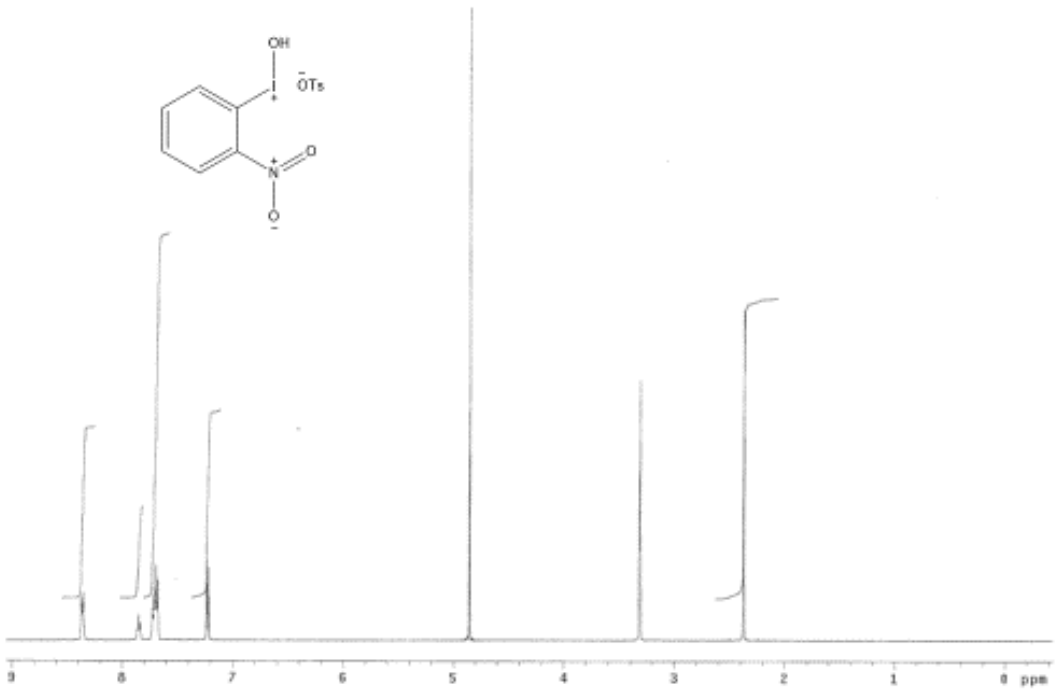
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OTs
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N
O
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2
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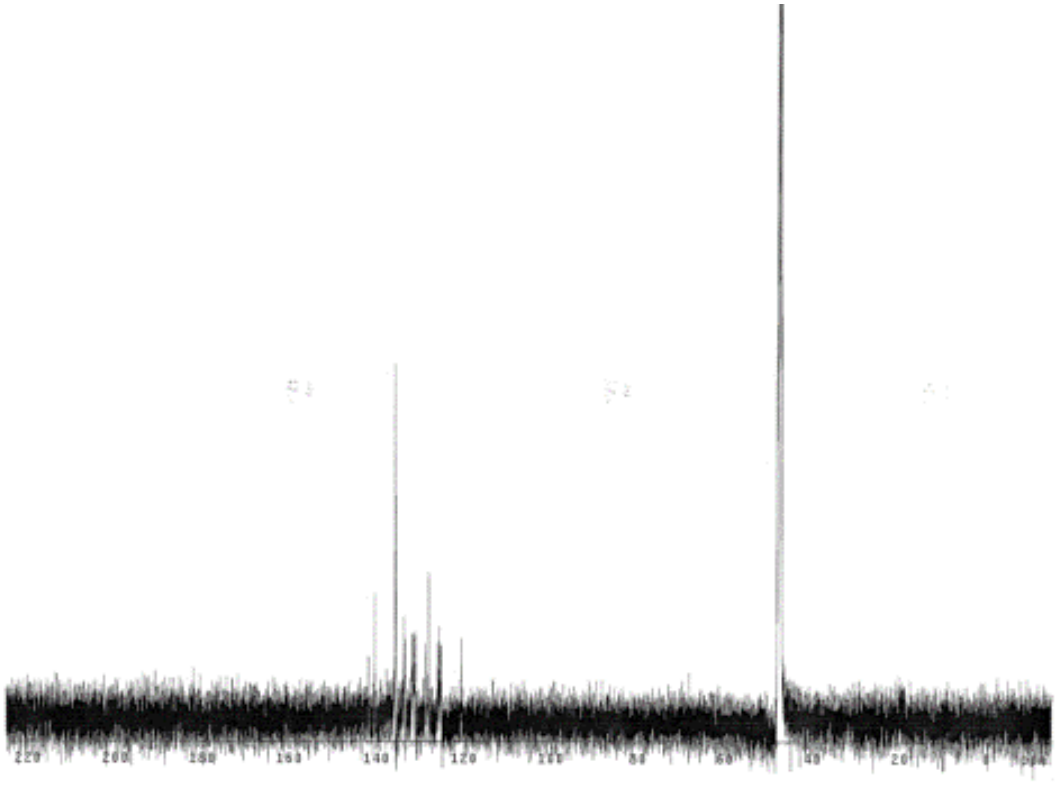
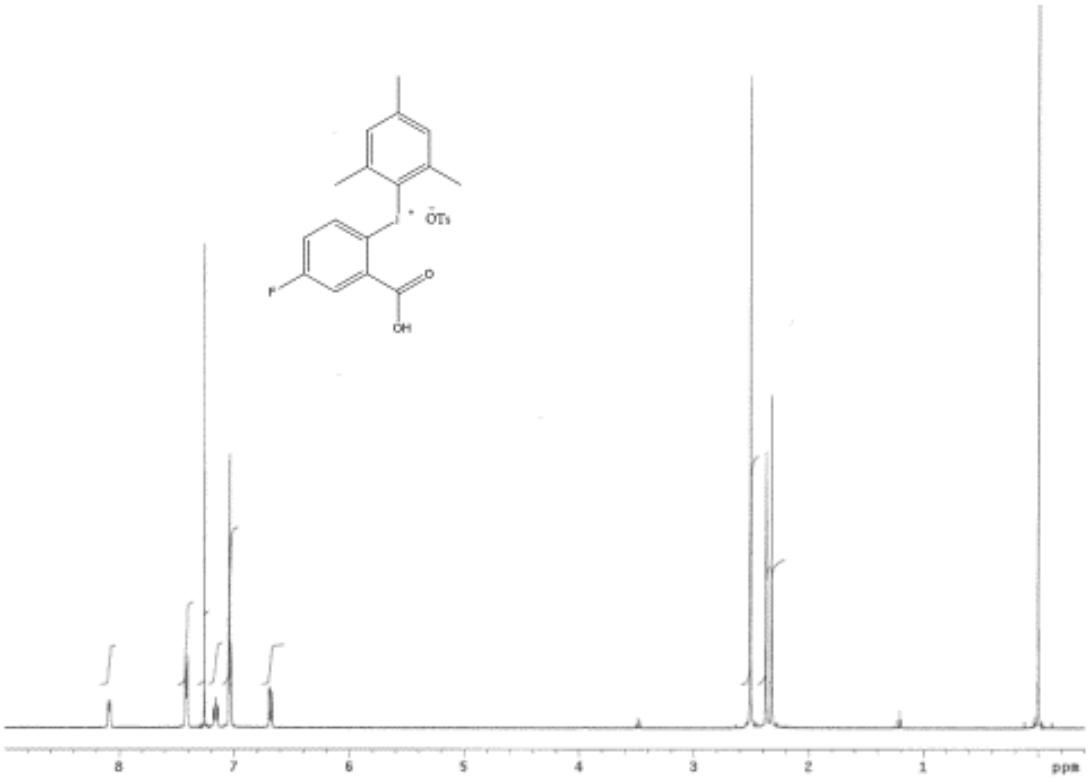
0 ppm

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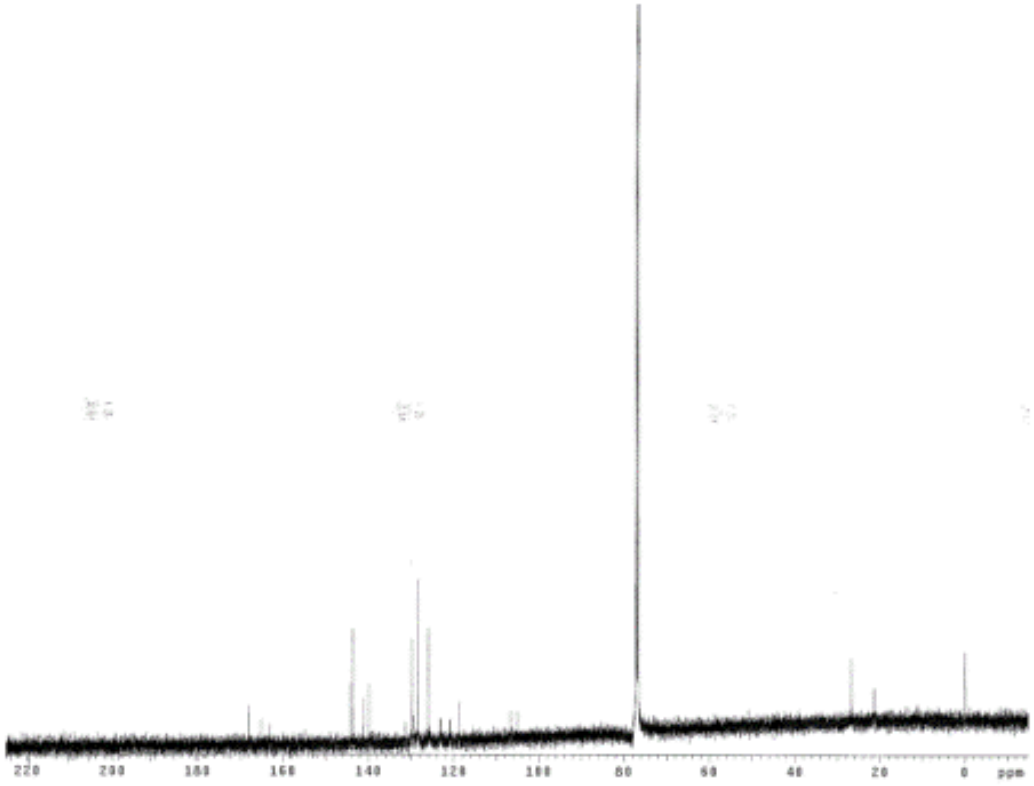
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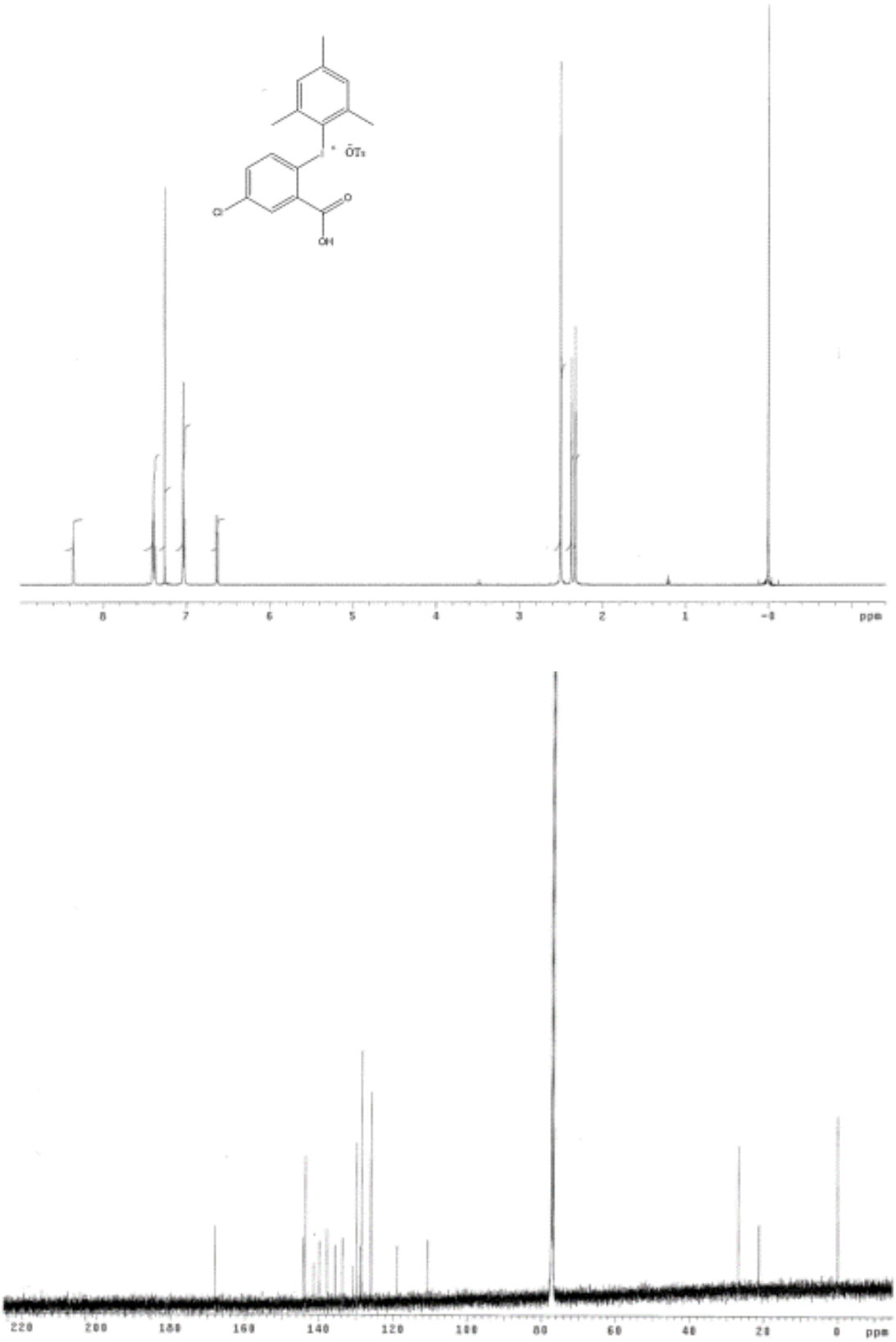
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Cl
O
OH
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7
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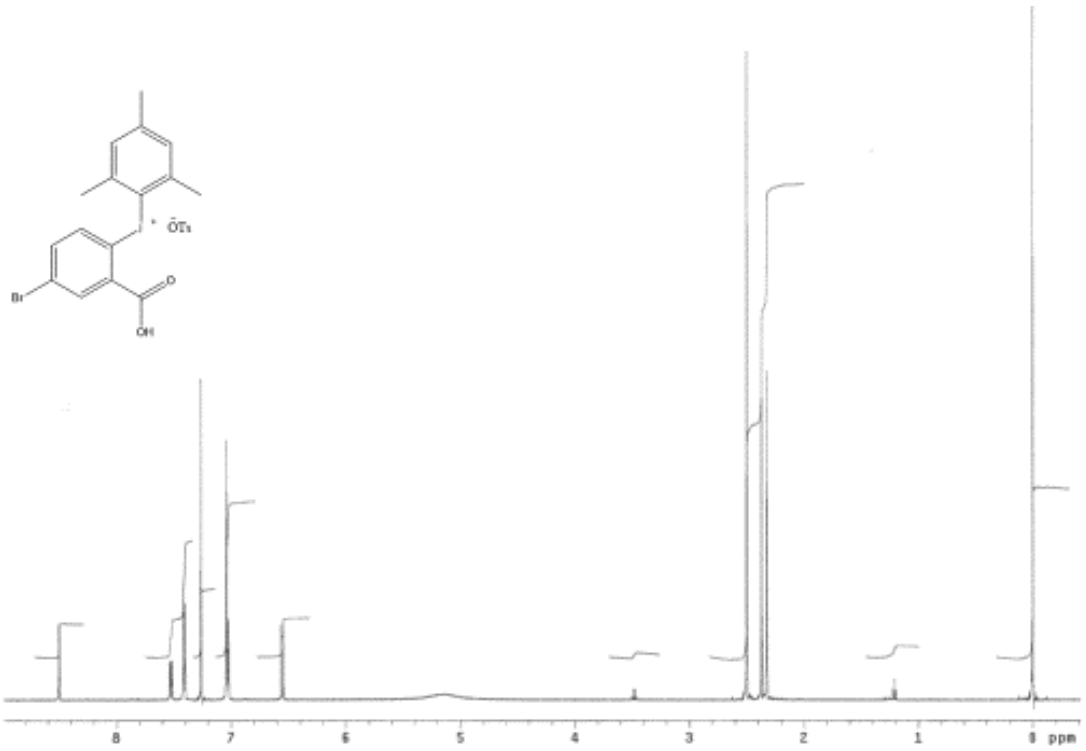
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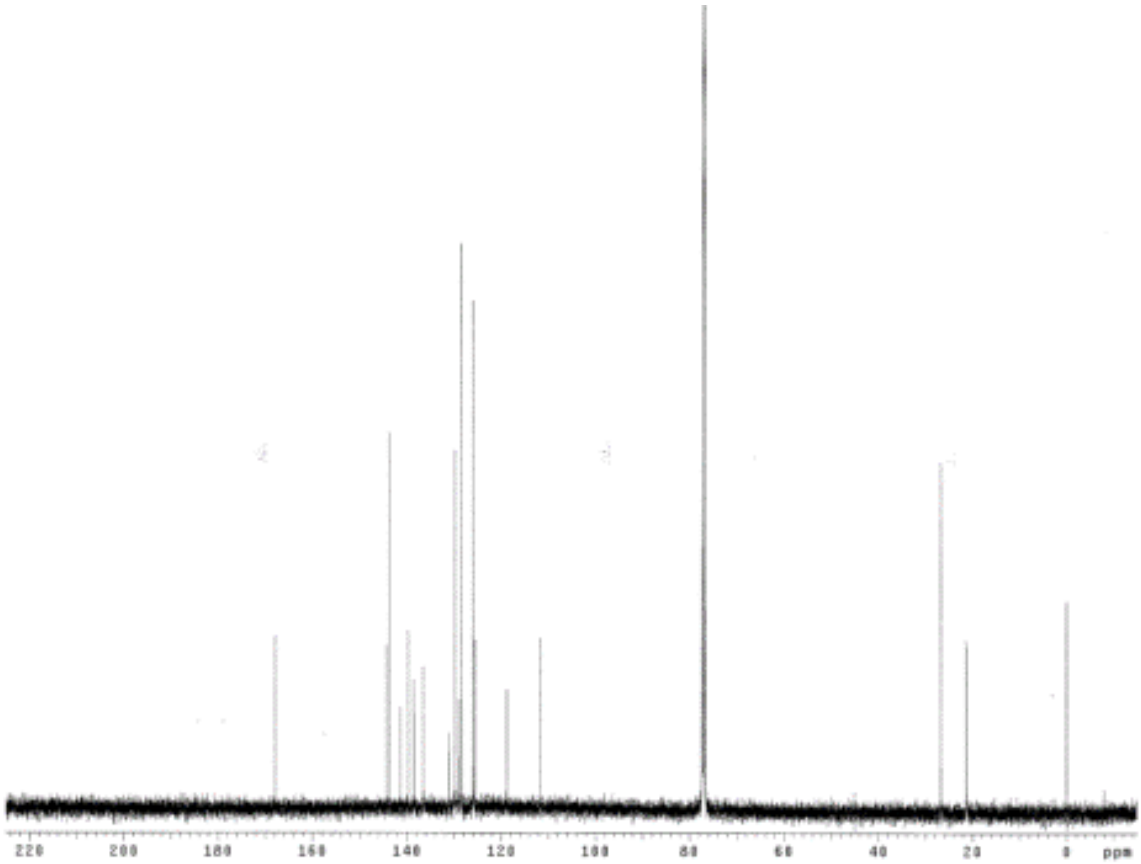
0 ppm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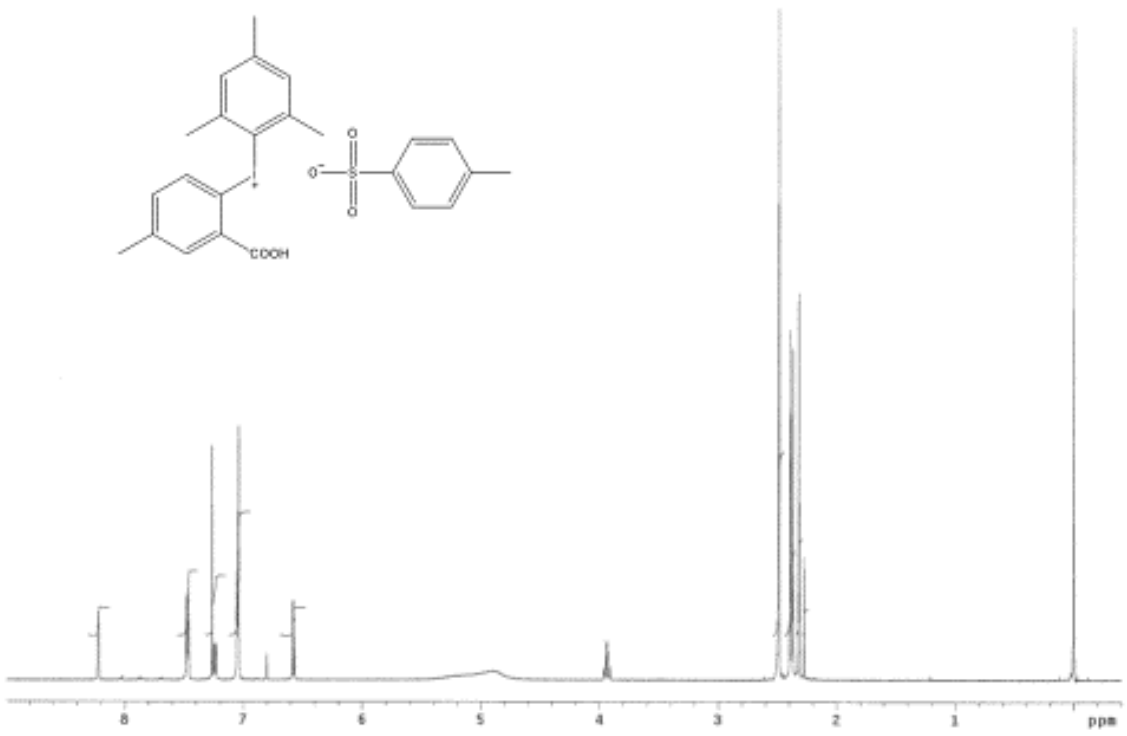
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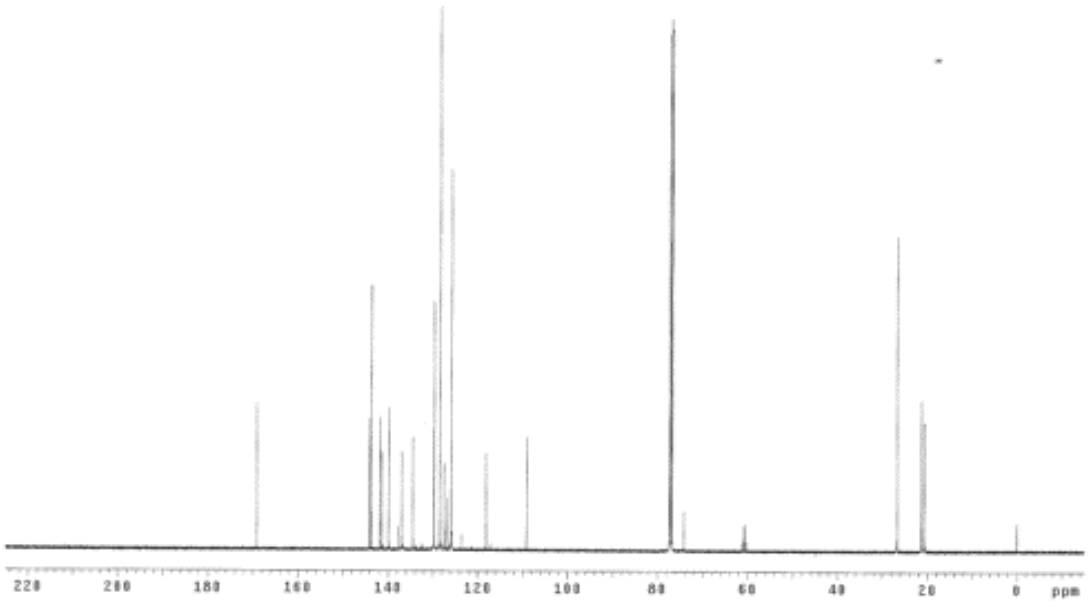
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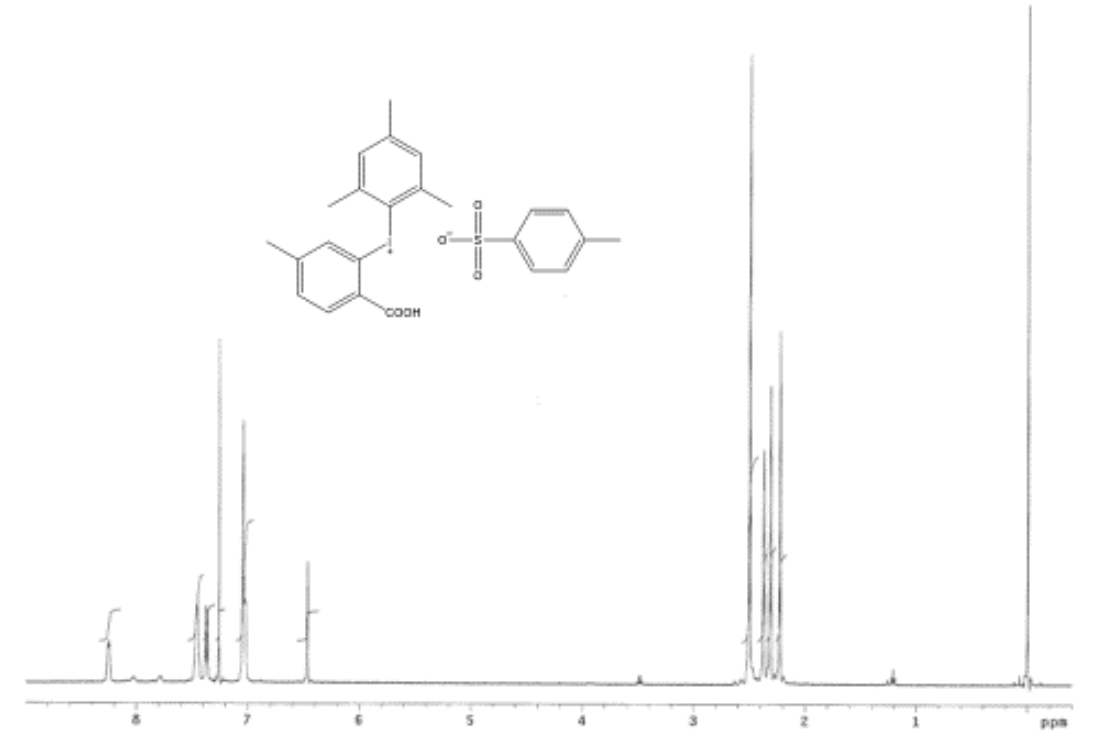
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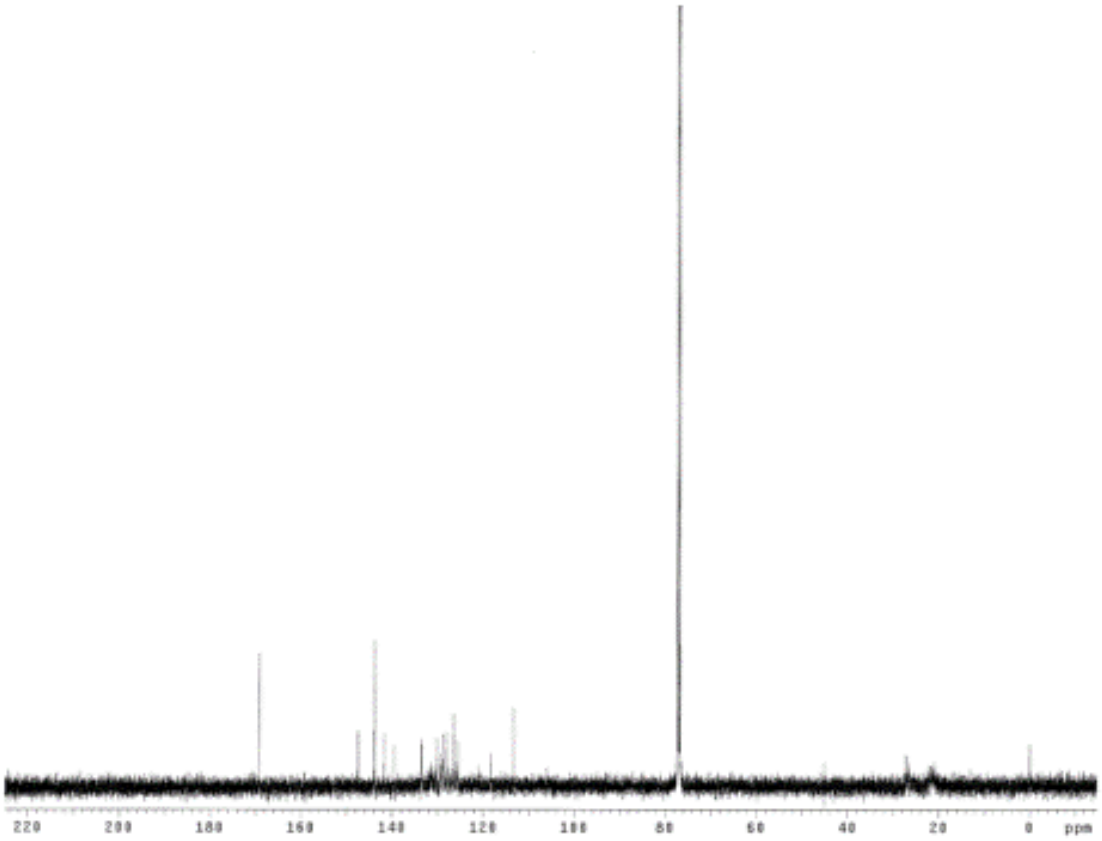
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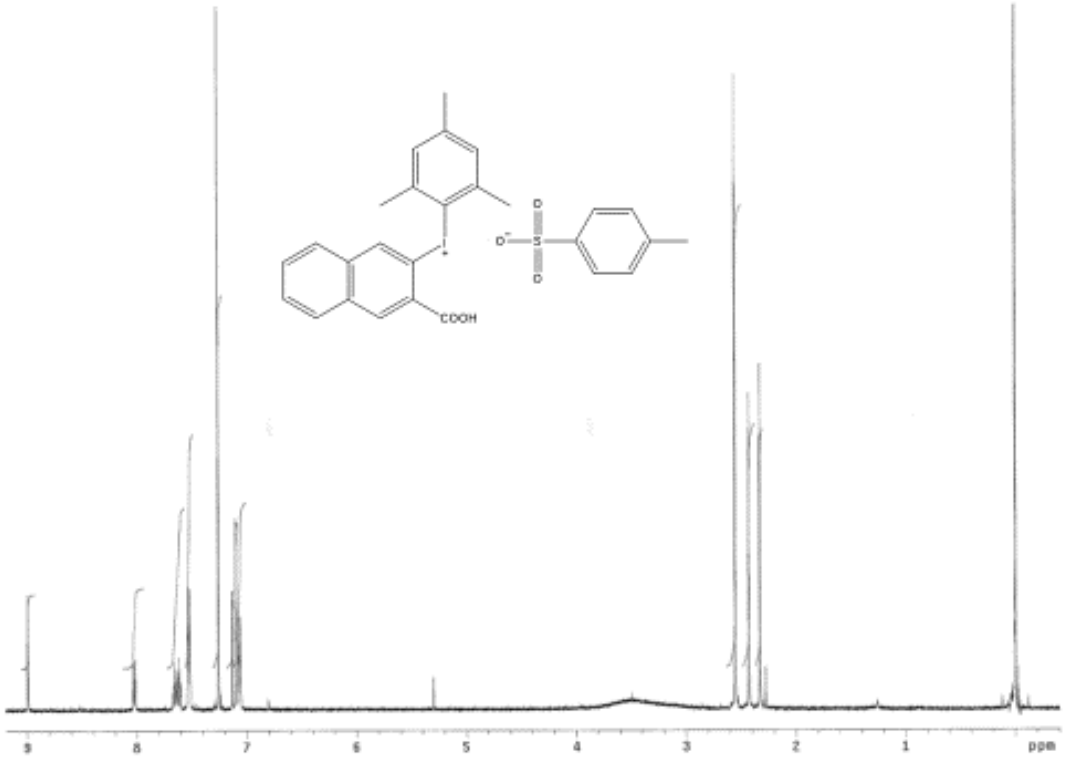
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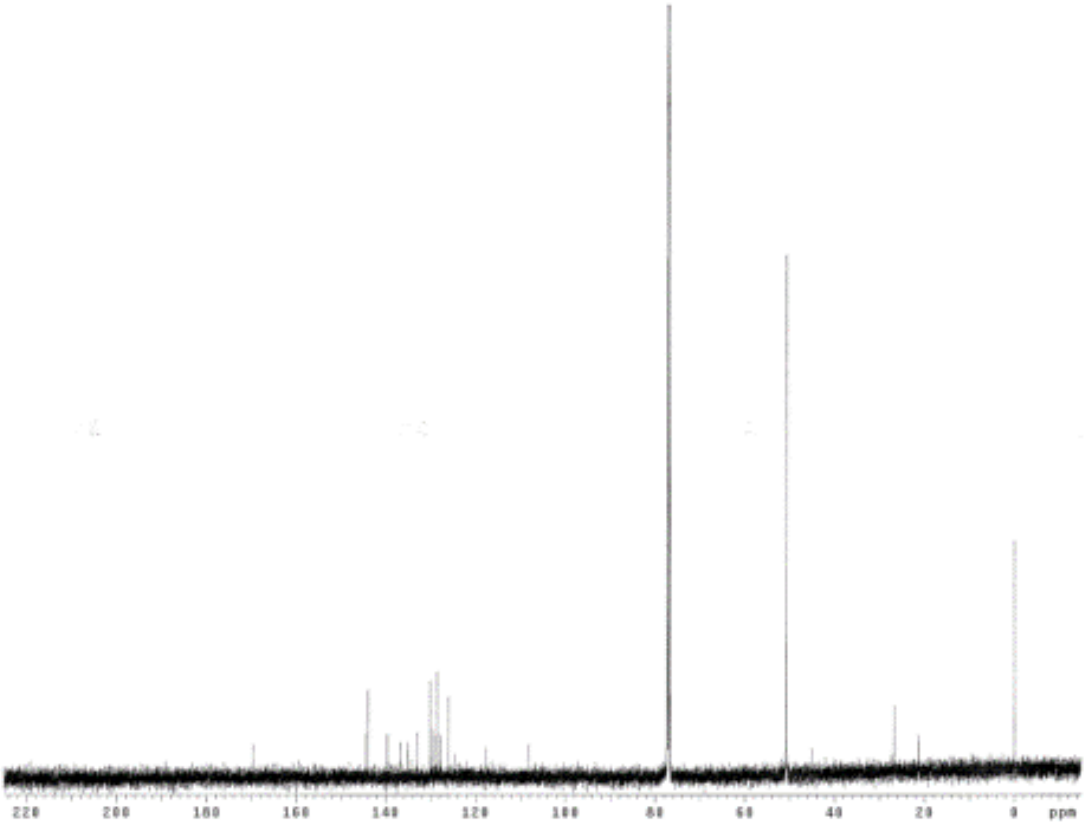
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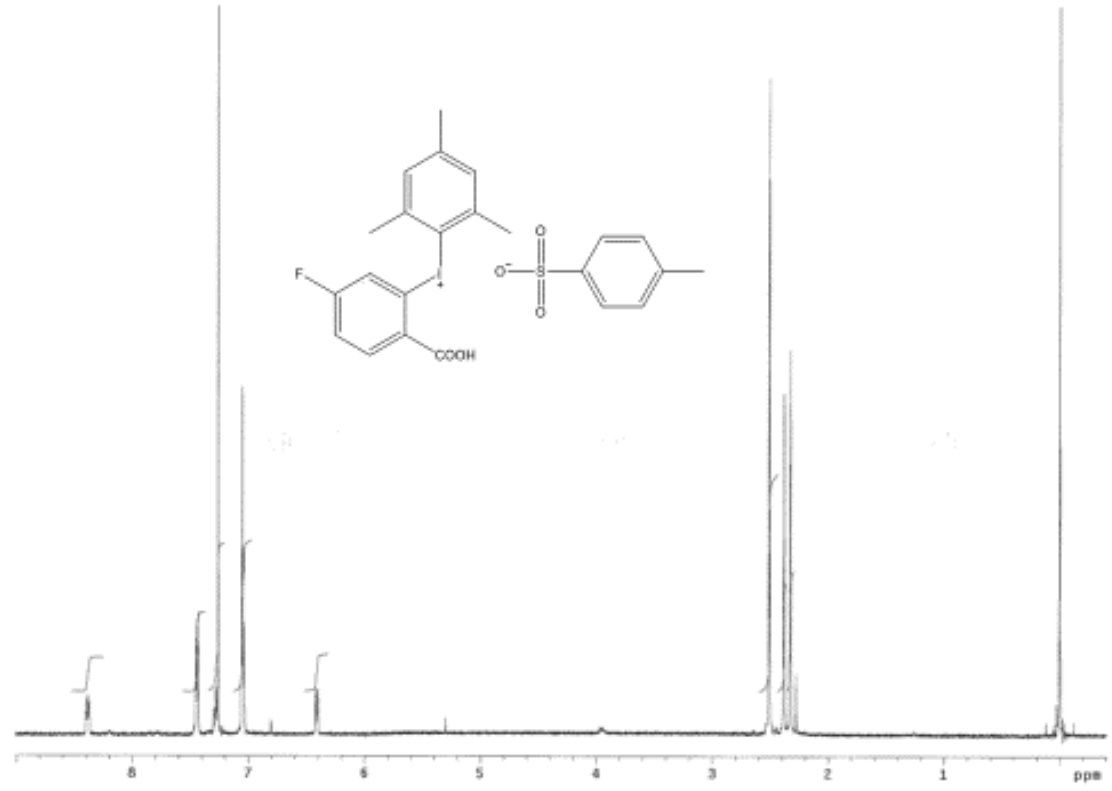
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COOH
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S
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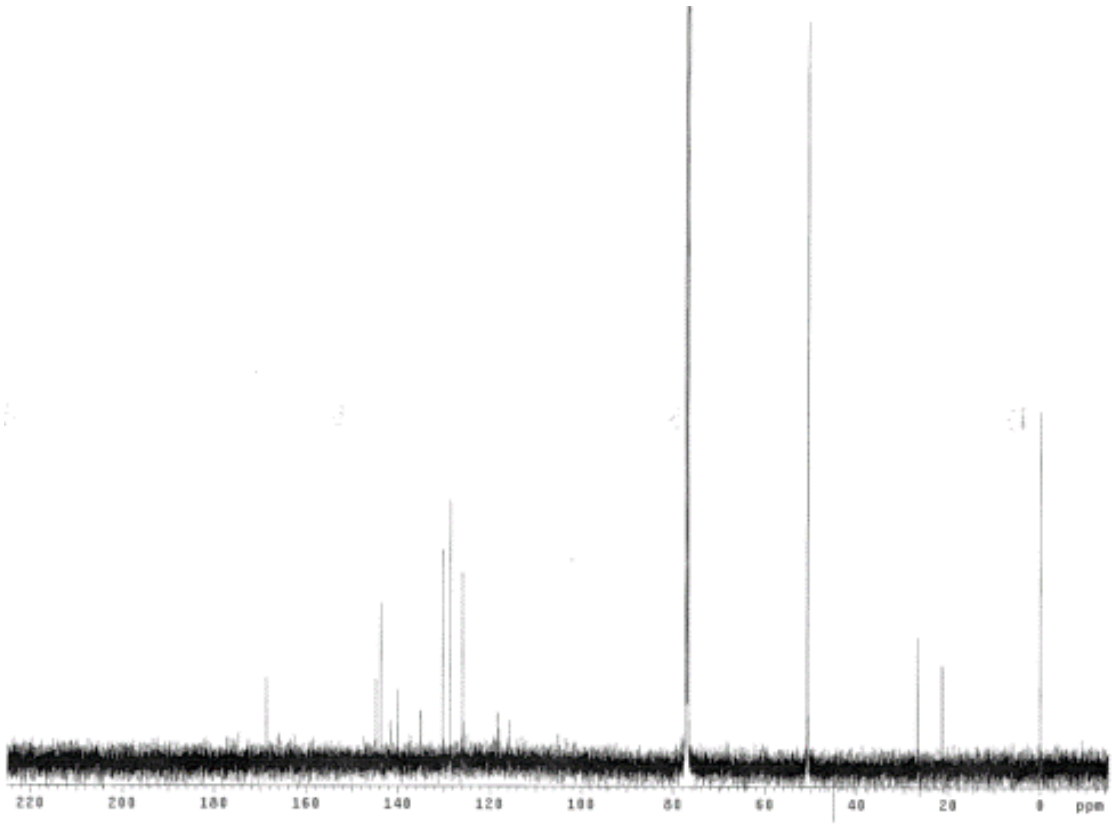
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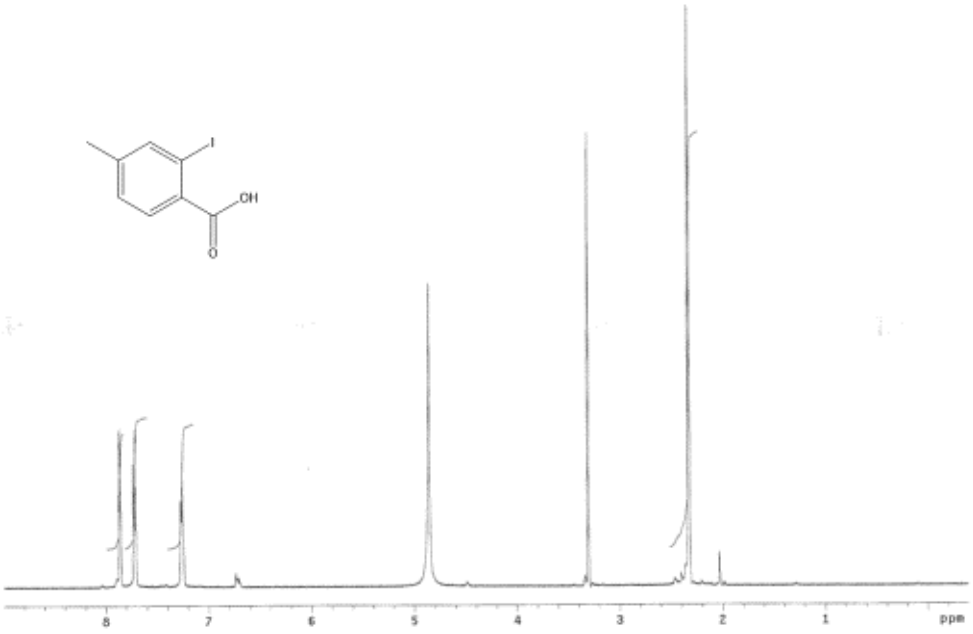
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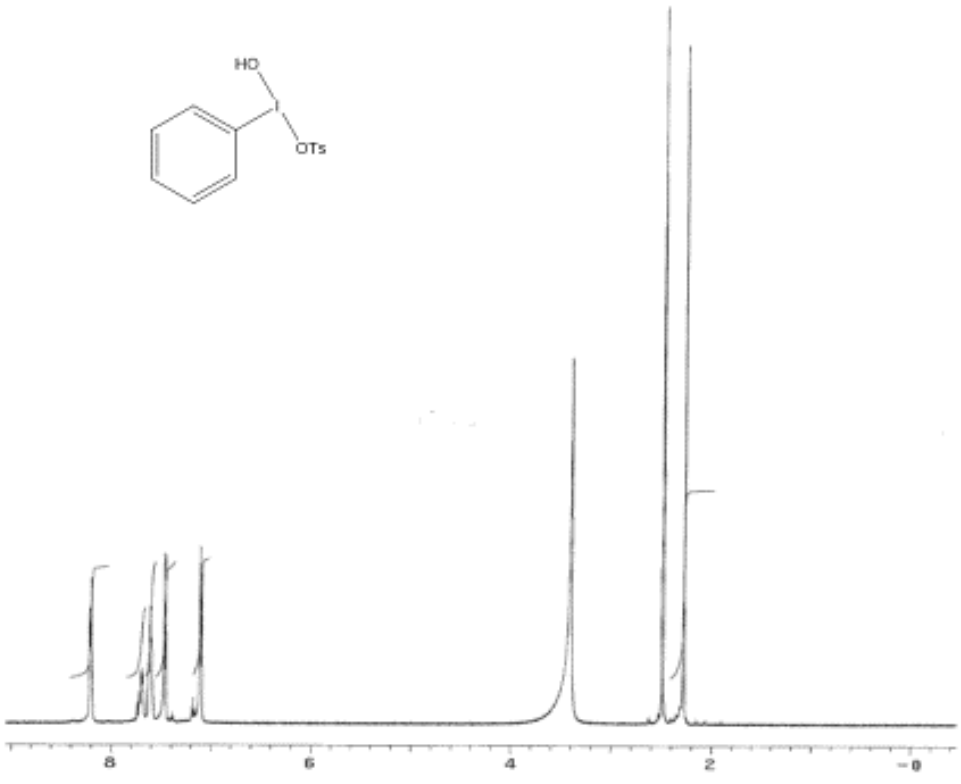
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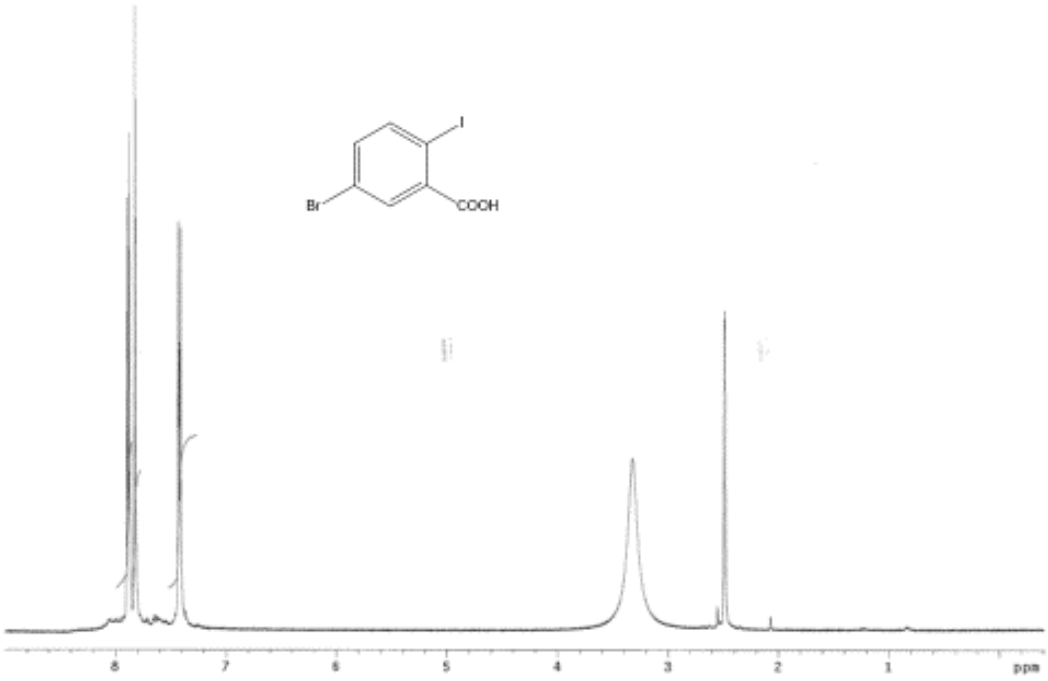
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Br
COOH
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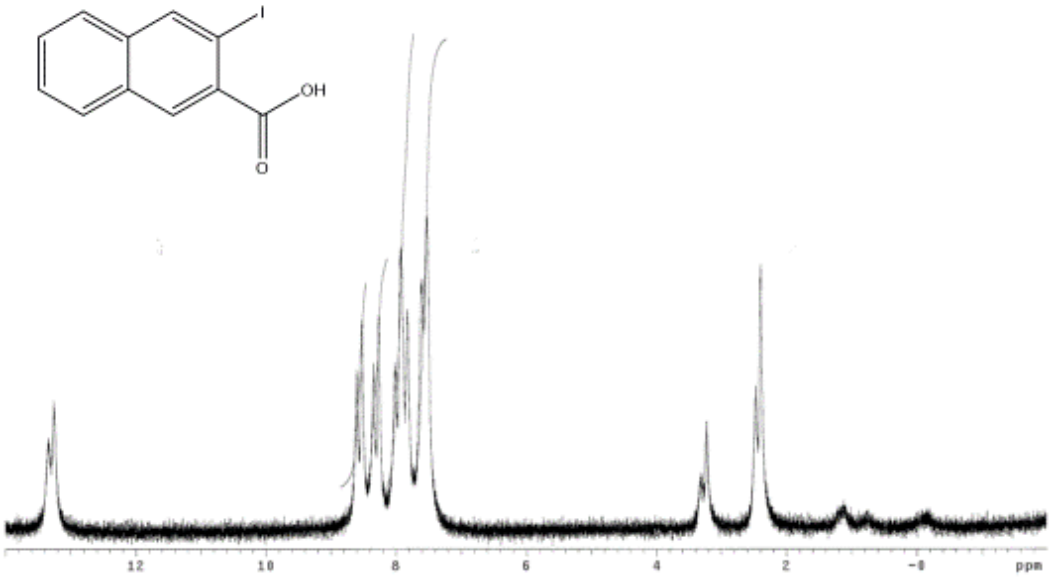
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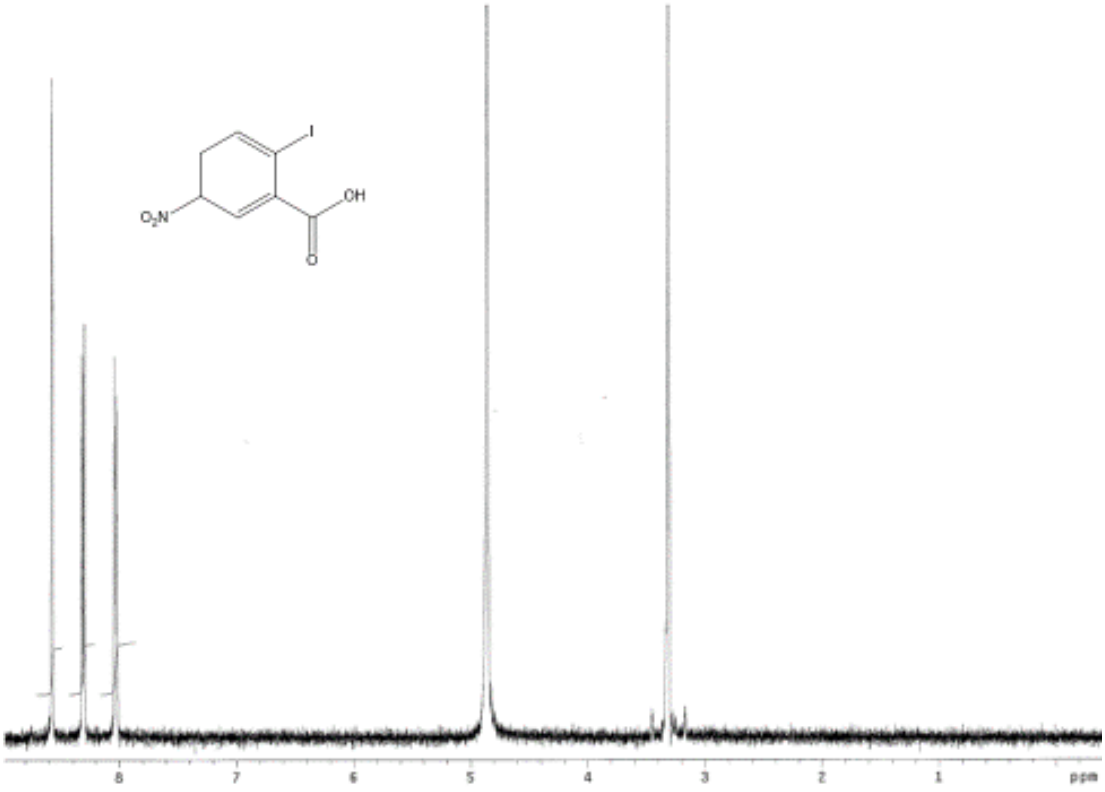
ppm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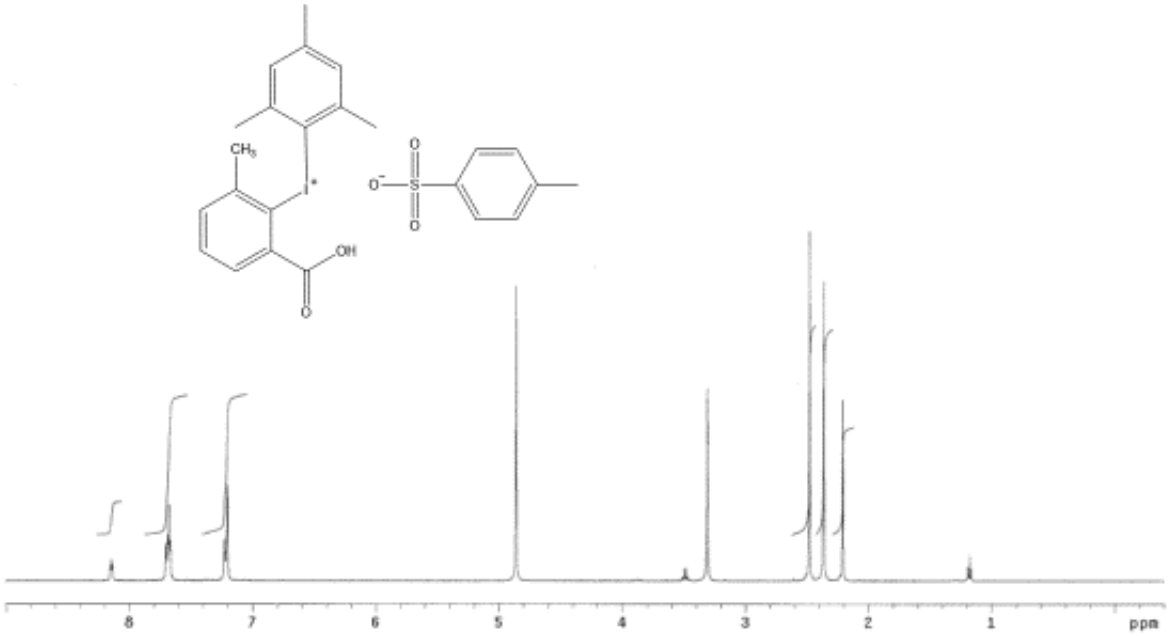
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S
O
O
OH
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4
3
2
1
ppm