João Cristóvão Santos Silva Macara

Licenciado em Química Aplicada

Investigation of novel sulfonylation methods

Dissertação para obtenção do Grau de Mestre em
Química Bioorgânica

Orientadora: Doutora Maria Manuel B. Marques,
Investigadora com agregação, FCT-UNL

Júri:

Presidente: Professora Doutora Ana Lourenço

Arguente: Professora Doutora Paula Branco

Vogal: Doutora Maria Manuel M. Marques

Outubro, 2017

FACULDADE DE
CIÊNCIAS E TECNOLOGIA
UNIVERSIDADE NOVA DE LISBOA

João Cristóvão Santos Silva Macara

Licenciado em Química Aplicada

Investigation of novel sulfonylation methods

Dissertação para obtenção do Grau de Mestre em
Química Bioorgânica

Orientadora: Doutora Maria Manuel B. Marques,
Investigadora com agregação, FCT-UNL

Júri:

Presidente: Professora Doutora Ana Lourenço

Arguente: Professora Doutora Paula Branco

Vogal: Doutora Maria Manuel M. Marques

Outubro, 2017

FACULDADE DE
CIÊNCIAS E TECNOLOGIA
UNIVERSIDADE NOVA DE LISBOA

Investigation of novel sulfonylation methods

"*I have not failed 700 times. I have not failed once. I have succeeded in proving that those 700 ways will not work. when I have eliminated the ways that will not work, I will find the way that will work.*"

Thomas Edison, 1931

AGRADECIMENTOS

Para começar, quero agradecer à Doutora Maria Manuel Barata Marques, que embora já tivesse uma equipa cheia de alunos, não hesitou em aceitar orientar esta dissertação de mestrado. Quero agradecer todo o conhecimento científico e prático que partilhou comigo. Foi um ano de aprendizagem em que a professora nunca desanimou independentemente dos obstáculos e em que estava sempre presente, quer seja telefone, e-mail ou mensagem.

Em seguida quero agradecer a todo o pessoal do laboratório. Quero agradecer à Patrícia Máximo por todos os quizzes musicais que fez comigo. À Daniela Peixoto por ter feito o papel de "mãe" todas as noites em que o trabalho não colaborava, e que ficava a fingir que ainda tinha trabalho para fazer. Ao Carlos Branco e ao André Sequeira por todas as noites bem passadas. Ao Rafael Mamede pela companhia e pela ajuda.

Um especial obrigado a todos os constituintes do grupo de investigação da Doutora Maria Manuel Barata Marques. Quero agradecer à Ana Mortinho pela sua enorme boa disposição. Quero agradecer à Sara Purificação pela ajuda que me deu. Muito obrigado ao Rafael Rippel e ao Fausto Queda, por todo o companheirismo. Um enorme obrigado à Cátia Santos e Marina Pires por me terem acolhido. Desde o início que estavam sempre prontas para me ajudar durante todo o processo, principalmente durante a fase de adaptação ao trabalho de bancada. Finalmente, quero agradecer ao Diogo Poeira, que foi quem aceitou partilhar o seu trabalho comigo e com quem eu mais partilhei esta experiência.

Gostava de agradecer aos meus amigos mais chegados, Sofia Santos, Vanessa Fadista e Pedro Ferreira. Foram inúmeras as pausas de almoço em que discutíamos as mais variadas PEG's que não funcionavam, curcubiturils que eram bem-mandados e resinas que mudavam de cor enquanto eu mandava mensagens e vocês se queixavam que não estava a prestar atenção ao jogo e a Sofia acabava por ficar muito vermelha e zangada porque "eu só me passo quando são erros parvos".

Quero desejar um grande obrigado aos meus pais, aos meus avós, aos meus irmãos e aos meus tios. Foram eles que aturaram todas as mudanças de casa, todos os desvaneios químicos, todos os jantares de arroz "unidos venceremos ", jantares tarde e por estarem sempre prontos a ajudar. E, mais importante, que me deram sempre força e incentivo para continuar. Em particular quero agradecer à Doutora Teresa Santos Silva não como colega, mas como sobrinho, por estar sempre na minha equipa.

Por último quero agradecer à Tânia Coelho. Quero agradecer por ter estado ao pé de mim numa das fases mais importantes da minha carreira. Por estar sempre disponível para fazer uma formatação. Por estar sempre à minha espera com uma palavra doce. Quero agradecer por me ter acompanhado e ajudado nesta aventura como se fosse dela e que certamente sem ela não teria sido possível completar. Muito obrigado.

RESUMO

As sulfonamidas são um grupo funcional muito importante, presente num vasto conjunto de compostos, e de grande interesse na indústria farmacêutica. Embora tenham sido feitos grandes progressos na sua síntese, os existentes métodos ainda são de versatilidade, economia atómica ou segurança limitada.

O uso de compostos de iodo hipervalente como transferidores de grupos funcionais é um recente tópico de grande interesse, mas que ainda não foi explorado para a transferência de sulfonilo. Os existentes métodos de sulfonilação e equivalentes de RSO_2 ainda têm desvantagens, como não serem compatíveis com aminas nucleófilas. Neste projeto reagentes derivados de benziodoxole são explorados pela primeira vez como transferidores de grupo sulfonilo criando a próxima geração de reagentes de sulfonilação.

Dois diferentes benziodoxolonas foram sintetizadas e testadas em diferentes condições para formar um intermediário, benziodoxolona de sulfonilo, capaz de transferir este grupo para uma amina nucleófila. Depois de inúmeros ensaios, descobriu-se que o cloro benziodoxolona foi a melhor escolha para esta transformação, em DCM, a -40 ºC, na presença de TBAI, dando aso a (fenilsulfonil)morfolina com 88% de rendimento.

O desenvolvido método foi aplicado a treze diferentes aminas nucleófilas e quatro sais de ácido sulfínico de sódio e foram obtidas sulfonamidas com rendimentos até 84%.

Em seguida, foi investigada o uso de benziodoxolona imobilizada num polímero solúvel, PEG-2000. O percursor de benziodoxolona foi peguilada com 58% rendimento. Depois de clorado, o reagente (38) foi testado na síntese de (fenilsulfonil)morfolina, obtida com 48% de rendimento. O ácido peguilado foi reciclado, convertido novamente no intermediário clorado (38) e reutilizado, formando a sulfonamida com 56% de rendimento.

Resumindo, um novo método de sulfonilação foi desenvolvido, sintetizando sulfonamidas com rendimentos entre moderado e excelente. Adicionalmente, o reagente de benziodoxolona foi imobilizado num polímero solúvel, facilitando o isolamento da sulfonamida, evitando o isolamento de intermediários e permitindo a recuperação do reagente de iodo.

Palavras-chave: Iodo hipervalente, Sulfonilação, Sulfonamida, Polietileno glicol

ABSTRACT

Sulfonamide is a very important functional group, present in a vast array of compounds and of great interest for the pharmaceutical industry. Despite the progress on the synthesis of sulfonamides, the existing methods are of limited versatility, atom economy or safety.

An emerging topic of interest is the use of hypervalent iodine compounds as functional groups transfer reagents, but so far, no example has been explored for the transfer of sulfonyl. Existing sulfonylation methods and RSO_2 surrogates still have drawbacks, as not being compatible with amine nucleophiles. In this project benziodoxolone-derived reagents were explored for the first time as sulfonyl transfer agents as the next generation of sulfonylation reagents.

Two different benziodoxolones were synthesised and tested under different conditions to form a sulfonyl benziodoxolone intermediate able to transfer this group to a nucleophilic amine. After several experiments, it was discovered that chloro benziodoxolone was the best choice for the required transformation, in DCM, at -40 ºC, in the presence of TBAI, affording (phenylsulfonyl)morpholine in 88% yield.

The developed method was applied to thirteen different nucleophilic amines and four sodium sulfinic acid salts achieving the corresponding sulfonamides with yields up to 84%.

Furthermore, the use of the benziodoxolone immobilized on a soluble polymer, PEG-2000, was investigated. The pegylation of a benziodoxolone precursor was achieved in 58% yield. After chlorination, the reagent (38) was tested on the preparation of (phenylsulfonyl)morpholine and it was obtained in 48% yield. The pegylated acid was recycled, converted into the chlorinated intermediate and re-used affording the corresponding sulfonamide in 56% yield.

Thus, a new sulfonylation method was developed, affording sulfonamides in moderate to excellent yields. In addition, the benziodoxolone reagent was immobilized in a soluble polymer, facilitating the isolation of the sulfonamide and avoiding isolation of intermediates while allowing the recovery of the iodine reagent.

Key words: Hypervalent iodine, Sulfonylation, Sulfonamide, Polyethylene glycol

LIST OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

LIST OF SPECTRA

ABBREVIATIONS AND NOMENCLATURE

^{13}C NMR	Carbon nuclear magnetic resonance
^{1}H NMR	Proton nuclear magnetic resonance
2-IBz	2-Iodo benzoic acid
Ac	Acetyl
Ar	Aryl
ATPase	Adenosine triphosphatase
COX-2	Cyclooxygenase
DABCO	1,4-Diazabicyclo[2.2.2]octane
DABSO	1,4-Diazabicyclo[2.2.2]octane bis (sulfur dioxide)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DMAP	4-dimethylaminopirydine
DMF	*N,N*-Dimethylformamide
DMP	Dess-Martin periodane
DMSO	Dimethylsulfoxide
Equiv	Equivalents
FT-IR	Fourier transform infrared spectroscopy
h	Hours
HIV	Human immunodeficiency virus
HOMO	Highest occupied molecular orbital
IBX	2-iodoxybenzoic acid
IR	Infrared spectroscopy
LG	Leaving group
L-Pro	L-Proline
LUMO	Lowest unoccupied molecular orbital
m	*meta*
MeCN	Acetonitrile
MeOH	Methanol
min	Minutes
Mp	Melting point
MSc	Master's degree in science
MW	Microwave
NMR	Nuclear magnetic resonance
NSAID	Non-steroidal anti-inflammatory drug
o	*ortho*

OTf	Triflate
p	*para*
PEG	Polyethylenoglycol
PES	Polyethersulfone
Ph	Phenyl
PhH	Benzene
R_f	Retardation factor
RSO_2	Sulfonyl group
rt	Room temperature
SOMO	Semi occupied molecular orbital
TBAI	Tetrabuthylaminnium iodide
*t*Bu	*tert*-Buthyl
TCICA	Trichloroisocyanuric acid
TCT	Cyanuryl chloride
TEA	Triethylamine
Temp	Temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography
Ts	Tosyl group
UV	Ultraviolet
XPhos	Dicyclohexyl(2',4',6'-triisopropyl-2-biphenylyl)phosphine

IR chart

w	Weak
m	Medium
s	Strong
br	Broad
vmax	Wavelength of absorption peaks

NMR chart

s	Singlet
d	Doublet
dd	Doublet of doublets
t	Triplet
m	Multiplet
δ	Chemical shift

1 INTRODUCTION

1.1 SULFONYL GROUP-CONTAINING COMPOUNDS

Sulfur is a non-metal element of the periodic table. The atomic sulfur is mostly found with the oxidation number of -2. This element is a yellow crystal, toxic as itself and foul smelling. Even so, organosulfur and metal sulphides compounds are essential to life and have many applications.[1] Routinely, sulfur compounds are present in the soil, in a vast variety of fruits and vegetables. The sulfur element is present in the amino acids cysteine, cystine and methionine. Additionally, it Is found in fertilizers, fungicides, pesticides, bactericides. Chemically speaking, sulfur containing reagents are of great importance.[2] Lastly, this element can be used to decorate furniture.

There are a wide variety of sulfur-containing functional groups. Particularly, the chemistry of sulfonyl containing compounds, RSO_2, is of special relevance. The sulfur atom possesses a lone pair in a high-lying σ-based HOMO resulting in a nucleophilic character, simultaneously, the sulfur dioxide's low-lying π-symmetry LUMO has its largest coefficient on sulfur, conceding electrophilic properties.[3] Additionally, it can have a SOMO stable enough to participate in radical reactions.[3] The mixture of these two elements fuels a diverse collection of functional groups. There are sulfonates, sulfones, sulfonamides, sulfonyl chlorides, sulfinates, sulfolenes, sultines, among many others. Figure 1-1 shows some representative examples of compounds containing the sulfonyl group with industrial application. The present thesis, focus on a specific sulfur containing functional group, the sulfonamides. This functional group not only is used as an amine protector,[4] as it is present in a wide range of natural products, biologically active compounds of great utility as herbicides, pesticides, plaguicides, surfactants, dyes and, most importantly, pharmaceuticals.[5]

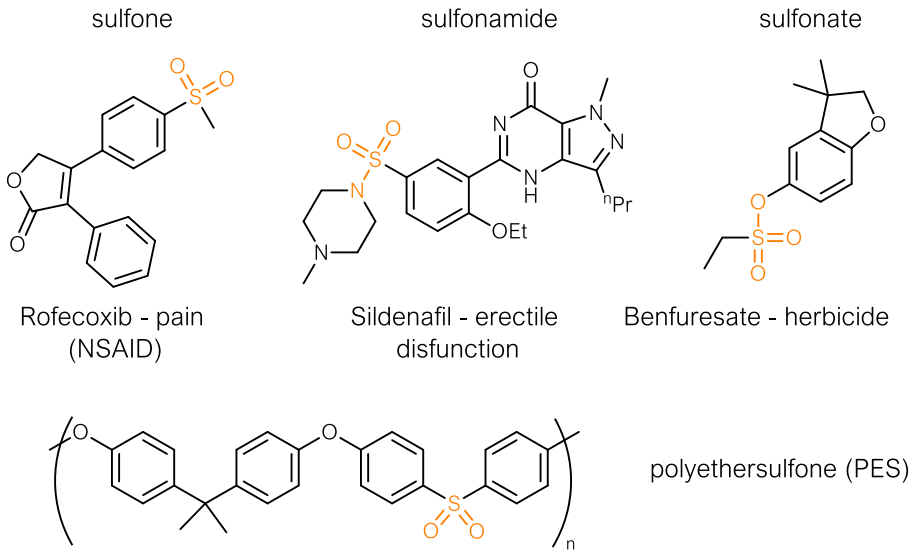


Figure 1-1 – Examples of sulfur containing compounds.[2]

1.1.1 Sulfonamide containing compounds - an important class of organic compounds for the industry.

There are many different biological properties inside the sulfonamide-containing drugs family. Until today, many compounds have been found which exhibit a big variety of properties such as HIV protease inhibitor, calcitonin inducer, anti-cancer, antibacterial, anti-inflammatory,[6] anticonvulsant, antiviral,[7] antifungal, COX-2 inhibitor, ATPase inhibitor,[8] antimigraine,[9] anti-hypertensive, antiglaucoma, antiprotozoal,[5] carbonic anhydrase inhibitor, caspase inhibitor.[10] They are also effective in the treatment of urinary, ophthalmic and intestine infections, scalds, ulcerative colitis, rheumatoid arthritis, male erectile dysfunction and obesity.[5] Figure 1-2 shows some sulfonamide containing drugs. Because of all these possible effects it is very important to have a simple, economic and high efficient synthetic method to prepare sulfonamides for industrial application.

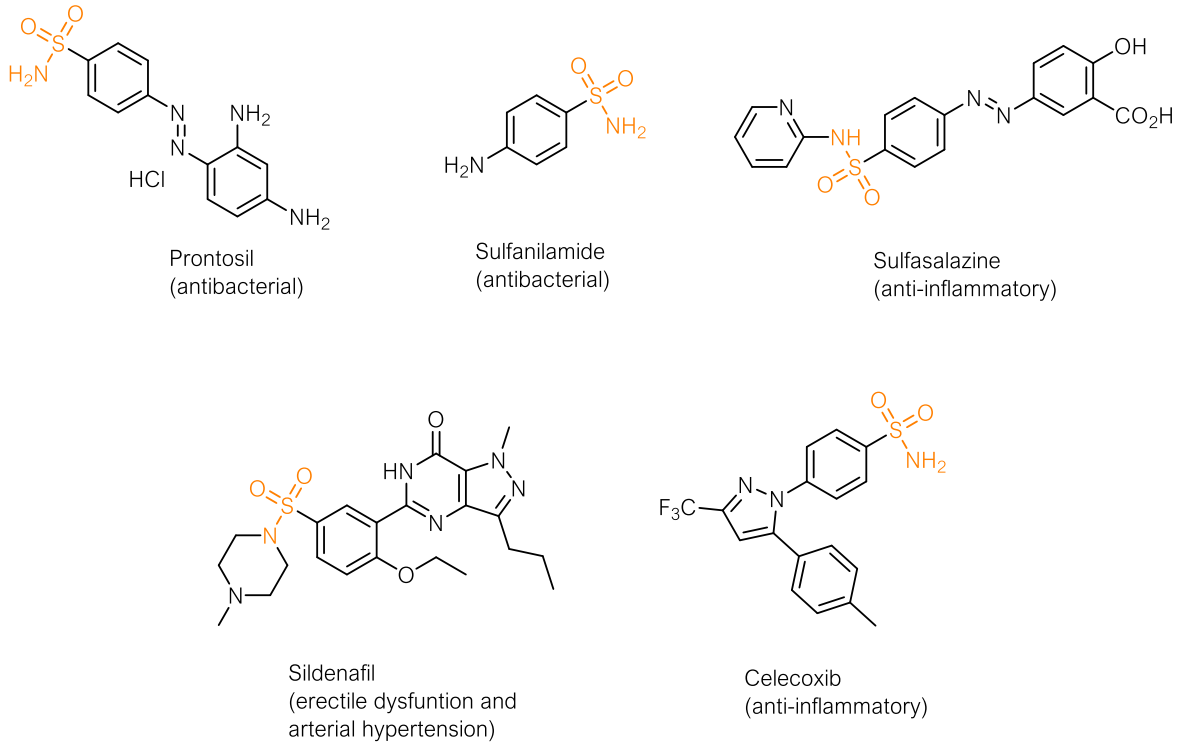
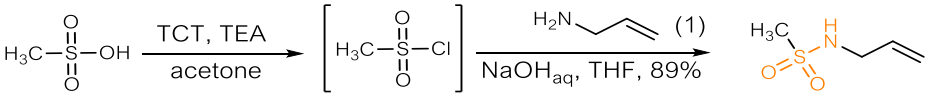


Figure 1-2 – Example of sulfonamide containing drugs.[7,11]

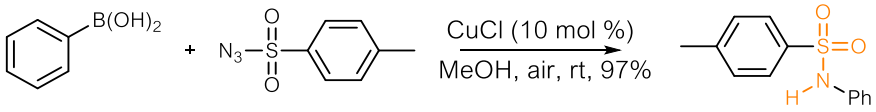
1.1.2 Synthesis of sulfonamide

In the past few decades, much effort has been put into discovering new synthetic methods to efficiently prepare sulfonamides. Traditionally, sulfonamides were synthesised through the nucleophilic attack of amino compounds to sulfonyl chlorides in the presence of a base (Scheme 1-1). Unfortunately, these electrophiles are difficult to handle or store and have poor functional group tolerance.[7]



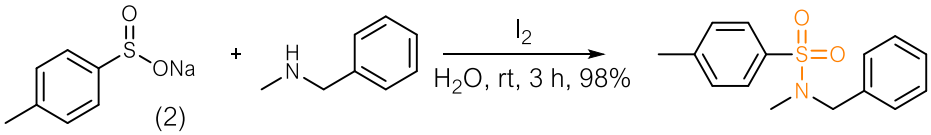
Scheme 1-1 – Synthesis of sulfonamides using sulfonyl chlorides.[10]

To overcome these drawbacks, new methods have been reported. One alternative method is the use of transition metal catalysed cross coupling of primary sulfonamides with aryl halides, arylboronic acids [4] (Scheme 1-2), alcohols, aryl nonaflates or hydrocarbons.[7] Although this method has filled some of the gaps of the previous mentioned method, by enabling the creation of sulfonamides without a nucleophilic amine, it still needs excess of base to balance the formed acid, has poor tolerance of functional groups and uses metal.[12]



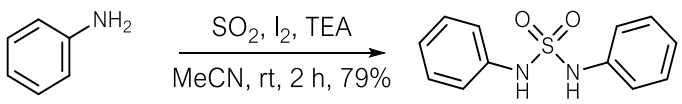
Scheme 1-2 – Synthesis of sulfonamides using Cu-catalysed cross coupling reaction of primary sulfonamides with arylboronic acids.[13]

Recently, an iodine-mediated or iodine-catalysed reaction has been reported. Iodine is a cheap element, readily available and eco-friendly. Yuan *et al.* have managed to synthesise sulfonamides reacting sulfinic acid salts with amines in the presence of molecular iodine (Scheme 1-3). [6,4] Although this method presents good to excellent results, works at room temperature and uses water has a solvent, it presents low compatibility with aromatic nucleophiles, has moderate reaction times and only works with secondary amines.



Scheme 1-3 – Synthesis of sulfonamides mediated by molecular iodine.[6,4]

The synthesis of sulfonamides through nucleophilic attack of an amine to sulfur dioxide has been reported by Rudkevich *et al* (Scheme 1-4).[14] Although simple and atomically economic this gas is toxic and foul-smelling, making it hazardous to use and difficult to handle.[3] So, there is a need for a more practical and safe protocol. A plausible solution for this safety problem relies on the use of SO_2 surrogates.

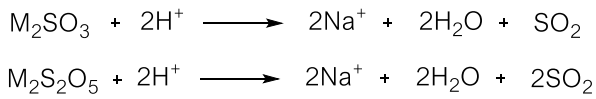


Scheme 1-4 – Synthesis of sulfonamides using sulfur dioxide.[14]

1.1.2.1 SO_2 surrogates

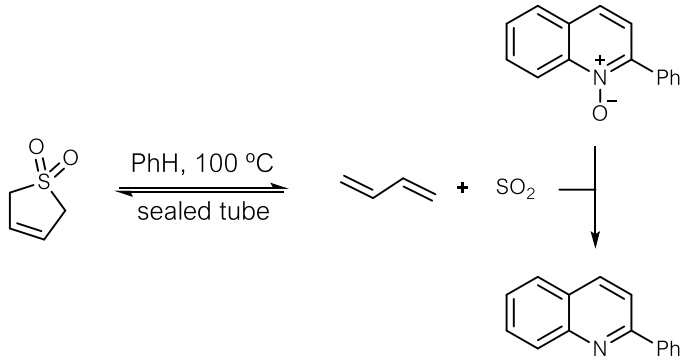
A surrogate is an easy to handle and safe compound, capable of releasing a specific molecular group while being as chemically inert as possible to avoid side reactions.[3] The substitution of a gas for a surrogate is a very practical choice, as it bypasses the need of pressurised gas cylinders and specialised pressure-

resistant equipment.[2] Historically, the first sulfonyl surrogates were the metal sulfite salts.[15] M_nSO_3 and $M_nS_2O_5$ release sulfur dioxide when in the presence of a bronsted acid (Scheme 1-5). Due to the fast gas release, it is still required to use pressurised systems to handle the toxic gas, making it partially failing as a surrogate.[3]



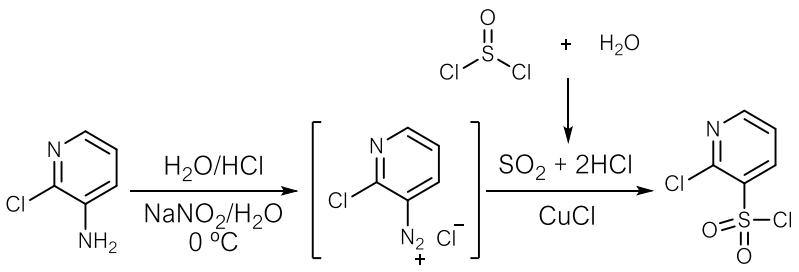
Scheme 1-5 – Metal sulfites decomposition and SO_2 release.[2]

Another compound that generates sulfur dioxide *in situ* is the sulfolene. Product of the [4+1] cheletopic reaction of butadiene with the wanted gas, sulfolene was firstly used to protect diene units.[3] It is synthesised by a reversible reaction, so, with the application of temperature, the sulfolene extrudes SO_2 to the reaction medium.[16] The application of sulfolene is on the reduction of N-oxide compounds (Scheme 1-6). No other uses have been found due to the necessary high temperature for the release of the gas, prone to cause undesired side reactions, and also due to the formation of the reactive butadiene co-product.[3]



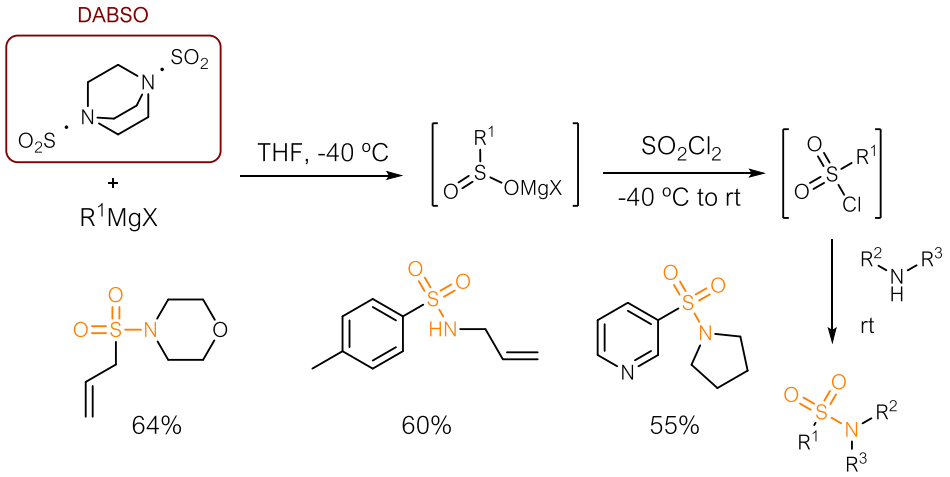
Scheme 1-6 – Sulfolene reversible reaction and application.[3]

AstraZeneca developed a procedure that uses thionyl chloride, for an improved Sandmeyer sulfonyl chloride formation [17] (scheme 1-7). The reaction of thionyl chloride with water releases SO_2 *in situ*. This process produces the gas *in situ* very rapidly and exothermically and so it is very difficult to control it.[15] Additionally, this procedure produces HCl as a by-product. For these reasons, very little application, other than the Sandmeyer chemistry, have been found.



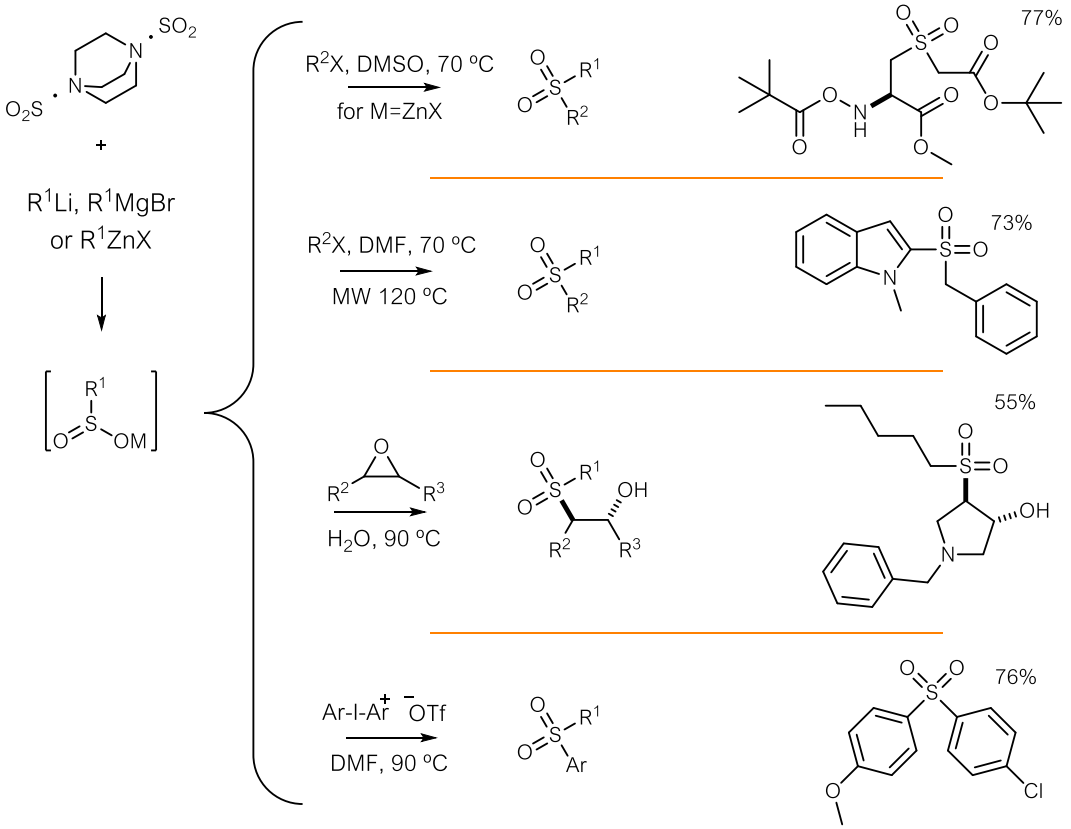
Scheme 1-7 – Thionyl chloride as an SO_2 surrogate in Sandmeyer reaction.[3]

Many SO_2 surrogates have been reported and already mentioned, but the most famous is DABSO.[15] DABSO was synthesised in 1988 [18] but its synthetic value was only discovered by Michael Willis years later.[3] DABSO is a salt of 1,4-diazabicyclo[2.2.2]octane (DABCO) complexed with two SO_2 molecules. It is synthesised through the condensation[19] or bubbling of SO_2 gas directly into DABCO.[3] The SO_2 surrogate DABSO is an easy-to-handle, bench-stable, air-tolerant white solid.[2]



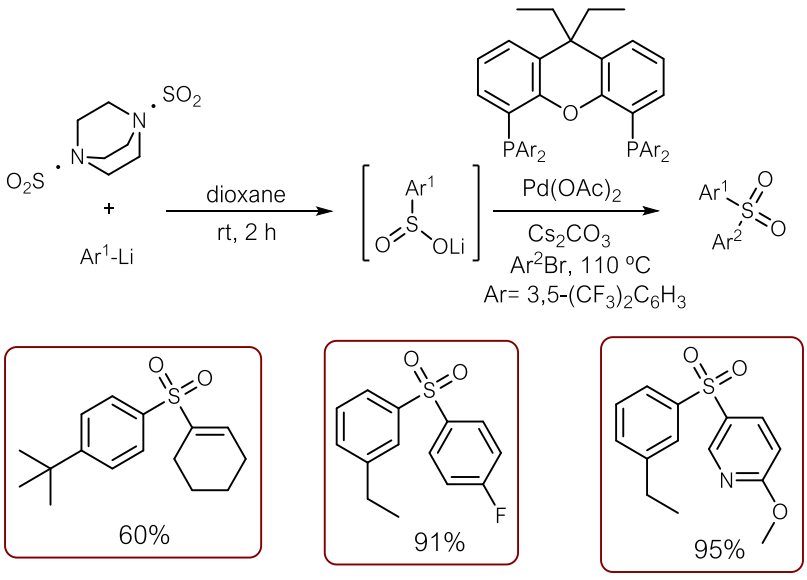
Scheme 1-8 – Synthesis of sulfinate salts and its subsequent use on the synthesis of sulfonamides using DABSO.[2]

In the past five years, many synthetic processes which include DABSO have been reported. The use of DABSO allows an easy metal-free synthesis of sulfinate salts (Scheme 1-8) and sulfones (scheme 1-9).[2]



Scheme 1-9 – Synthesis of sulfones using DABSO.[2]

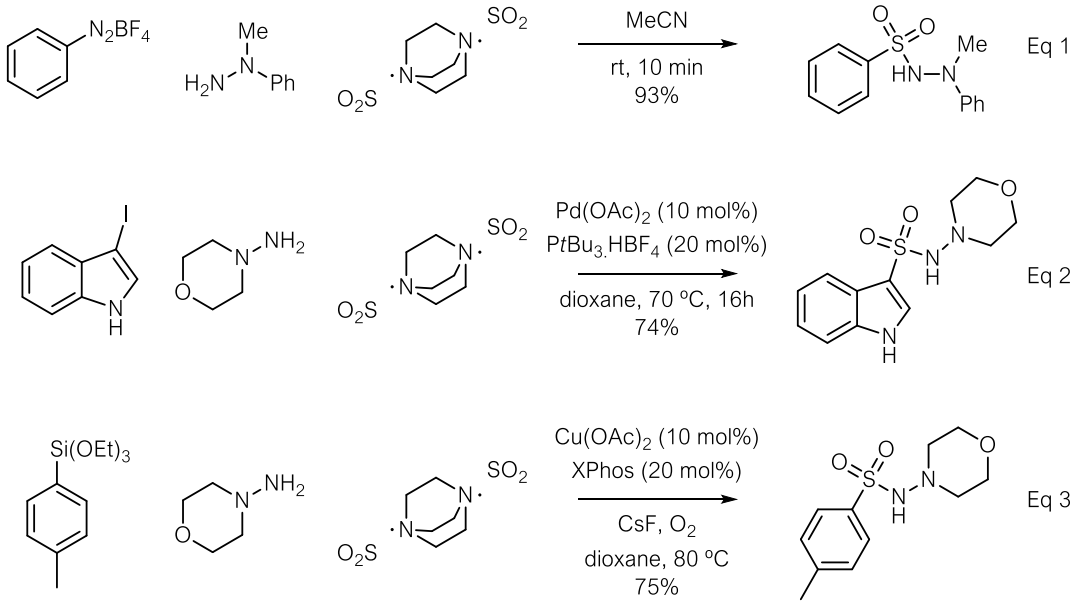
DABSO has also been reported on the syntheses of diarylsulfones via Pd(0) catalysed reactions (Scheme 1-10).



Scheme 1-10 – Pd-catalysed synthesis of diarylsulfones using DABSO.[20]

Due to the fact that the use of DABSO in the synthesis of sulfonyl-containg coumponds has only been recently discovered, it's scope is still limited. Concerning the synthesis of sulfonamides, DABSO still

presents several drawbacks. Either requires the use of metals, multi-step conditions or the use of sulfonyl chloride, which implies thorough purification processes.[21] Furthermore, direct use of DABSO with amines for sulfonamide synthesis has not yet been reported. What is already known is its direct reaction with hydrazines, stronger nucleophiles, to afford N-aminosulfonamides. (Scheme 1-11)



Scheme 1-11 – Metal-free aminosulfonylation using DABSO. Eq 1 – Waser approach;[20] Eq 2 - Willis approach;[22] Eq 3 - Wang approach.[23]

In sum, many different synthetic methods and strategies for generation of sulfonamides already exist, the so far discussed processes represent only a representative sample. Despite the great progress on the sulfonylation reactions and SO_2 surrogates, there is room for improvement, in particular amine nucleophiles remain mostly incompatible with these coupling reactions. Thus, there is still need to find a new method, a simple, efficient, non-toxic and green approach.

1.2 HYPERVALENT IODINE

1.2.1 Iodine

Iodine has attracted a lot of attention of the synthetic community due to its low cost, water tolerance, non-toxicity and commercial availability.[24] This element was first isolated from the ash of seaweeds in 1811 by B. Courtois.[25] By 1819 it was utilised as pharmaceuticals, KI for the cure of goiter and tincture of iodine as an antiseptic.[25] In the mid-1800s, organoiodine compounds were used for the Hofmann's alkylation of amines, the Williamson ether synthesis and the Wurtz coupling reactions.[25]

Iodine is the biggest halogen, making it the less reactive. It posesses the most polarization and least electromagnetization of the group which enables the formation of stable polycoordinated, multivalent compounds.[25] As the other components in this periodic element tables' group, iodine is a good oxidizing agent because of its 7 valence electrons. The normal oxidation state is 1, but it can also be 3, 5 and 7.

When the oxidation state is different than one, it is said to be hypervalent. The hypervalent organoiodine compounds have a chemistry similar to the derivatives of mercury(II), thallium(III), lead(IV), osmium(VI) and chromium(VI).[26] So similar, that the reaction of this class of compounds are commonly discussed in terms of oxidative addition, ligand exchange, reductive elimination and ligand coupling.[27]
The most common hypervalent iodine compounds are I(III) and I(V). The hypervalent iodine compounds are included in many different areas, such as transition metal catalysed biomimetic oxygenation, catalytic immidations azidations and other synthetic applications.[28] Nowadays, the use of some of these compounds as oxidizing agents is so well studied that they are implemented both in research and in the industry.

1.2.2 The discovery of hypervalent iodine reagents

The first hypervalent organic compound was $PhICl_2$, synthesised in 1886 by Willgerodt.[25] Since then, many new iodine hypervalent compounds have been discovered with a wide variety of physical and chemical properties. Beringer and Lillien published in 1960 the first protocol for 1-phenylbenziodoxolone in *Organic Syntheses.*[29] For many years, the chemistry of the hypervalent iodine was only curiosity driven. It was only since the beginning of the millennium that synthetic application for this class of compounds was found.

The hypervalent iodine compounds can be acyclic with intermolecular bonds to ligands or cyclic with intramolecular bonds. The firsts acyclic compounds although being able to react as oxidants, showed very little efficiency. The main reason was the existence of an extensive network of intermolecular secondary bonds resulting in polymeric structures.[30] Due to the polymeric nature, the acyclic compounds have very little solubility in most organic solvents and low thermal stability reducing drastically its reactivity. To overcome this drawback, in the beginning of the 21st century, chemists cyclised the iodine centre, partially disrupting the secondary bonding, facilitating the solubilization.[28] In addition, the incorporation of the iodine atom into a five-membered ring created a bridging effect of the apical and the equatorial positions.[31] Lastly, the three-atom four-electron centre, between the iodine, the ligand and the transferable group and the two iodine's lone pair, form a bond weaker than a normal covalent bond, making it more reactive.[32] This was when the reactivity of the hypervalent iodine compounds started to prevail and they gained great importance in organic synthesis as metal transition alternatives.

1.2.3 Cyclic hypervalent iodine reagents

The hypervalent iodine's family of compounds can either be acyclic, pseudocyclic or cyclic. (Figure 1-3) Considering the last two types, its compounds usually incorporate an aromatic ring to increases the stabilization through overlapping the aromatic ring's orbitals with the iodine's.[33] More specifically, there is an overlap of the lone pair of electrons on the iodine to the π-orbitals of the benzene ring.[28] The cyclic compounds have a covalent bond to the *ortho* ligand, conferring the biggest thermal stability.[34] The pseudocyclic have a non-covalent bond to the *ortho* ligand, making it more reactive.

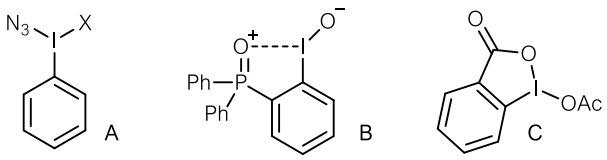


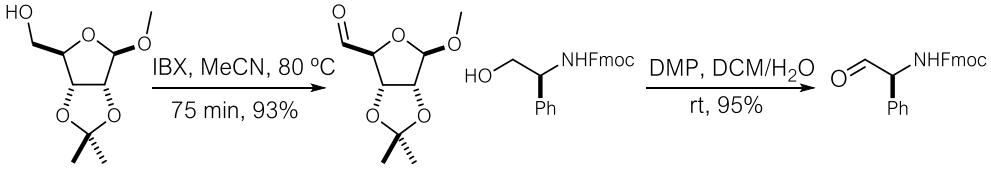
Figure 1-3 – Example of the types of cyclicity in hypervalent iodine's compounds. (A) Non-cyclic; (B) Pseudocyclic; (C) Cyclic.

1.2.4 Cyclic hypervalent iodine as oxidizing agents

The two most famous hypervalent cyclic iodine oxidizing agents are the 2-iodoxybenzoic acid (IBX) and the 1,1,1 - Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one, better known as the Dess-Martin periodane (DMP) (Figure 1-4).

Figure 1-4 – (A) - IBX; (B) - DMP

IBX is best suited to cleanly convert alcohols to carbonyl compounds.[35] Latter, based on the IBX, DMP was synthesised as an oxidizing agent capable of convert primary and secondary alcohols to aldehydes and ketones, respectively, at room temperature (Scheme 1-12).[36]



Scheme 1-12 – Example of oxidation reactions carried by IBX and DMP.[28]

While both are mild and selective oxidizing agents. IBX is capable of oxidation of glycols to α-ketones or α-diketones without cleavage, while DMP, due to its acetate groups, is more soluble in the organic solvents, and thus more versatile and effective.[28] Importantly, the synthesis and use of IBX and DMP inspired the scientific community to explore the chemistry of hypervalent iodine reagents and, eventually, stimulated the investigation of the group transferring property of this class of compounds.

1.2.5 Hypervalent iodine compounds as atom-transfer reagents

In 2006 Togni *et al*. reported for the first time 1-(trifluoromethyl)-1,2-benziodoxol-3(1*H*)-one, (Figure 1-5 A), and trifluoromethyl-1,3-dihydro-3,3-dimehtyl-1,2-benziodoxole, (Figure 1-5 B). These molecules are both, CF_3 surrogates, capable of transferring this group under a wide variety of conditions.[37]

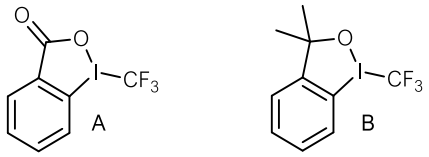
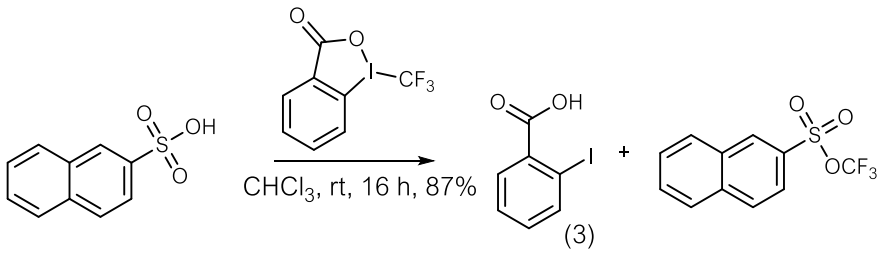
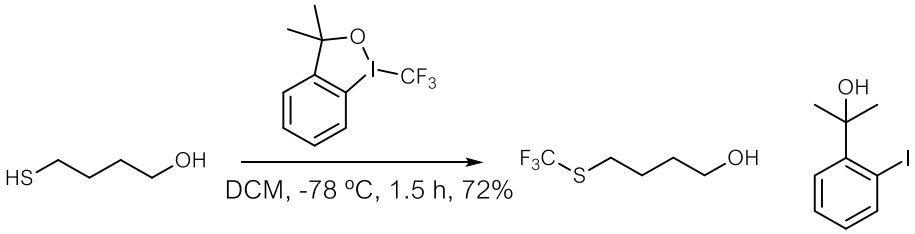


Figure 1-5 – CF_3 transfer reagents reported by Togni *et al.*[38]

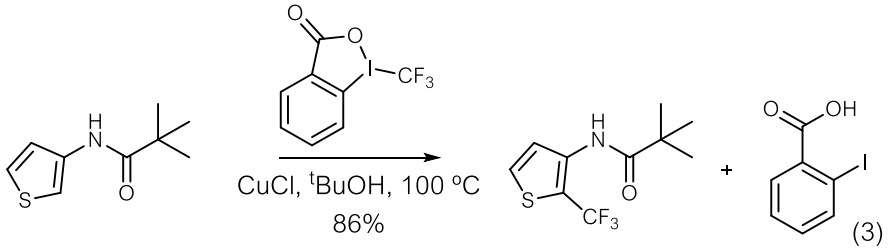
The hypervalent cyclic iodine is capable of acting as an electrophilic synthon of a normally nucleophilic group, in a phenomenon called umpolung of reactivity.[32] Togni's laboratory has successfully performed the trifluormethylation of sulfonic acids (Scheme 1-13),[39] of thiols in the presence of hydroxyl groups (Scheme 1-14)[39] or even the creation of new C-C bonds (Scheme 1-15).[37]



Scheme 1-13 – Trifluoromethylation of 2-naphthalenesulfonic acid.[39]

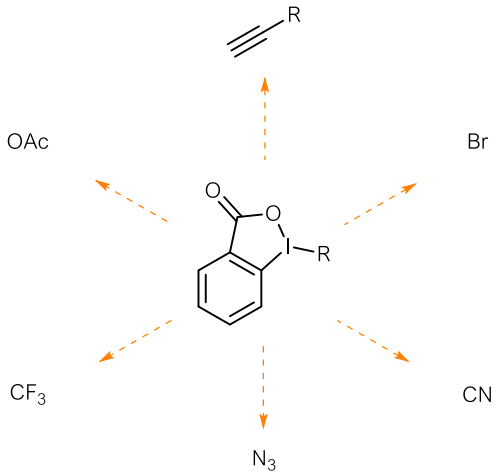


Scheme 1-14 – Trifluoromethylation of 4-mercaptobutanol.[37]



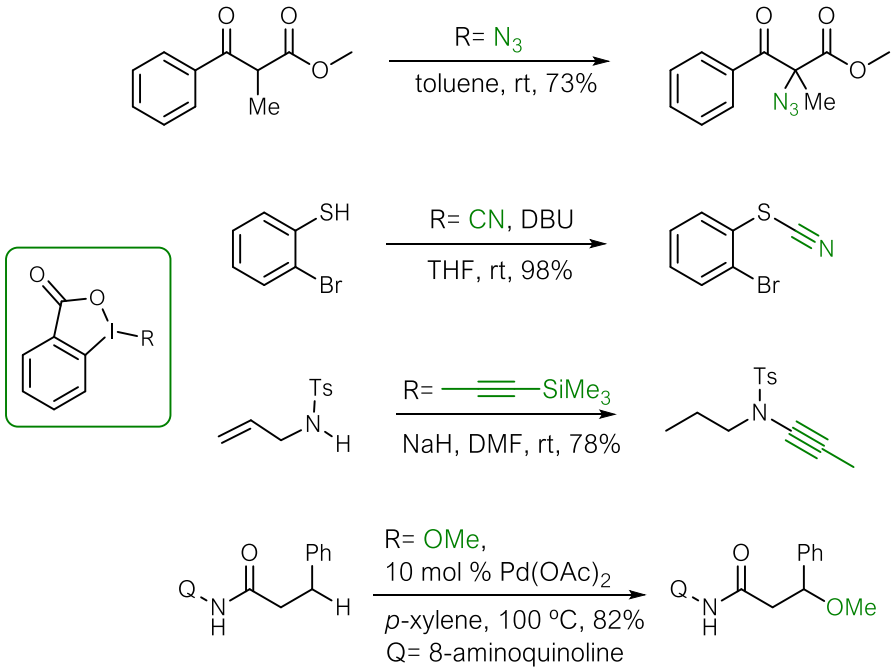
Scheme 1-15 – *Ortho* trifluoromethylation of *N*-(thiphen-3-yl)pivalamide.[37]

The Togni's newly discovered chemistry has a very large scope with excellent results, e.g. successful trifluoromethylations of a wide array of functional groups, with good selectivity. This great discovery, has stimulated the community to explore similar reagents that are able to carry umpolung reactions. Thus, several examples of the transfer of functional groups mediated by hypervalent iodine reagents have been recently reported (Scheme 1-16).



Scheme 1-16 – Reported hypervalent iodine transfer reagents.[32]

Using the benziodoxol(on)e moiety, many other functional groups can be transferred, such as the transfer of alkynes, halogens, acetate, trifluoromethyl, azides and cyanides, generating new protocols to create C–C, C–O, C–X, C–N, C–H, C–S and C–P bonds.[32] (Scheme 1-17)



Scheme 1-17 – Reported examples of reactions using a benziodoxolone moiety surrogate to create new bonds.[32]

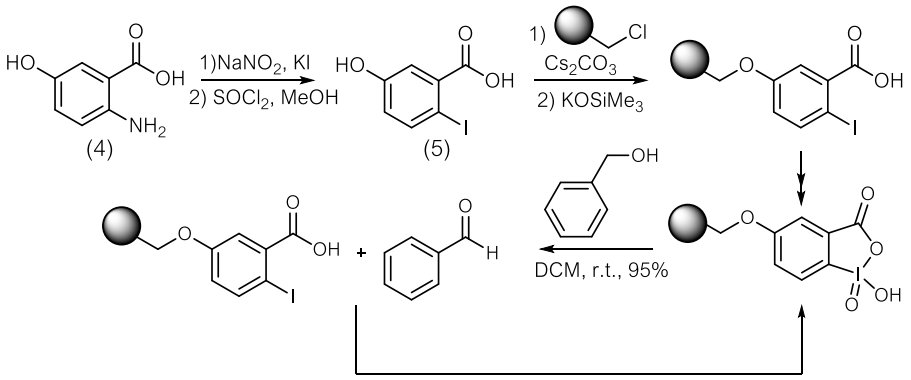
1.2.6 Hypervalent iodine reagents immobilized on a solid support

As the environmental awareness rises, so does the demanding to apply the principles of the green chemistry in organic synthesis. Thus, there is a great interest in the reutilization of reagents, in the development of atom economy procedures, on the use of non-toxic and safe reagents, to improve the sustainability of synthetic procedures, among others. The immobilization of reagents on a solid (polymeric)

support combines the advantages of solution-phase synthesis with the easy purification and recovery of polymer-supported reagents.[40] The immobilization of reagents or substrates in a solid support allows a fast and simple isolation process compared to traditional chromatographic purifications, avoiding the use of large volumes of organic solvents. The combination of the simple purification processes and the possible reutilization of the reagent makes the use of a polymer-supported approach very tempting. While using polymer-supported synthesis it is possible to cope with the ever growing pharmaceutical and agrochemical industries by simplifying the orchestrated multi-step organic synthesis and shortening combinatorial chemistry library's construction time.[41]

Considering the immobilization of hypervalent iodine reagent, the immobilization of IBX on a polymer support has already been reported by Rademann and co-workers that prepared an oxidizing polymer.[40] The immobilization of IBX not only facilitated the purification processes and lowered the reaction times, but also permitted the reutilization of the hypervalent iodine compound. The resultant benzoic acid was easily isolate, and subject to oxidizing conditions to regenerate IBX once again.

The IBX is a reactive molecule, so it could not be directly attached to the polymer. The strategy adopted by Rademann and co-workers relied on the attachment of 2-iodo benzoic acid to the polymer via an ether linkage, and subsequent oxidation carried on the polymer (Scheme 1-19). It is important to notice that the 5-hydroxy-2-iodobenzoic acid is not a commercial molecule, it was prepared from commercial 5-amino-2-iodobenzoic acid.



Scheme 1-18 – Polymer attachment procedure[40] and example of an application.[42]

Some efforts have been made to synthesise oxidizing polymers based on hypervalent iodine compounds. There already exists an hand full of examples, including IBX.[42] However, the immobilization of hypervalent iodine reagents is still limited to few examples.

A great number of polymers and resins have the essential properties to be used in this type of reactions. In this master thesis, polyethyleneglycol (PEG)-2000 has been explored as a soluble solid support for the immobilization of a benziodoxolone. The choice PEG-2000 rests upon its high solubility in dichloromethane and extremely low solubility in diethyl ether, facilitating the work-up procedure and recovery of the reagent. Additionally, it is a cheap and non-toxic polymer

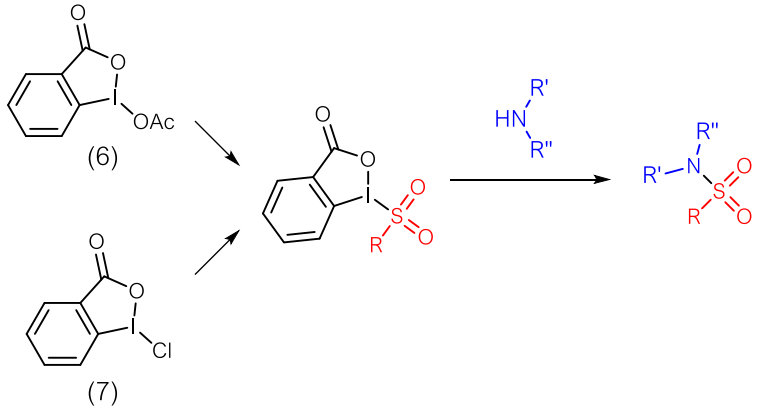
2 DISCUSSION AND RESULTS

2.1 OBJECTIVES

The main aim of this Master's thesis, was to develop a new simple, environmentally friendly and high yielding synthetic method to produce sulfonamides from benziodoxolone-based reagents, according to Scheme 2-1. This protocol would avoid the use of gaseous SO_2 or the traditional sulfonylation procedures that require the use of sulfonyl chlorides or oxidation of the corresponding sulfides.

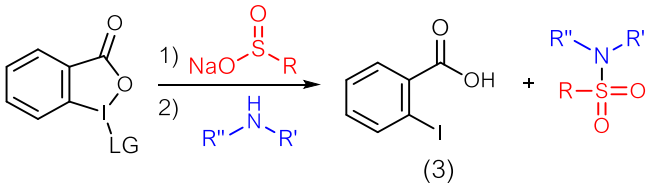
This project aimed at:

- explore benziodoxolone-based reagents to transfer the sulfonyl group to different amines, thus developing a novel sulfonylation reagent, taking advantage of the benziodoxolone-based reagents properties;
- investigate different benziodoxolones and sulfinic acid salts, using different reaction conditions to promote the coupling of the sulfonyl group with the benziodoxolone scaffold;
- study the reaction conditions to transfer the sulfonyl moiety into amines;
- screen several amines and sulfinic acid salts in order to investigate the scope of the reaction;
- immobilize the benziodoxolone-based reagent on PEG-2000 and perform the synthesis of different sulfonamides with recovery of the transfer reagent.



Scheme 2-1 – General benziodoxolone mediated sulfonylation

The precedent work from Togni on the electrophilic trifluoromethylation by use of hypervalent iodine reagents inspired us to explore the benziodoxol(on)e moiety for the transfer of sulfonyl containing groups - RSO_2 group - to amines and so synthesise sulfonamides. First effort was dedicated to the preparation of a suitable benziodoxolone-based compound that could react with a sulfinic acid salt to produce an intermediate that could further transfer the sulfonyl moiety to an amine (Scheme 2-2).



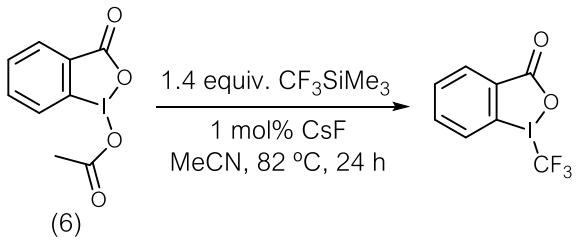
Scheme 2-2 – General synthetic approach

The synthetic plan proposed relied on the attack of a sodium sulfinate salt to a benziodoxolone with a good leaving group, exchanging it by the sulfonyl group without destroying the benziodoxolone moiety. The next step envisaged the use of a nucleophilic amine to attack the intermediate at the sulfur atom, leading to a new sulfonamide synthesis. In a more advanced stage of the project, after establishment of the optimized reaction conditions, the immobilization of the transfer reagent would enable the recovery of the released 2-iodobenzoic acid from the crude, and to re-use it. This would lead to an atom effective reaction towards a less wasteful process.

This project is part of a recently initiated PhD project, and the present dissertation is about my contribution to this work.

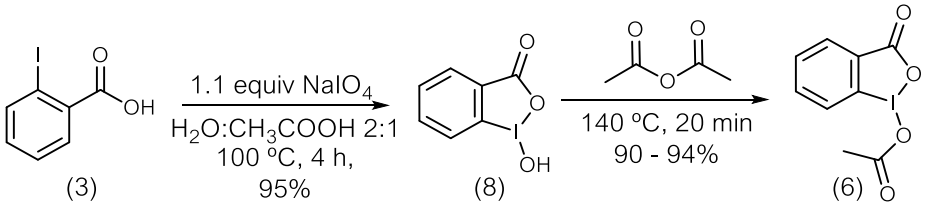
2.1.1 Preparation of the oxybenziodoxolyl acetate (6)

To synthesise a good RSO_2 group transferable compound, it is necessary to have a benziodoxolone precursor possessing a good leaving group and a structure compatible with the reaction conditions. Thus, this study initiated with the preparation of two benziodoxolone derivative precursor, with different leaving groups bound to iodine atom. The first to be considered was acetyl benziodoxolone (6). Reported by Togni and co-workers,[38,37] it was treated with (trifluormethyl)trimethylsilane (Scheme 2-3), creating an electrophilic trifluoromethylation reagent.



Scheme 2-3 – Togni's reagent synthesis procedure.[38]

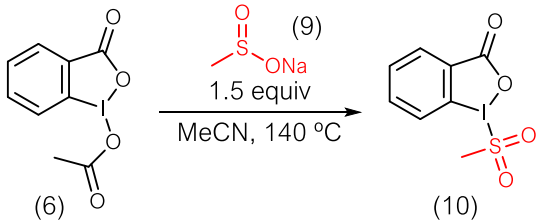
The synthesis of oxybenziodoxolyl acetate (6) is a two-step process that initiates with the oxidation of commercial 2-iodobenzoic acid followed by a simple acetylation (Scheme 2-4). Thus, compound (6) was prepared according to the reported protocol.[38] The two reaction steps worked smoothly and with very high yields (see Section 3.2.1 and 3.2.2). The first step consisted on a cyclization of the iodobenzoic acid (3), an easy and high-yielding protocol and there was no need to further purification after filtering and washing the crude with water. The second step relied on the acetylation of the compound (8) with acetic anhydride under reflux conditions to afford compound (6) in 90 - 94% yield. The isolation of the pure product was obtained simply by concentrating the crude under vacuum.



Scheme 2-4 – Synthesis of acetyl benziodoxolone

2.2 STUDIES TOWARD THE SYNTHESIS OF A SULFONYLBENZIODOXOLONE INTERMEDIATE

According to the established synthetic plan, the benziodoxolone derivative (6) previously prepared was next reacted with a sulfinic acid salt to investigate the possible formation of a key intermediate, a benziodoxolone derivative possessing a sulfonyl group, in an unprecedented approach (see Section 3.4.1). Thus, first experiments were carried with oxobenziodoxolyl acetate (6) and the sodium methylsulfinate (9) in acetonitrile (Scheme 2-5). The choice of this sulfinate salt was based on the easy analysis of the corresponding NMR spectra, a signal at high field distant from the benziodoxolone signals.



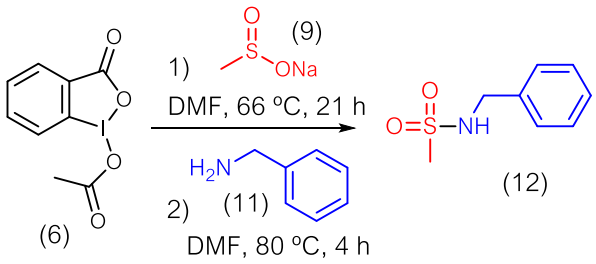
Scheme 2-5 – Reaction of oxobenziodoxolyl acetate (6) with sodium methylsulfinate.

The reaction showed promising results through TLC analysis, with two high R_f compounds, 0.85 and 0.76, at mid reaction which evolved to a single R_f = 0.89 spot. The crude was purified through a silica chromatographic column, but no compound was isolated. The results obtained suggested that either the reaction scale was too small or the benziodoxolone intermediate was not stable enough to survive the purification conditions. Thus, an experiment was carried in a higher scale. The TLC analysis showed a third compound of lower R_f, (0.71). Once again, the crude was purified through a silica chromatographic column. Two fractions were isolated and analysed using ^{1}H NMR spectroscopy. The NMR spectra of the first fraction showed a mixture, with signals of 4 aromatic protons at 8.02 - 7.21 ppm and 2 signals of aliphatic protons at 1.29 ppm. The spectra of the second fraction showed the same 4 aromatic signals at 8.03 - 7.20 ppm and two new three-proton singlets at 3.31 ppm and 2.71 ppm. Despite of the many efforts to isolate a pure compound and proceed for further characterization it was not possible to take any conclusion at this stage, since the samples decomposed rapidly. In a more advanced stage of the project further efforts were performed in order to identify and characterize the intermediates formed and observed on the TLC (see Section 2.12 NMR studies)

2.3 One-pot synthesis of N-benzylmethanesulfonamide (12)

On the previous assays it was possible to conclude that it wasn't a problem of reaction scale, so a change in strategy was needed. Due to the difficult solubilisation of the benziodoxolone (6), the solvent was reconsidered and *N*,*N*-dimethylformamide (DMF) was next investigated.

It was also considered to add an amine (11) to the reaction mixture (containing the benziodoxolone (6) and the sulfinic acid salt (9)), without isolation of the proposed sulfonylated benziodoxolone derivative. The choice of the benzylamine was based on its aromaticity, facilitating the identification of the product by both TLC and NMR spectra, due to the distinct signals from the amine and the sulfinic acid moieties in ^{1}H NMR, at different regions (see Section 3.4.2).



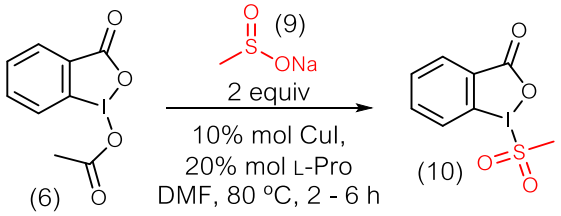
Scheme 2-6 – Attempt to synthesise N-benzylmethanesulfonamide

The TLC analysis showed two compounds, one with high R_f = 0.71 and another at R_f = 0.50. The first compound had the same R_f (0.71) as the one observed in the previous trials, realized in the absence of amine, as well as in the control. This observation led to the conclusion that this compound could not be neither the sulfonamide (12) nor the methylsulfonylbenziodoxolone (10). The second compound was so dim, that no further analysis was possible. Thus, alternative reaction conditions were considered to produce the desired sulfonamide.

2.4 Copper catalysed methylsulfonylbenziodoxolone (10)

A new approach was taken inspired on the work of Dawei Ma, where sulfones are synthesised using sulfinic acid salts and an haloarene, catalysed by Cu(I).[8] It was envisaged that the synthesis of methylsulfonylbenziodoxolone (10) could be promoted by a system of copper iodide and L-proline (Table 2-1) (see Section 3.4.3).

Table 2-1 – Experiments carried to prepare 1-(methylsulfonyl)benziodoxolone promoted by CuI



Entry	(6) (mmol)	(9) (mmol)	Temp (°C)	Time (h)	Observations
1*	0.36	0.80	rt to 80	25.5	Complex mixture at rt and 80 °C
2*	0.34	--	rt to 80	25.5	Single small spot at rt that evolved to a complex mixture
3	0.17	0.35	80	2.3	Single dragging spot
4	0.17	--	80	2.3	Complex mixture

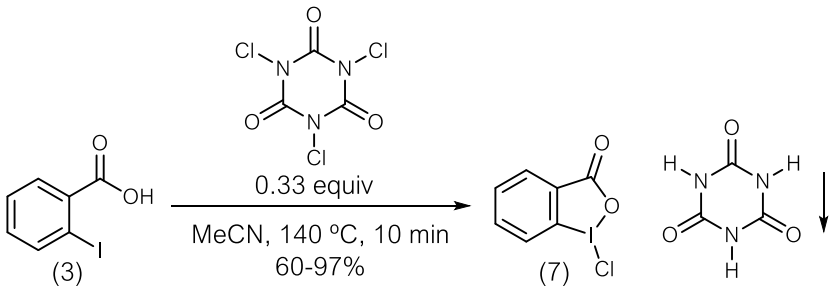
*The first 18 h of this experiment were conducted at rt, the last 7.5 h were at 80 °C

Thus, an attempt was performed (Entry 1) and a control reaction was carried in parallel (Entry 2), where no sodium methyl sulfinate was used. Sodium methyl sulfinate (9) was added to the benzoiodoxole (6), in DMF at room temperature, in the presence of CuI and L-Pro, and the reaction carried for 18 h at room temperature followed by more 5.5 h at 80 ºC (Entry 1). The TLC analyses revealed two compounds with high R_f, 0.83 and 0.70, in both the reaction and the control, and two long and dragged spots which occupied the half bottom of the plate. The compounds were present in both crude, so no further investigation or purification was performed.

A last effort was made using the same copper catalytic system, having in mind the possibility of an eventual degradation of the intermediate due to a long reaction time. So, another reaction was carried with the difference that the reaction stayed at 80 ºC for only 1.5 h (Entry 3). The TLC analysis of both the reaction (Entry 3) and the control (Entry 4) was identical to the previous reactions, with the dragging and the R_f = 0.82 and 0.69 spots, so this strategy was abandoned.

2.5 STUDIES USING CHLORO BENZIODOXOLONE (7)

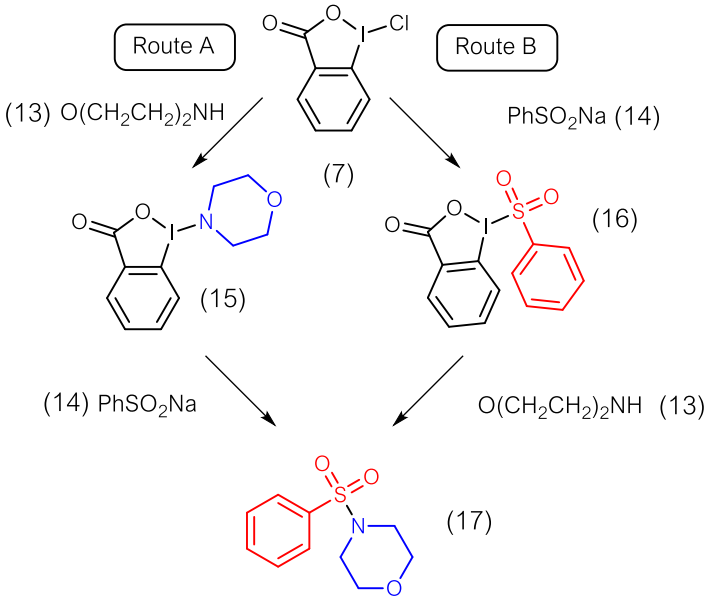
At this point, facing the results obtained, a different benziodoxolone precursor was considered. Chloro benziodoxolone (7) was also used by Togni and co-workers in the preparation of trifluoromethylated compounds.[35] Chloro benziodoxolone, possesses a good leaving group, and can be synthesised from 2-iodobenzoic acid (3) by a one-step procedure, using trichloroisocyanuric acid as the chlorination reagent (Scheme 2-7) (see Section 3.2.3). Although the procedure to attain (7) is simple and more direct than the one used to prepare acetyl benziodoxolone (6), the isolation of this compound from the reaction mixture needs to be done while hot, because (7) is soluble in hot acetonitrile, while the cyanuric acid is insoluble. This isolation process makes room to loses, lowering the yield of the transformation.



Scheme 2-7 – Synthesis of chloro benziodoxolone (7).[35]

Due to the high usage, the compound (7) had to be synthesised several times (a total of five). The yields varied from 60% to 97%. The better results were obtained among the smaller scales. By increasing the scale, it becomes more difficult to dissolve the product from the crude's precipitate because it is not possible to maintain the acetonitrile hot enough. In the 1.6 mmol scale a 60% yield was obtained, but it was not the best result due to the fact that the original protocol did not described the need to use hot acetonitrile nor to heat up the glass material in the filtration process.

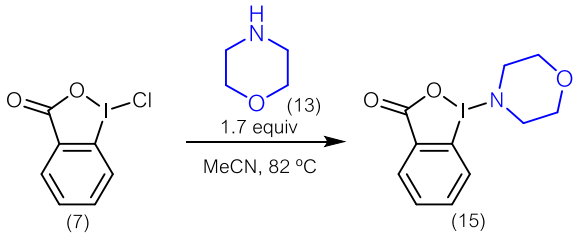
Concerning the formation of the sulfonamide, two different pathways were considered, depending on the order of addition of reagents (Scheme 2-8). Route A involves the reaction of the amine with the benziodoxolone followed by addition of the sodium sulfinate salt leading to the nucleophilic attack of the sulfur atom to the amine. Route B involves the reverse order of reagents' addition.
Morpholine was chosen as the amine partner for these experiments, because it has a cyclic structure, locking the nitrogen non-ligand pair of electrons outside of the ring. This enables a higher exposure of the electrons for the nucleophilic attack. Additionally, it is a secondary amine, preventing the same nucleus to perform a second nucleophilic attack. The sodium phenyl sulfinate salt was chosen because it's NMR fingerprint does not overlap with the morpholine's. Besides, both reagents are commercially available and cheap.



Scheme 2-8 – The two possible pathways: Different order of reagents addition and outcome

2.5.1 Studies toward the synthesis of morpholine benziodoxolone (15)

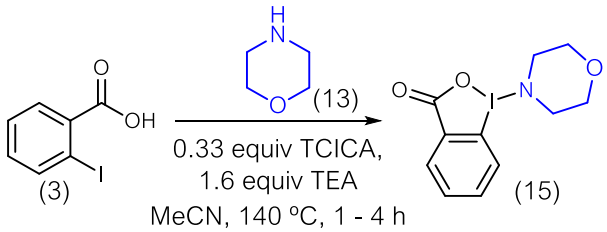
Route A was first investigated (Scheme 2-8), consisting on the reaction of chloro benziodoxolone (7) and morpholine (13) in acetonitrile, as it is the solvent in which the hypervalente iodine compound is soluble (see Section 3.5.1). The reaction run for 2 h and after TLC analysis only a dragging spot was found, indicating an inseparable mixture. A second trial was performed, at the same scale, but with the double of the solvent's volume, but same result was found.



Scheme 2-9 – second generation's 1st and 2nd assays

Based on the last experiment's observation, a one-pot approach was tested to prepare the benziodoxolone bound to morpholine (Table 2-2). The aim was to use the commercial 2-iodo benzoic acid and convert it to the desired intermediate, using TCICA followed by addition of the amine, without isolation of (7) (see Section 3.5.2). The results obtained are summarized on Table 2-2. This approach would avoid the purification step of the chloro benziodoxolone, making the protocol simpler.

Table 2-2 – Results from the one-pot attempt to synthesise morpholine benziodoxolone (15)



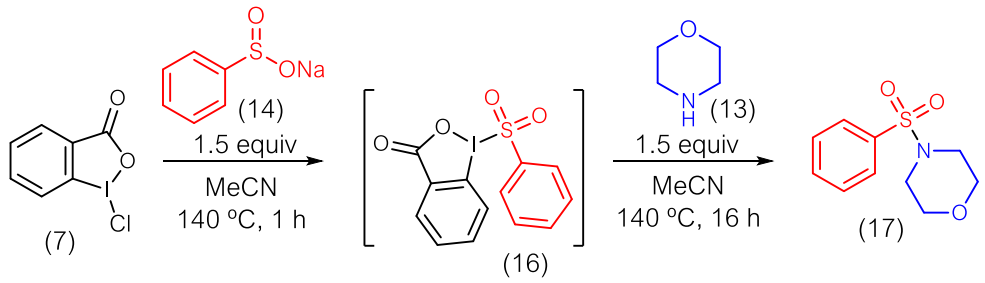
Entry	(3) (mmol)	TEA (mmol)	Time (h)	Observations
1	0.82	-	2.5	Complex mixture
2	0.88	1.4	1	Separation through chromatographic column
3	0.85	1.4	3	Complex mixture

The TLC analysis of the first experiment showed two compounds with R_f of 0.94 and 0.84, with the lower being less concentrated. The preliminary analysis showed promising results, although the lower compound being the same R_f as the control, as time went by, both spots converged to a dragging spot with no possible isolation (Entry 1).

A second and the third assays started simultaneously (Entries 2 and 3), with triethylamine, in order to understand if the presence of a tertiary basic amine would facilitate the formation of the product. The role of the base would be the removal of the amine's proton after the attack to the iodine, favouring the morpholine benziodoxolone (15) formation. The TLC analysis of the second assay (Entry 2) showed the same compounds observed previously (Entry 1) and a dragging spot which was also present in the TLC of the third experiment (Entry 3). Even though, purification through chromatographic column of the third trial was performed, it was fruitless, since the desired compound was of low amount. The results observed indicate that this approach was not suitable for the desired transformation.

2.5.2 Studies of a one-pot approach involving chloro benziodoxolone, sodium benzenesulfinate and morpholine

Next the route B (Scheme 2-8) was explored. An experiment was conducted with the chloro benziodoxolone (7) and the sodium benzenesulfinate (14) in acetonitrile (see Section 3.6.1). After refluxing for 24 h, the work-up was done, to remove the NaCl resulting as a by-product, and the crude was purified through chromatographic column. The isolated compound was analysed through ^{1}H NMR spectroscopy and showed signal that integrated to a total of 21 aromatics protons, leading to the conclusion that it was not the desired intermediate (16) (Scheme 2-10).



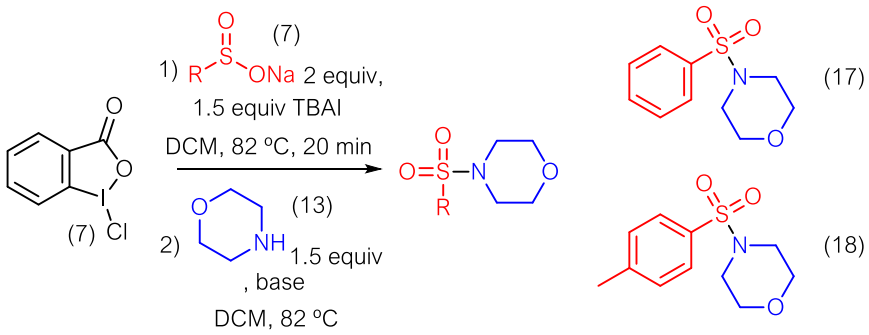
Scheme 2-10 – Sucessfull one-pot procedure for the synthesis of sulfonamide (17)

Simultaneously, a colleague (MSc Diogo Poeira) also working on route B, achieved the synthesis of sulfonamide 4-(phenylsulfonyl)morpholine (17) with 40% yield by a one-pot procedure, where chloro benziodoxolone, sodium benzenesulfinate and morpholine were added, in this order, without isolation of the intermediate (16) (Entry 1, Table 2-3). This result stimulated us to continue exploring this approach and indicated that phenylsulfonylbenziodoxolone (16) might be a very reactive intermediary, opposite to the electrophilic trifluormethylation compound explored by Togni's group.[37]

Although the proof of concept was achieved, the protocol had to be optimized to improve the sulfonamide's yield. Thus, several factors were considered: reaction's conditions (solvent, temperature, time, reagents stoichiometry), the presence of an additive, steric hindrance, the need of a base among others.

In order to understand the versatility of the procedure, if it is compatible with different substituents at the sulfur atom, different sodium sulfinic acids were investigated (Table 2-3) (see Section 3.6.2).

Table 2-3 – Results obtained in the one-pot synthesis of sulfonamides via route B



Entry	(7) (mmol)	R (mmol)	(13) (mmol)	Base (mmol)	Time (h)	Observations
1*	0.27	Phenyl (0.53)	0.81	--	16	(17) η= 40%
2	0.56	Tosyl (0.98)	1.62	--	16	(18) η= 40%
3	0.53	Methyl (0.93)	1.62	--	16	Complex mixture
4**	0.72	Methyl (1.3)	2.32	--	6.5	Complex mixture
5	0.71	Methyl (1.3)	2.32	TEA (0.72)	16	Complex mixture
6	0.72	Phenyl (1.3)	2.32	TEA (1.1)	16	Complex mixture
7	0.73	Phenyl (1.3)	1.16	K_2CO_3 (0.81)	16	(17) η= 35%
8	0.73	Phenyl (1.3)	1.16	Cs_2CO_3 (0.80)	16	TLC showed (17) in low quantity

*This assay was conducted by MSc Diogo Poeira. **The morpholine was added 9.5 h after the sodium sulfinic salt instead of 1 h.

When sodium tosylsulfinate (2) was used, the corresponding sulfonamide was isolated in 40% yield (Entry 2). Sodium methylsulfinate (9), an aliphatic and smaller molecule was also tested (Entry 3) however, no evidence of the sulfonamide was found.

In order to understand if a longer reaction time was required for the formation of the intermediate compound, the reaction time was extended (9.5 h; Entry 4), followed by addition of the amine however, the result was the same.

Next, the presence of a base in the reaction mixture was considered, and TEA was added after the addition of the morpholine but without any change on the results (Entry 5), indicating that, at least in that quantity,

it does not interfere in the sulfonamide's formation. So, a second assay with triethylamine in a higher amount was performed (Entry 6), but the result did not change.

Two other bases were investigated, using potassium carbonate (Entry 7) and cesium carbonate (Entry 8). The crude from the trial with potassium carbonate showed the presence of the sulfonamide (17) (characteristic at R_f = 0.79), which was isolated in 35% yield, a second compound of R_f = 0.89, of equal intensity and another compound at R_f = 0.55 (in a smaller amount).

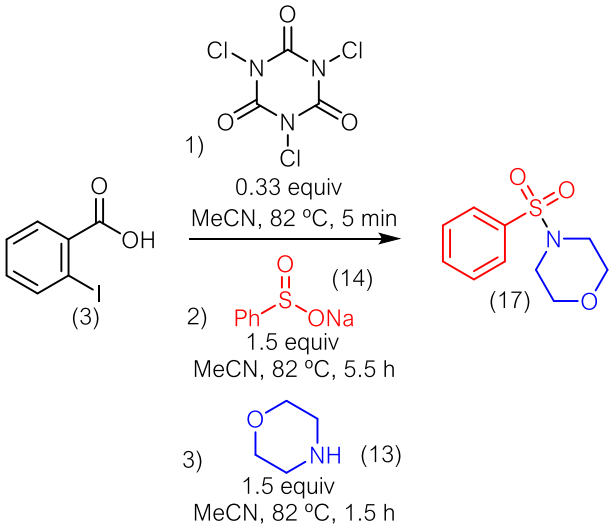
The crude from the trial with caesium carbonate showed the same three compounds (as in Entry 7) and they presented itself equal intensity, so no effort was put in isolating the sulfonamide (17).

These three assays were of utmost importance, as they showed there is not the need to use a base, either because it did not work or because the corresponding yield was inferior of the experiments carried in the absence of base.

One possible explanation for the fact that no base is required to remove the amine's proton after its attack could be due to the presence of chlorine, which can remove it, but is captured by the sodium ion, present in a stoichiometric quantity. A second possible explanation is the sulfinic acid salt itself, which is basic, but it only was charged with an excess of 0.5 equiv, insufficient quantity to remove the proton. Thus, the proton's capture might be done by the benziodoxolone's side product, 2-iodobenzoate. For each chloro benziodoxolone that reacts with the salt and, eventually, the amine, a 2-iodobenzoate is formed, removing the proton from the intermediate and then favouring the formation of the sulfonamide.

2.5.3 One-pot procedure from 2-iodobenzoic acid to sulfonamide

A one-pot procedure toward the sulfonamide starting from the 2-iodobenzoic acid was investigated (Scheme 2-11) (see Section 3.7). The experiments were monitored by TLC, and a sample was collected between the sequential additions; cyclization, addition of sodium benzenesulfinate and addition of morpholine. However, after the addition of the morpholine, no sulfonamide was found.



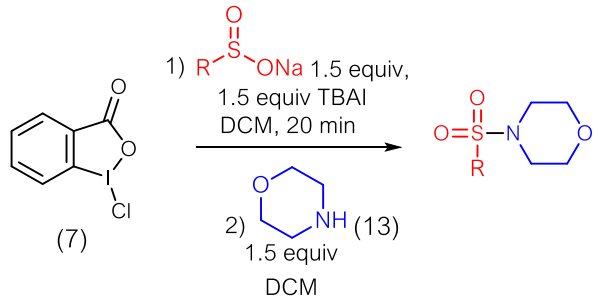
Scheme 2-11 – One-pot multi-step sulfonamide (17) synthesis

2.6 STUDIES USING TBAI

There had always been a problem transversal to all experiments involving the use of chloro benziodoxolone (7), its solubility. This hypervalent iodine compound suffers from low solubility in most organic solvents at low temperatures, only being completely soluble in hot acetonitrile. This characteristic strongly limits the reaction conditions.

The adopted solution for this problem has been addressed by Hamashima and co-workers where the authors used tetrabutylammonium iodide (TBAI).[43] This salt is a phase-transfer agent, which helps in the solubilization of the chloro benziodoxolone (7). One of the drawbacks of using this salt is its removal from the crude, where several washings are required to completely remove it. Several experiments were carried to investigate the influence of the presence of TBAI in the reaction of the benziodoxolone (7) with sodium sulfinic acid (14) and morpholine (13) according to Table 2-4 (see Section 3.8.1).

Table 2-4 – Resume of the experiments for the sulfonamide formation using TBAI



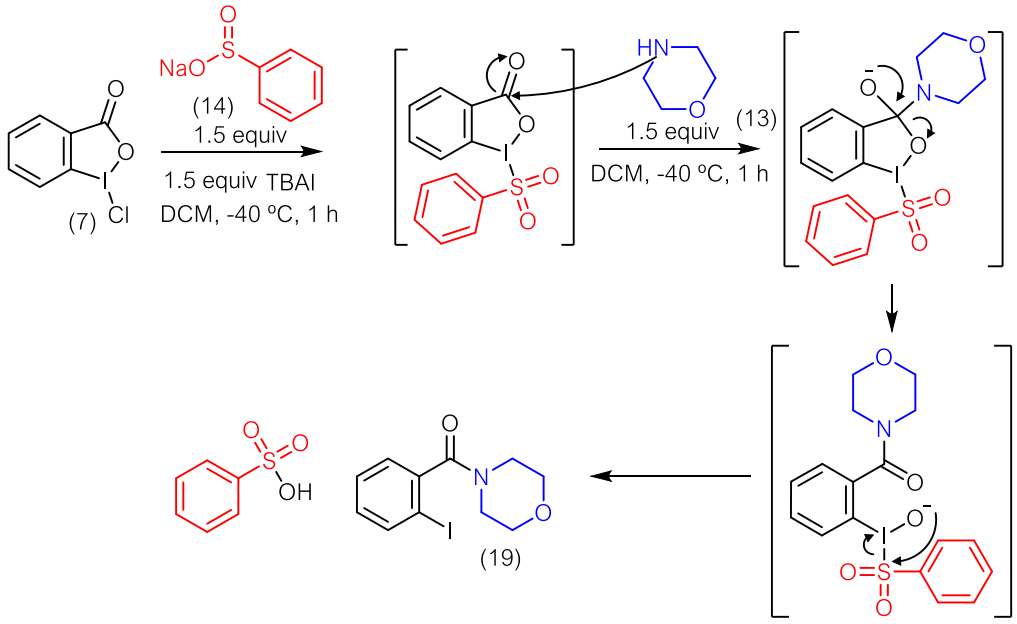
Entry	R (mmol)	Temp (ºC)	Time (h)	η (%)	Observations
1	Camphor (0.8)	40	16	--	Complex mixture
2	Methyl (1.1)	40	16	--	Complex mixture
3	Tosyl (1.1)	40	16	--	Complex mixture
4	Phenyl (1.1)	-78	3	--	Nearly pure sulfonamide (17) before workup
5*	Phenyl (1.1)	-78	2.5	(17) 82.7	Nearly pure sulfonamide (17)

*different work-up: only washed with water

To start, sodium camphorsulfinate was considered (Entry 1), and although the solubilisation was complete, the resulting TLC analysis showed a complex mixture of 4 compounds with close R_f's between 0.71 and 0.46. The desired product is a completely aliphatic sulfonamide meaning that, even if synthesised, it would not be one of the four compounds detected at UV light. For this reason, no effort was taken to isolate the products formed.

Sodium methylsulfinate was also tested under these reaction conditions and, as expected, the TLC analysis showed a more complex mixture than the attempts without the TBAI, with a dragging and two compounds standing out (Entry 2). Thus, no conclusion was possible to obtain.

Next, it was decided to use sodium tosylsulfinate which had previously proven to afford the corresponding sulfonamide (Entry 3). The TLC showed two compounds at R_f 0.85 and 0.64. The compounds were isolated and analysed by NMR spectroscopy, and it was concluded that one of the products formed consisted of an amide (19), formed with the morpholine and the benziodoxolone (Scheme 2-12). This meant that the nitrogen did not attack the sulfur atom as expected but instead attacked the carbonyl group. Even if the conversion to the amide was not quantitative, any percentage converted would lower the possible sulfonamide formation, as it consumes and disables the benziodoxolone and the morpholine. So, the current objective was to prevent the amide's side reaction as much as possible.



Scheme 2-12 – Mechanism proposed for the formation of amide (19)

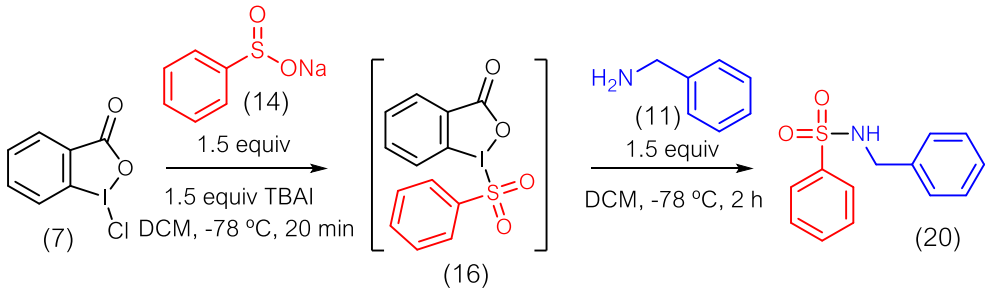
The adopted strategy to avoid the formation of this side product was by lowering of the reaction temperature. If the sulfonamide's pathway has a lower activation energy than the amide's, by decreasing the reaction temperature, the desired pathway would be favoured. Thus, the reaction's stoichiometry was maintained while the temperature was brought down to -78 ºC. The TLC analyses of the crude showed almost quantitative sulfonamide production (Entry 4). One important remark from this trial was that after 1.5 h the sulfonamide's formation did not evolve. However, the sulfonamide was not found among the chromatographic column's fractions. A TLC analysis of the work-up's aqueous phase showed evidence of

the sulfonamide. A plausible explanation relies on the fact that during work-up, by washing with hydrochloridric acid, lowered the pH level, and the protonation of the sulfonamide might have occurred, transferring it to the aqueous phase. To solve this drawback, the hydrochloridric acid used to remove the amine of the crude was substituted with more washes with water.

Thus, the reaction was repeated once more, at -78 ºC and with the modified the work-up (Entry 5). Once again, the reaction TLC analysis showed almost quantitively amounts of sulfonamide and the work-up consisted on washings with water and brine. The sulfonamide was successfully isolated through chromatographic column in 83% yield.

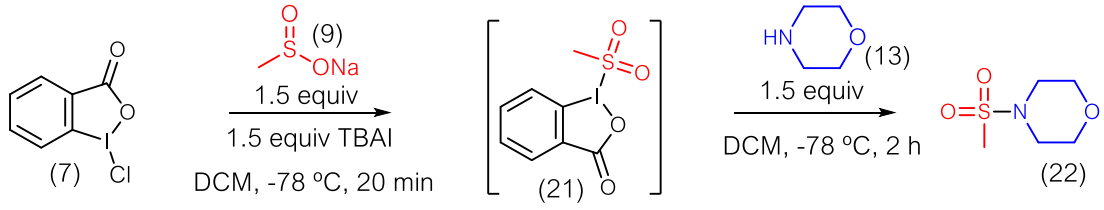
2.7 TBAI-MEDIATED SYNTHESIS OF DIFFERENT SULFONAMIDES

Using the previously established procedure, sodium benzenesulfinate (14) and benzylamine (11) were investigated (Scheme 2-13) (see Section 3.8.2). The TLC analyses of the crude after 2 h showed a complex mixture, suggesting that primary amines are not the most suitable reagents for the used protocol, and this could represent a limitation of the present approach.



Scheme 2-13 – Attempt for the synthesis of N-benzylbenzenesulfonamide (20).

In parallel, a trial with sodium methylsulfinate and morpholine was performed (Scheme 2-14) (see Section 3.8.2). The reaction was quenched after 1 h, when the benziodoxolone was completely consumed. The 4-(methylsulfinate)morpholine (22) was not successfully isolated due to difficulties associated with its detection.



Scheme 2-14 – Attempt for the synthesis of 4-(methylsulfonyl)morpholine (22)

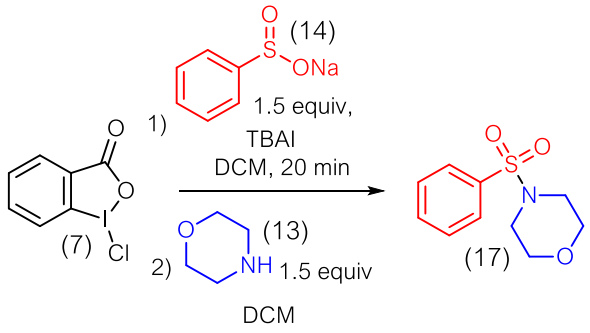
At this point, it was clear that the previously established reaction conditions were suitable for the sulfonamide (17) but did not work when applied to other amines or sulfinic acid salts. Thus, new conditions were investigated in order to establish a general protocol compatible with different substrates.

According to the work of Zhdankin and co-workers,[34] when using the benziodoxolone moiety to perform azidation of aldehydes, it is possible to lower the TBAI's stoichiometry to a point where the yield raises.

Another possible optimizable condition is temperature. A reaction with temperature closer to the room temperature and lower quantities of TBAI would be more economical and environmentally friendly (see Section 3.8.3).

Table 2-5 summarizes the results obtained in the optimization experiments.

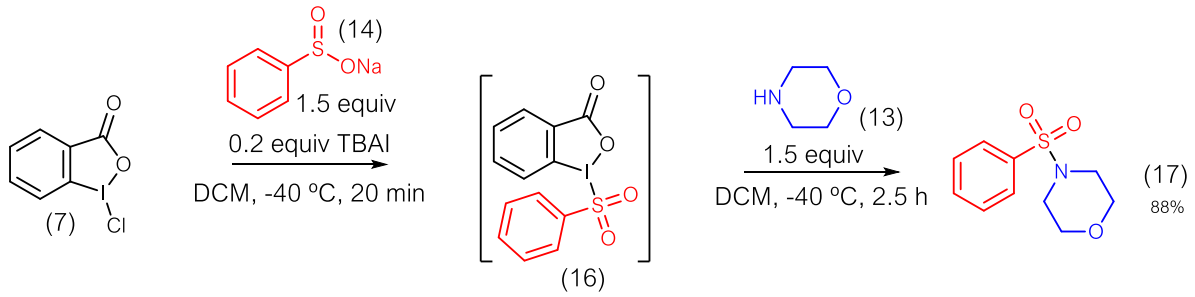
Table 2-5 – Optimization experiments for the synthesis of sulfonamide



Entry	7 (mmol)	TBAI (µmol)	Temp (°C)	Time (h)	(17) η (%)	Observations
1	0.18	89	-40	16	84.1	Pure product after work-up
2	0.18	97	0	3	--	No product found
3	0.18	37	-15	1.5	--	No product found
4	0.18	37	-40	2.5	88.0	Pure product after work-up

The first assay of the Table 2-5 involved raising the temperature to -40 ºC, and lowering the TBAI to 89 µmol, from 1.5 to 0.5 equiv (Entry 1). The reaction went smoothly and the TLC analysis was so clean that a simple filtration through pad of silica was enough to obtain the pure sulfonamide in 84% yield. The second entry was performed at 0 ºC but no product was obtained. Entry 3 was performed at -15 ºC plus the TBAI was lowered to 37 µmol (0.2 equiv) but no product was obtained too.

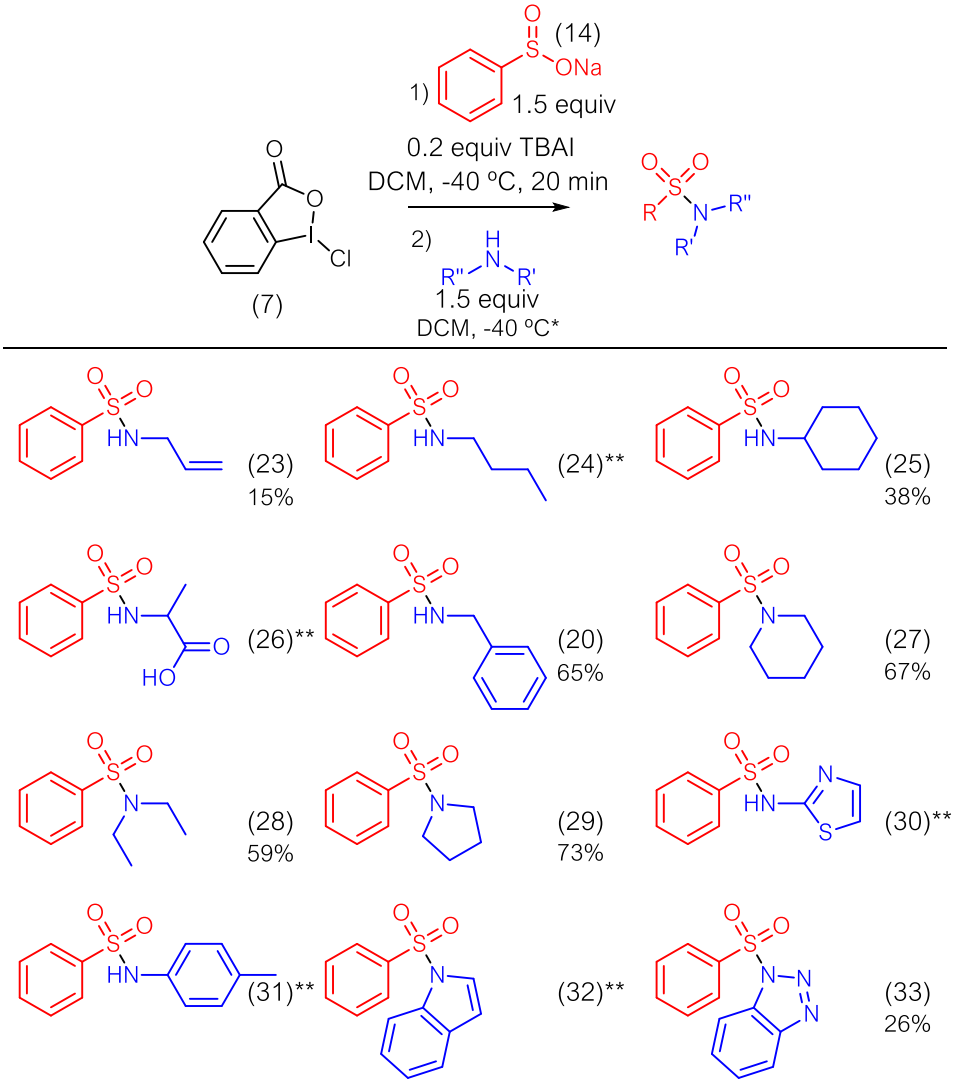
A last assay was performed using 0.18 mmol of chloro benziodoxolone (7), 37 µmol of TBAI and 182 µmol of sodium benzenesulfinate followed by 24 µL of morpholine in dichloromethane at -40 ºC for 2.5 h (entry 4). When finished, the crude was filtered through a pad of silica, and (benzenesulfinate)morpholine (17) obtained pure with an 88% of yield. Thus, the optimal reaction conditions had been established.



Scheme 2-15 – Optimized one-pot synthesis of 4-(benzenesulfonyl)morpholine (17)

2.8 SCOPE OF THE REACTION – INVESTIGATION OF DIFFERENT AMINES

With the optimal conditions in hand for the sodium benzenesulfinate and morpholine combination, the next step consisted on investigation the reaction scope, experimenting different amines and sodium sulfinates. Starting with the amines, an array of aromatic, aliphatic, primary and secondary amines were tested. All the assays were performed with sodium benzenesulfinate, as it was the salt with most successful results so far (Scheme 2-16) (see Section 3.9.1).



Conditions: (7) (0.18 mmol), (14) (0.27 mmol), TBAI (0.041 mmol), amine (0.28 mmol)
* time varied from 2 h to 16 h
** not observed

Scheme 2-16 – Reaction scope: different amines

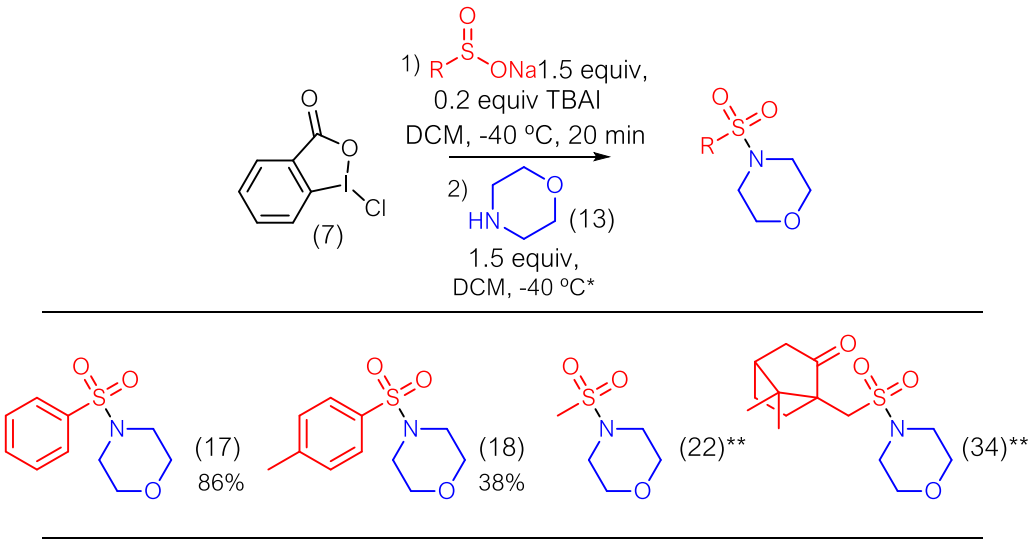
A total of thirteen different nucleophilic amines were tested: eight aliphatic and five aromatic. Considering the aliphatic group, the five primary amines presented lower yields, 0-65% than the three secondary amines, 59-84%. The same pattern was not observed for the aromatic amines. One plausible explanation is that having two N-H bonds, the aliphatic primary amines have the possibility to react with more than one (phenylsulfonyl)benziodoxolone (16) diminishing the overall sulfonamide's yield. However, no evidence of a disubstituted product was obtained (by NMR spectroscopy).

When alanine was used, no reaction was observed because this molecule holds not only a primary amine as well as a carboxylic acid. One alternative would consist on using the alanine methyl ester.

Regarding the use of indole, the TLC analysis of the crude presented an extremely complex mixture, reason why the crude was not purified. The indole molecule possesses a very distinct chemistry. It presents more than one reactive position which might be responsible for the complexity of the crude.

It is worth noticing that all experiments were performed in a very small scale, making the yields very susceptible to variations, and further experiments are needed.

After having the amines tested, it was time to test different sodium sulfinic salts. For this purpose, it was used the amine which produced the higher yield sulfonamide, morpholine. Three sodium salts were tested, methylsulfinate, tosylsulfinate and camphorsulfinate (Scheme 2-17) (see Section 3.9.2).



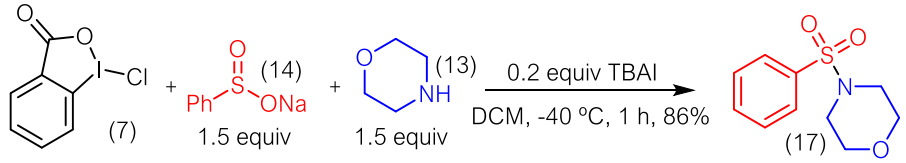
Conditions: (7) (0.18 mmol), sodium sulfinic salt (0.27 mmol), TBAI (0.041 mmol), (13) (0.28 mmol)
* time varied from 1 h to 2 h
** not observed

Scheme 2-17 – Reaction scope: different sodium sulfinic acid salts

Sodium tosylsulfinate afforded the corresponding sulfonamide but only in 38% yield. Both remaining salts were fruitless. In the sodium methylsulfinate trial, the corresponding sulfonamide was not found in the crude, compared to an authentic sample previously prepared (see Section 3.3.2). The sodium tosylsulfinate's crude revealed to be a complex mixture and the sulfonamide, if formed, was not found. Studies to improve these results are still ongoing in the lab.

2.9 CASCADE APPROACH

A different protocol was investigated, consisting on the simultaneous addition of all the reagents instead of the sequential addition used in the previous attempts. Morpholine and sodium benzenesulfinate were used, and as expected, the corresponding sulfonamide (17) was synthesised in a shorter reaction time (1 h) and in 86% yield (Scheme 2-18) (see Section 3.9.3).

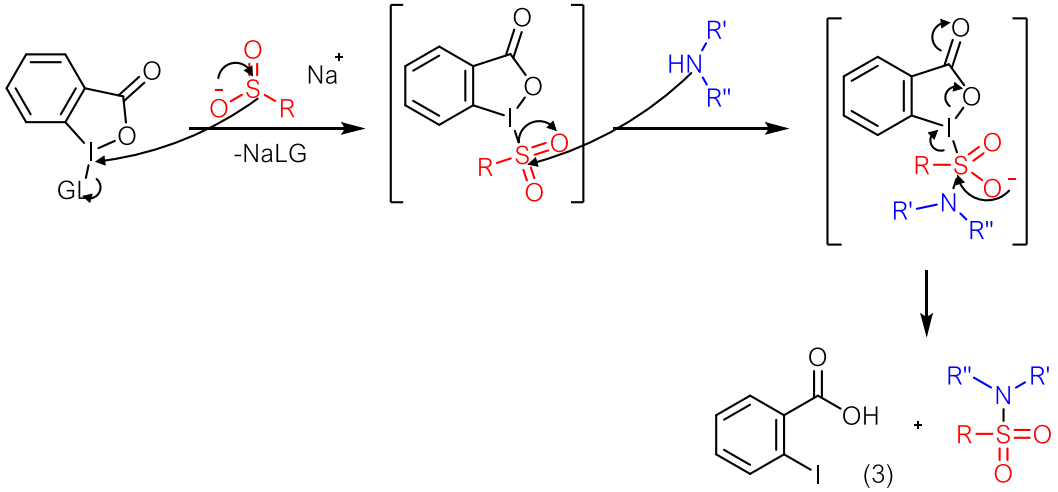


Scheme 2-18 – Cascade approach towards sulfonamide (17)

This protocol is faster and more attractive for industrial applications. One drawback was that the purification of (17) required preparative chromatography, as the crude's TLC showed more than one compound, contrary to the sequential addition protocol that avoids the use of a chromatographic separation.

2.10 MECHANISM STUDIES

Based on the collected data, the following mechanism was proposed (Scheme 2-19).



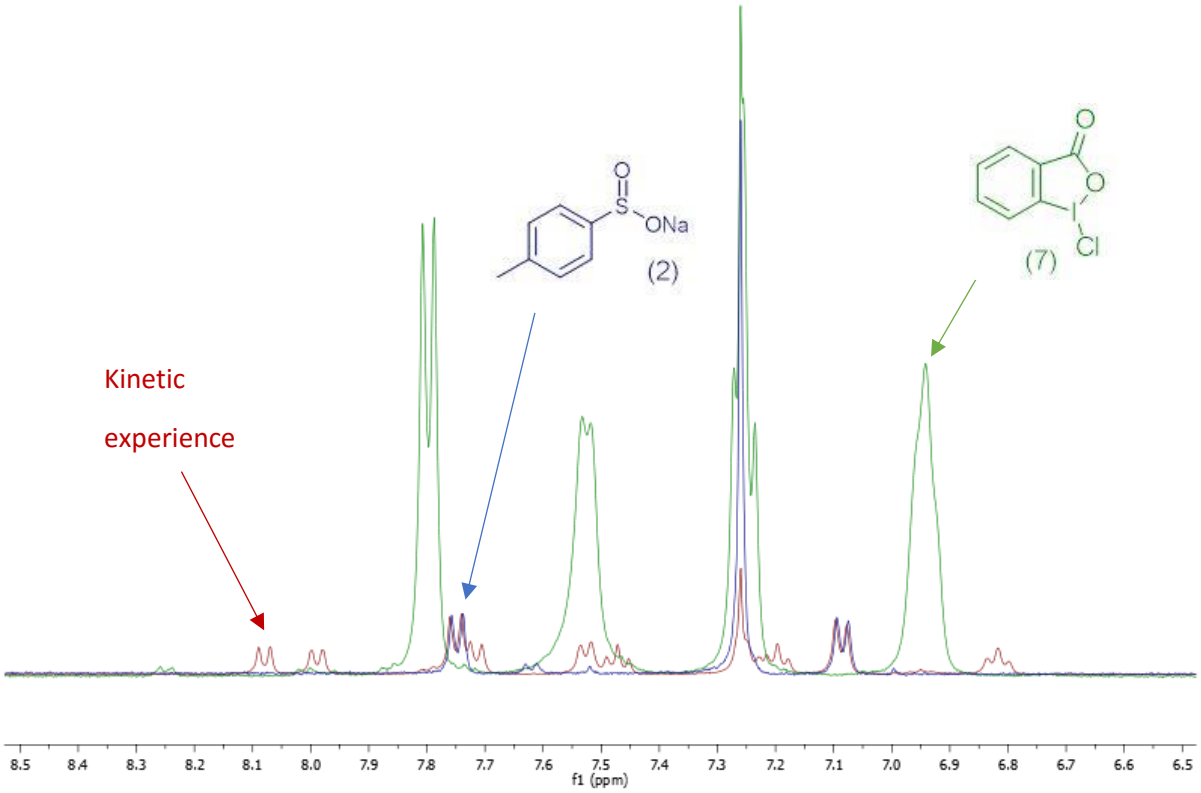
Scheme 2-19 – Proposed mechanism for the sulfonamide formation

The proposed mechanism starts with the sulfur's nucleophilic attack to the iodine and synthesis of the sulfonyl benziodoxolone, a very reactive intermediate which could not be isolated so far. Then, the nucleophilic amine is added and attacks the sulfur. The quenching separates the iodine moiety from the newly formed sulfonamide and opens the five-member ring to afford the 2-iodobenzoic acid (3). The result that give strength to this route is the lack of sulfonamide synthesis when the sulfinic acid salt and the amine are mixed without the benziodoxolone.

In order to shed some light into the reaction's mechanism, a NMR experiment was performed. An appropriate NMR tube was charged with a mixture of benziodoxolone (7), sodium sulfinic salt (2) and TBAI in DCM at room temperature. A total of 43 ^{1}H NMR spectra were performed in an interval of 35 minutes.

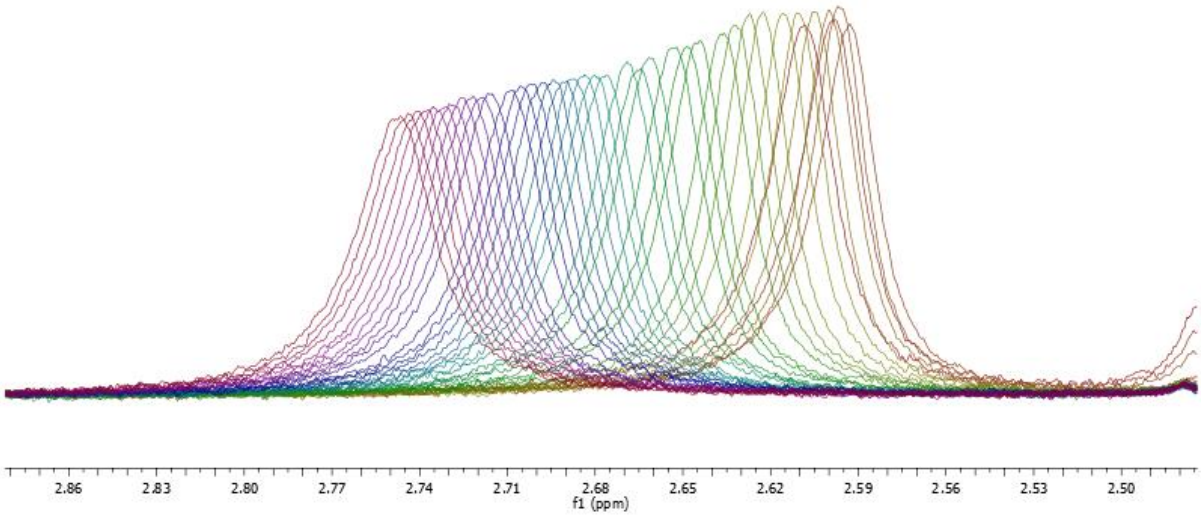
After analysis of the acquired spectra, the only signal which varied in chemical shift was a small singlet which changed from 2.60 ppm to 2.75 ppm. The rest of the spectral profile maintained equal throughout the experiment's time. The spectrum 2-1 shows a compilation of the two reagents' spectral profile, (7) and

(2), with a representative spectrum of the kinetic experiment.



Spectrum 2-1 – Superposition of the aromatic region: a representative sample of the kinetic experiment and the reaction's reagents

From this superposition, it is possible to observe a new, different compound and remaining sodium tosylsulfinate (2) in the NMR tube. The compound has a total of 8 aromatic protons and a signal at 2.30 ppm characteristic of a methyl group from the tosyl moiety, which are compatible with the hypothesised transfer reagent. Even so, no 2-D spectra were performed, so the studies are only preliminary data that needs further investigation.



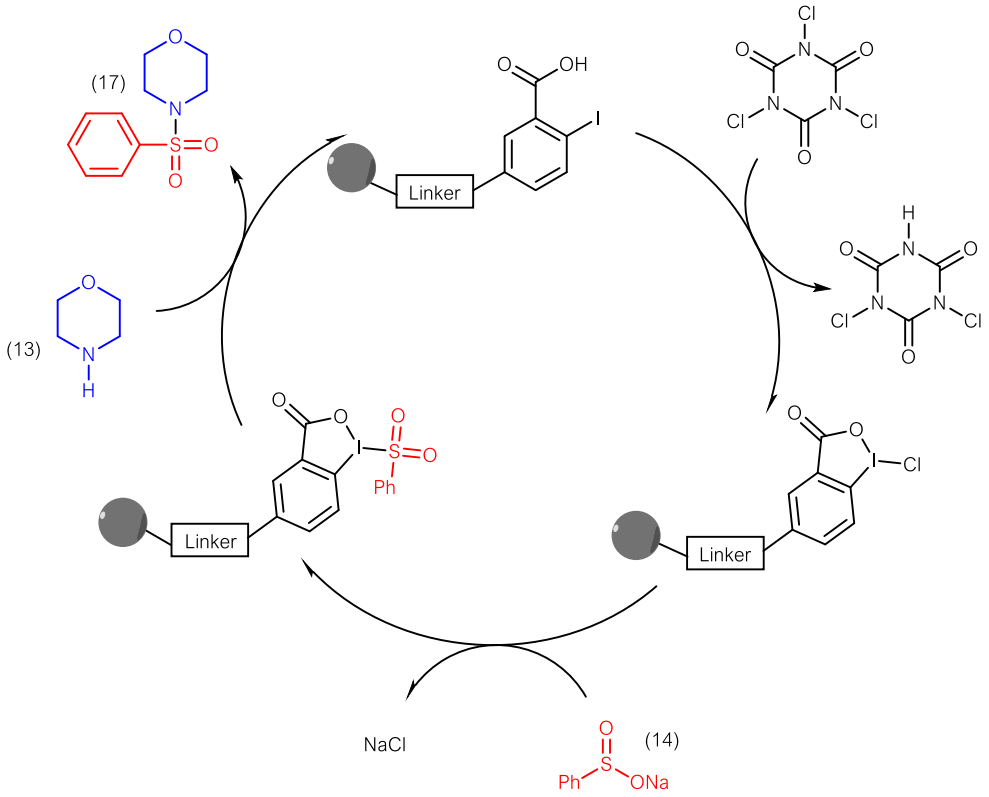
Spectrum 2-2 – Superimposed spectra of the kinetic experience

The Spectrum 2-2 highlight's the shift presented on the kinetic experience. This observation suggests the formation of a new chemical species that might be the hypothesised intermediate. Considering these results, more experiments, in different conditions, are necessary to allow a more detailed analysis.

2.11 Polymer-supported approach

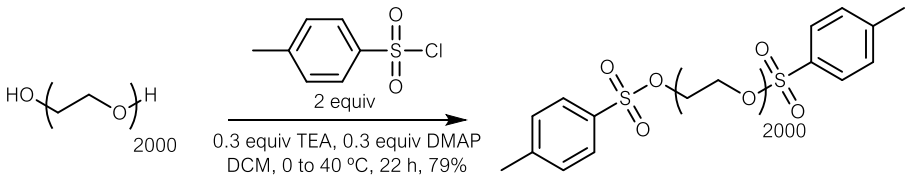
A successful adaptation to polymer-supported is a great asset to research and industrial environments. In this approach, polyethylene glycol (PEG) was used. This polymer is available in a wide variety of molecular weights, varying from 200 to 4000. It is inexpensive, thermally stable, non-toxic and can be recovered. PEG can be used as a reaction medium or solid-liquid phase transfer catalyst, enabling the reduction of the organic solvent volume's.[44]

The plan envisaged the immobilization of the 2-iodobenzoic acid (3) in PEG-2000, to transform it in the benziodoxolone (38), to conduct the sulfonylation, to recover the PEG with 2-iodobenzoic acid attached (37) at the end of the reaction, and repeat the whole process testing the reutilization capacity (Scheme 2-20).



Scheme 2-20 – Cycle of the polymer-supported approach

PEG-2000 is a common denomination for a mixture of PEG chains of different lengths which medium mass is 2000 g/mol, and each chain ends with a hydroxyl group. To achieve PEG functionalization, a protocol previously used by the group was adopted.[45] Thus PEG-2000 was converted in the tosyl derivative, creating an electrophile centre with a good leaving group (see Section 3.10.1.3).



Scheme 2-21 – Procedure adopted for the tosylation of PEG 2000.[45,44]

Triethylamine was chosen as it is a bulky base, incapable of acting as a nucleophile itself. DMAP, or 4-dimethylaminopyridine, is a catalyst used in esterification reactions. The 79% yield obtained is due to the difficulty in the isolation process, consisting in the precipitation of the product with diethyl ether. This process, although simple, gives way to losses as it is based on the PEG-2000's insolubility in this solvent. Additionally, even though this polymer is bench-stable as a white solid, when submitted to a moderate to high temperature, it melts, increasing the solubility in diethyl ether. Moreover, PEG-2000 is soluble in water, making it susceptible to the air's humidity. Lastly, due to the size of the polymer chain, by TLC analysis is difficult to differentiate starting materials from modified PEG. All these characteristics are transversal to all PEG-2000 related protocols.

Regarding the linkage of the benziodoxolone moiety to PEG, it was decided to use an ether group as a binding group, which is stable group under the reaction conditions used. With this type of bond in mind, a 2-iodobenzoic acid like molecule had to be synthesised, more precisely the 5-hydroxy-2-iodobenzoic acid (35) (Figure 2-1).

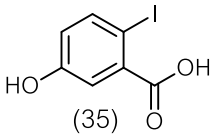
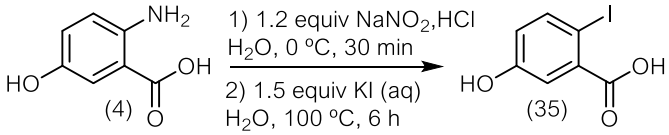


Figure 2-1 – 5-hydroxy-2-iodobenzoic acid (35)

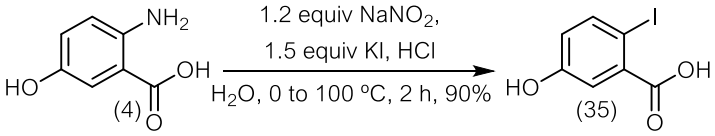
The desired acid is not commercially available, so 2-amino-5-hydroxybenzoic acid had to be converted via formation of the corresponding diazonium salt (Scheme 2-22) (see Section 3.10.1.1). The first procedure to synthesise 5-hydroxy-2-iodobenzoic acid was based on the work of Usuki and co-workers, which also coupled this molecule to a polymer.[46] No product was found.

The rationalization of this problem comes from an unclear order of addition of the reagents. Not only the concentrated hydrochloridric acid is poured over the sodium nitrite, as this happened before the addition of the water.



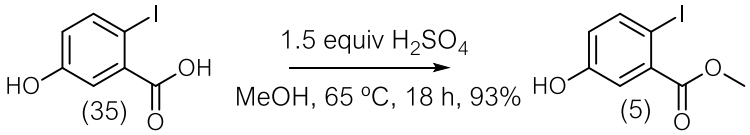
Scheme 2-22 – 1st protocol to synthesise 5-hydroxy-2-iodobenzoic acid (35).[46]

A second attempt based on the work of Mimura and co-workers was performed.[47] Contrarily to the first procedure, the concentrated hydrochloridric acid was added to an aqueous solution of 2-amino-5-hydroxybenzoic acid and sodium nitrite followed by the addition of the potassium iodide. The reaction afforded compound (35) in 90% yield.



Scheme 2-23 – 2nd protocol to synthesise 5-hydroxy-2-iodobenzoic acid (35).[47]

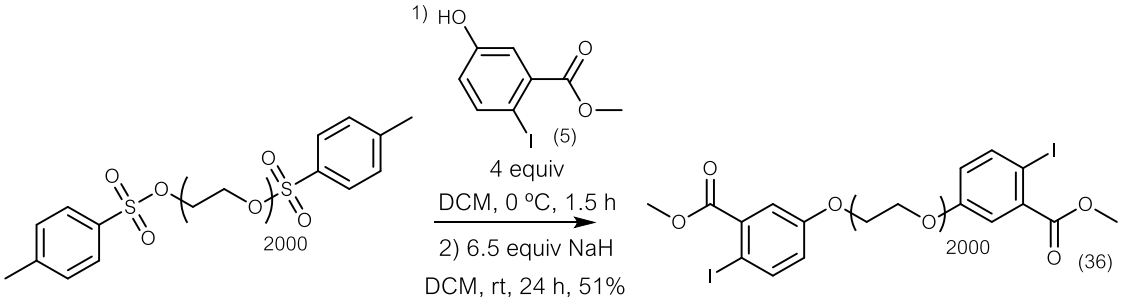
To obtain the coupled 5-hydroxy-2-iodobenzoic acid in the PEG 2000, an additional step is required, the protection of the carboxylic acid via an esterification – involving a simple procedure (see Section 3.10.1.2). The ester group is easy to remove and inert to the coupling conditions.[47] This transformation is a simple mixture of 5-hydroxy-2-iodobenzoic acid and hydrosulfuric acid in methanol overnight. The first time performed, the procedure did not work due to the impurities present in the 5-hydroxy-2-iodobenzoic acid. The second attempt was successful and compound (5) was isolated in 93% yield (Scheme 2-24).



Scheme 2-24 – Synthesis of methyl 5-hydrozy-2-iodobenzoate (5).[47]

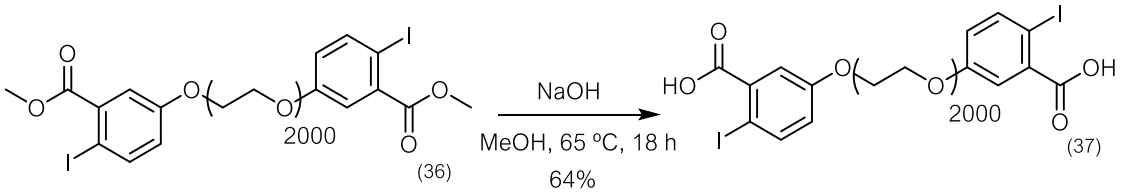
2.12 A SULFONYLATION APPROACH ON A SOLUBLE POLYMER

The first step towards the polymer-supported approach to the sulfonamide's synthesis was the coupling of the benziodoxolone precursor, methyl 5-hydrozy-2-iodobenzoate (5), to the polymer, under anhydrous conditions (see Section 3.10.2). The procedure started by treating the PEG-(OTs) with the benzoate, followed by the addition of sodium hydride and after 24 h the product was obtained in moderate yield (51%) (Scheme 2-25). This moderate yield could be due to the isolation process or from the protocol itself.



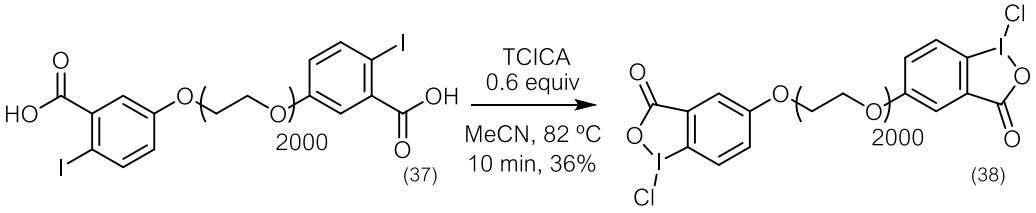
Scheme 2-25 – Pegylation of the benzoate.

The next step consisted on the hydrolysis of the benzoate to benzoic acid (36) with a moderate yield (64%) (Scheme 2-26) (see Section 3.10.2.2).



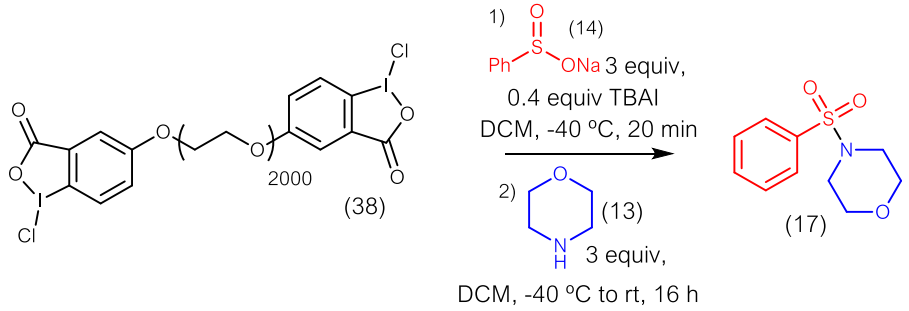
Scheme 2-26 – Benzoate hydrolysis on PEG-2000

To achieve the Compound (38), the benziodoxolone formation using TCICA was adapted from the previous experiments on solution-phase (see Section 3.10.3). This procedure culminated in a low yield of 36%. This cyclization is difficult because it cannot be performed with a high excess of TCICA, as it is difficult to remove from the medium. Additionally, PEG-2000 is not very soluble in hot acetonitrile (Scheme 2-27).



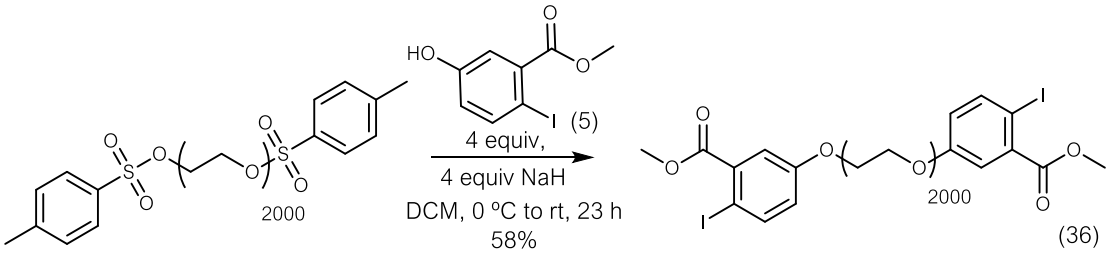
Scheme 2-27 – Formation of benziodoxolone on PEG-2000

Although the coupling reaction was performed with one gram of polymer, after a sequence of steps of low to moderate yields, not much reagent was still available. Even in a low scale, an assay was performed using the chloro benziodoxolone coupled to PEG, morpholine and sodium benzenesulfinate (see Section 3.10.4), however no sulfonamide was found (Scheme 2-28).



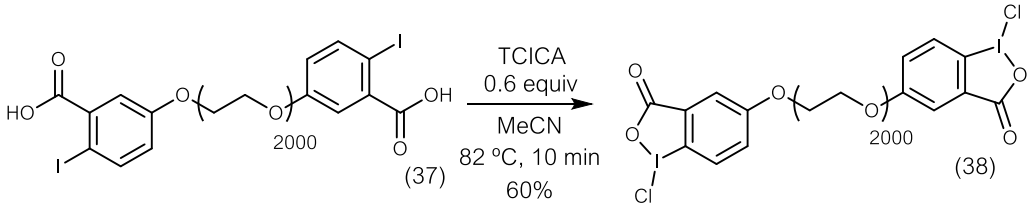
Scheme 2-28 – 1st attempt to prepare the sulfonamide on PEG-2000.

With no 2-iodobenzoic acid coupled to PEG-2000 left, a new and larger scale protocol was performed. This time the coupling reaction was modified and, instead of having both the PEG and the benzoate in the flask from the beginning, PEG was added to a benzoate solution (Scheme 2-29) (see Section 3.10.2.1). Having excess of benzoate, the completion of the reaction was favoured, and the yield was slightly higher. The NMR analysis of the resulting product showed the reaction was not complete, with a mixture of benzoate and tosyl coupled to PEG-OH terminals. This obstacle might be overcome by increasing the reaction's time and/or temperature. Due to the lack of time, no further optimizations were performed.



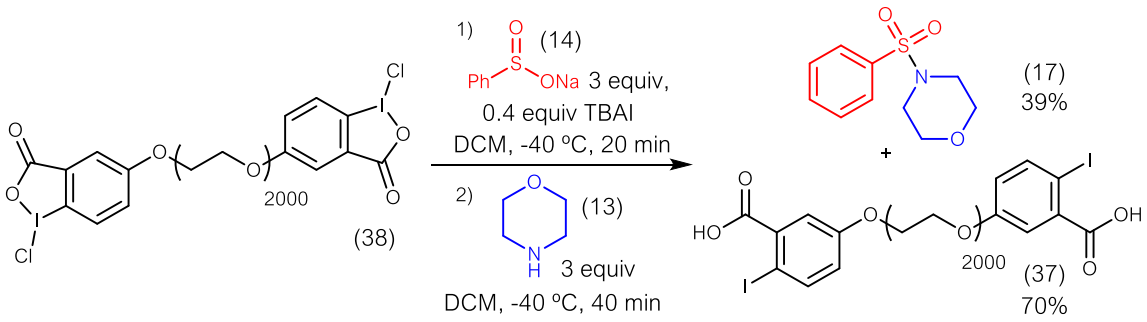
Scheme 2-29 – A different protocol to pegylate the benzoate

The benzoate hydrolyses to benzoic acid was performed with the previously tested protocol and with a similar yield (64%) (see Section 3.10.2.2). The resulting benzoic acid was cyclised to the benziodoxolone (38) (Scheme 2-30) using the same protocol (see Section 3.10.3). In the work-up, the crude was washed with dichloromethane instead of hot acetonitrile, as it dissolves better the polymer without dissolving the cyanuric acid, and the yield increased to 60%. It is possible to use this solvent because the chloro benziodoxolone moiety is dissolved in the polymer which can be than dissolved in dichloromethane.



Scheme 2-30 – New procedure to prepare benziodoxolone scaffold in PEG-2000

Finally, the polymer-supported sulfonamide's synthesis could be tested once again (see Section 3.10.4). The previous protocol was repeated in a 90 µmol scale, and 40 min after, (phenylsulfonyl)morpholine (17) was present in the reaction crude. The sulfonamide was isolated in 39% yield along with 70% of the polymer (37) recovered. The proof of concept was achieved but the recovery and reutilization of the bonded reagent was still to be tested (Scheme 2-31).



Scheme 2-31 – Reutilization of a recovered benziodoxolone scaffold in PEG-2000 on the reaction of formation of the sulfonamide (17)

Once again, the recovered polymer was cyclised with a 78% yield and the sulfonylation protocol tested. Sulfonamide was once again found in the crude, although the isolation process was not as effective as in the previous assay, it was possible to obtain sulfonamide in a similar yield (56%). It was proved that is possible to reutilize the hypervalent iodine compound when it is coupled to a polymer.

2.13 Final remarks

A new sulfonylation method was developed relying on the use of hypervalent iodine reagent. It may still be in an early phase and needs further optimization, but it has already showed very promising results. This method uses mild conditions, short reaction times and, once immobilized, the reagent can be reutilized, thus reducing waste and facilitating isolation of the product. According to Willis and co-workers, a surrogate must comply to three specifications: must be stable, easy-to-handle and safe, must release the functional group in a control matter and, lastly, the carrier must be chemically inert.[3] Analysing the developed protocol, it possesses all the specifications of a competent surrogate. Lastly, taking in consideration the possibility of an industry adaptation, this synthesis has even increased impact (Table 2-6).

Table 2-6 – Difference between the already reported methids and the benziodoxolone-based approach

Reported sulfonylation method	New benziodoxolone mediated method
Sulfonylation reagents difficult to handle and store	Stable or commercial compounds; Benziodoxolone synthesised *in situ*
Use of additional reagents at large excess	TBAI used (0.2 equiv.)
Low atom efficiency	Atom economical
Most have the necessity of using metals	Metal-free
Most limited hydrazines	Compatible with primary and secondary, aliphatic and aromatic amines
Compatible with amines when sulfonyl chloride or metal catalysis are used	Sulfonyl chloride and metal-free protocol
Use of gaseous SO_2	No SO_2 gas used
Most require high reaction times	Small reaction times
Water can be used as solvent	use of organic solvents/compatible with PEG
Energy consuming and difficult processes	Simple, straightforward and fast
No reports of polymer-supporteds synthesis	Polymer synthesis compatible

Although experiments have been performed to understand the mechanism of this new reaction, including a NMR experiments, it is still not clear. What is known is that the presence of the benziodoxolone reagent is crucial for sulfonamide formation. Additionally, when the reaction is carried under heating conditions attack of the amine to the carbonyl group occurs with formation of the amide (19), as a side product.
Several conditions were investigated, including, solvent, reaction temperature, order of addition of reagents and equivalents of reagents. Different approaches were considered in order to identify and isolate a key intermediate that could shed some light in the mechanism and reaction applicability. It was also found that morpholine does not react with benziodoxolone (7), however, the sulfinic acid salt react and, after addition of an amine, the corresponding sulfonamide can be obtained. The results obtained suggest that a nucleophilic attack of the sodium sulfinate to the chloro benziodoxolone's iodine occurs with subsequent nucleophilic attack of the amine to the sulfur atom.

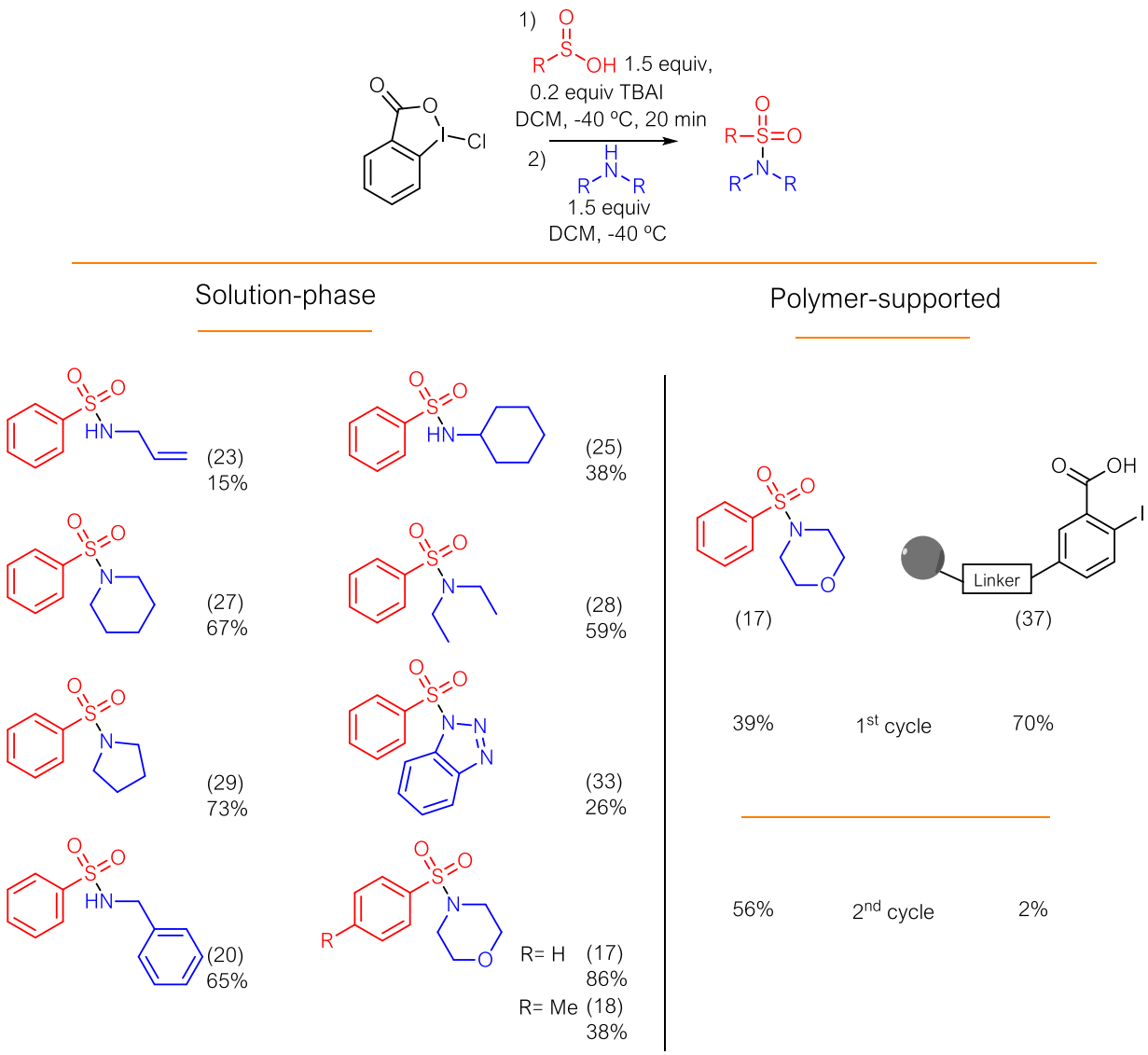


Figure 2-2 – Resume of all synthesised sulfonamides

Regarding the scope, a total of 13 different nucleophilic amines were tested and the yields were up to 88%, in a 50 mg scale. This group of amines included a combination between aromatics or aliphatics with primary or secondary, covering a diverse variety of nucleophilic amines. It was concluded that secondary amines give away better results and, regarding the aromaticity, it is the aliphatics examples which are better. Additionally, 4 different sodium sulfinic salts were tested. Although the two aromatic salts presented good to excellent yields, the two aliphatic amines showed no results.

Despite the experiments conducted further work is still required to improve the scope of the method. Additionally, a great deal of effort must be done in order to broaden the sodium sulfinic salt scope.

Concerning the polymer-supported approach, it was demonstrated that an PEG-2000 immobilized benziodoxolone can perform the sulfonylation reaction affording the sulfonamide (17) in 56% yield. This protocol presents several advantages over reported sulfonylation methods, as the reagent can be recovered and re-used, facilitates isolation of the product, allows mild reaction conditions, avoids isolation

and purification steps, reducing the organic solvents used. PEG-2000 is a soluble polymer support enabling simple reaction conditions as well as product separation from the benziodoxolone reagent.
To the best of our knowledge, there are no reports of benziodoxolone moieties capable of transferring sulfonyl groups immobilized in polymers, and thus this work consists on the first report of sulfonylation reaction using pegylated benziodoloxone reagent.

2.14 FUTURE WORK

As previously concluded, further optimization is still required and is ongoing in our laboratory. A wider array of amines and sodium sulfinate salts will be tested to enlarge the scope.
All the polymer-supported steps must also be optimized, to increase the impact of the approach. After optimization, another essential point is to assess how much life cycles this coupled reagent has, testing how many times it could be reutilized. Additionally, it is imperative to test the scope of the polymer-supported approach. Even though the polymer-supported present many advantages, it would be of great interest to see if the sulfonylation method was compatible with water. This modification would remove completely the use of organic solvents and decrease even further the already low associated toxicity.
Additionally, the Togni's benziodoxole should also be adapted to a similar protocol. The substitution of the carbonyl group with two methyl groups, would prevent the amide formation and probably enhance the solubility of the compound. Having such a different chemistry, its study would be very important. Also, the study of both would enable to make a bridge between the benziodoxolone and the benziodoxole, helping to understand both mechanism and the limitations.
Lastly, this developed protocol is just the tip of the iceberg. Proving it can transfer sulfonyl groups opens room for many other functional groups. It is of great importance to test the ability to do the umpolung of highly nucleophilic compounds. So, efforts will be made to discover which other groups can also be transferred by the benziodoxolone moiety.

3 EXPERIMENTAL PROCEDURE

3.1 GENERAL INFORMATION

The experimental part of this work involved the use of general laboratory procedures.

All reagents and solvents were acquired commercially and used without further purification, unless otherwise mentioned.[48] All of the mentioned solvents were, when necessary, dried using typical methods.[48] Molecular sieves were activated by heating at 300 °C in a muffle furnace for 3 h.

Analytical TLC was performed on Merck Keiselgel GF 254 0.2 mm plates supported on aluminum. Preparative TLC was performed using Merk Keiselgel 60GS254 silica gel for TLC supported on a glass surface with the described eluent for each case. Column chromatography was performed using Merck Keiselgel 60A silica gel (70-200 mesh) and the described eluent for each case.

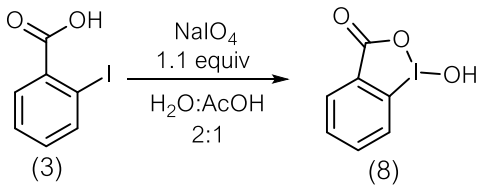
Melting points were measured using a Stuart scientific melting point apparatus. Measured melting points were not corrected.

IR spectra were acquired using a Perkin-Elmer Spectrum 1000 FT-IR spectrophotometer. Transmittance of the sample was acquired on between 4000 and 600 cm-1 and the samples were supported on KBr pellets. The IR bands are classified as weak (w), medium (m) or strong (s), and broad (br) when such is the case.

NMR spectra were acquired with Bruker ARX 400 or Bruker Avance III 400 spectrometers. ^{1}H-RMN and ^{13}C-RMN spectra were measured at 400 and 101 MHz, respectively. The samples were prepared on 5 mm NMR tubes using $CDCl_3$, MeOD or DMSO-d_6 as solvents and the corresponding trace $CHCl_3$, MeOD or DMSO-d_6 as reference signals. The NMR signals are described with chemical shift (δ, in ppm), source of signal (R-H) and relative intensity of signal multiplicity (nH, with n being the number of protons) of NMR signals are described as singlet (s), doublet (d), doublet of doublets (dd), triplet (t) and multiplet (m) with coupling constant (J) being given in Hz.

3.2 SYNTHESES OF REAGENTS

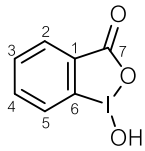
3.2.1 Synthesis of hydroxy benziodoxolone (8) [38,37]



(3) (8)

A round-bottom flask was charged with 2-iodobenzoic acid (2.0 g, 8.1 mmol) and sodium periodate (1.9 g, 8.8 mmol) dissolved in 12 mL of a solution of 30% acetic acid in water. The suspension stirred at 120 °C for 4 h in the shelter of light. After cooling to room temperature, 45 mL of water were added and stirred at

0 °C for 1 h. The solution was filtered. The solid was washed with water and acetone and dried under vacuum. The product (8) was scraped and 2.02 g were stored (94.8%).



(8)

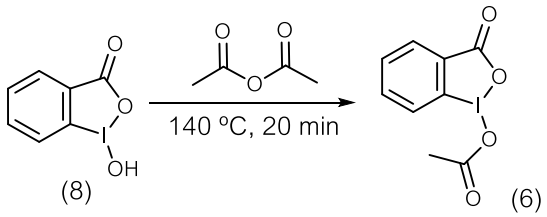
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, *J* = 7.5, 1.1 Hz, 1H, H2), 7.99 – 7.92 (m, 1H, H5), 7.84 (d, *J* = 8.0 Hz, 1H, H3), 7.70 (t, *J* = 7.3 Hz, 1H, H4).

IV (KBr) ν_{max} (cm^{-1}): 3084 (s, C-H aromatics), 2880 (b, OH), 1585 (s, C=O), 584 (s, C-I)

Mp: 209 – 214 °C

The presented spectral data is in accordance with the literature.[49]

3.2.2 General procedure for synthesis of oxybenziodoxolyl acetate (6) [38,37]



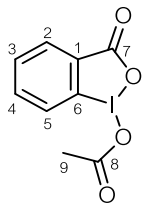
(8) (6)

A round-bottom flask was charged hydroxybenziodoxolone (8) and acetic anhydride. The solution stirred at 140 °C for 20 min. After cooled to room temperature, the solvent was concentrated under vacuum affording the product (6) pure.

The following table summarises the assays based on the previous protocol.

Table 3-1 – Resume of the synthesis of oxybenziodoxolyl acetate

Entry	(8) (mmol)	Solvent (mL)	(6) (g)	(6) η (%)	Observations
1	1.9	1.25	0.53	90.5	No complications
2	3.87	2.5	1.1	93.6	No complications



(6)

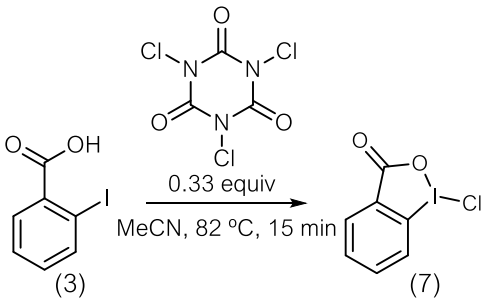
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (dd, *J* = 7.5, 1.2 Hz, 1H, H2), 8.02 (dd, *J* = 12.0, 4.9 Hz, 1H, H5), 7.86 (d, *J* = 8.2 Hz, 1H, H3), 7.78 (t, *J* = 7.4 Hz, 1H, H4), 2.26 (s, 3H, H9)

IV (KBr) ν_{max} (cm^{-1}): 3082-3062 (m, C-H aromatics), 2928 (m, C-H aliphatics), 1685 (s, C=O), 1611 (s, C=O), 1124 (m, C-O), 585 (s, C-I)

Mp: 196 – 202 °C

The presented spectral data is in accordance with the literature.[50]

3.2.3 Synthesis of chloro benziodoxolone using TCICA[38,37]

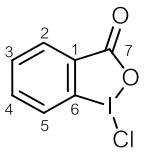


(3) (7)

A round-bottom flask was charged with 2-iodobenzoic acid (3) (1.03 mg, 4.2 mmol) dissolved in 7.5 mL of acetonitrile. The mixture stirred for 5 min at 82 °C. TCICA (0.37 mg, 1.6 mmol) dissolved in a small portion of acetonitrile was added to the mixture. The mixture stirred at 82 °C for 10 min. While still hot, the crude is filtered through a hot hirsch funnel with a pad of cellite and washed with hot acetonitrile. The resulting crude was concentrated under vacuum.

Table 3-2 – Resume of the synthesis of chloro benziodoxolone

(3) (mmol)	TCICA (mmol)	(7) (g)	(7) η (%)	Observations
4.2	1.6	--	--	Complications during work-up.
2.0	0.74	0.56	97.3	Filtered three times through a hot Hirsch funnel
20.2	7.8	3.4	59.9	Filtered twice through a hot Hirsch funnel
10.3	3.7	2.8	97.3	Filtered three times through a hot Hirsch funnel
20.2	10.1	4.5	79.2	Filtered twice through a hot Hirsch funnel. Reacted again with TCICA due to lack of reaction completion.



(7)

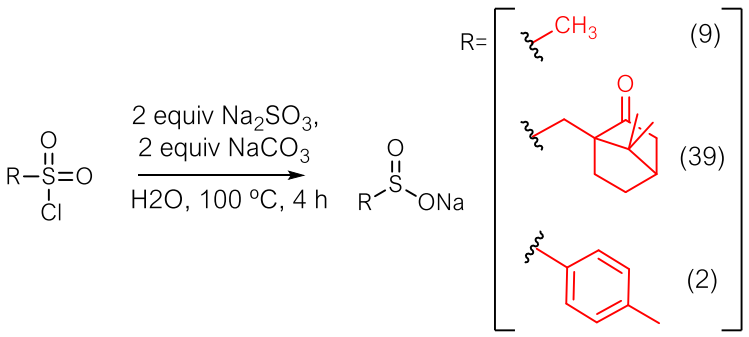
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.5, 1H, H2), 8.21 (d, *J* = 8.5 Hz, 1H, H5), 7.99 (t, *J* = 11.4, 1H, H3), 7.79 (t, *J* = 7.3 Hz, 1H, H4).

IV (KBr) ν_{max} (cm^{-1}): 3080 (m, C-H aromatics), 1685 (s, C=O), 1125 (s, C-O)

Mp: 158 – 163 °C

The presented spectral data is in accordance with the literature.[38,31]

3.2.4 Synthesis of sulfinic acid salts[51]



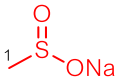
A round-bottom flask was charged 4-tosylsulfonyl chloride (217 mg, 1.1 mmol), sodium sulfite (265 mg, 2.1 mmol) and sodium hydrogenocarbonate (180mg, 2.1 mmol) dissolved in 4.2 mL of water. The mixture

stirred at 100 °C for 4 h. After cooled to room temperature, the water was evaporated and the mixture was extracted three times with hot ethanol. The product was recrystallized, filtered and stored.

The following table summarises the assays based on the previous protocol.

Table 3-3 – Resume of the synthesis of sodium sulfinic acid salt

Entry	R (mmol)	Product (g)	η (%)	Observations
1	Tosyl (1.14)	0.024	11.9	Difficult extraction and recrystallization
2	Tosyl (11.1)	0.5	25.4	Difficult extraction and recrystallization
3	Tosyl (24.3)	1.4	31.4	Difficult extraction and recrystallization
4	Methyl (15.3)	1.3	85.7	Difficult extraction and recrystallization
5	Camphor (5.1)	1.0	82.1	Difficult extraction and recrystallization

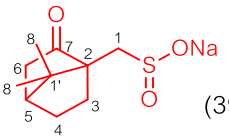


(9)

^{1}H NMR (400 MHz, DMSO-d_6) δ 1.91 (s, 3H, H1).

^{13}C NMR (101 MHz, DMSO-d_6) δ 50.3 (s, C1').

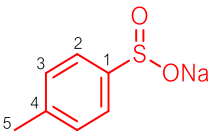
The presented spectral data is in accordance with the literature. [52]



(39)

^{1}H NMR (400 MHz, DMSO-d_6) δ 2.86 (d, *J* = 14.6 Hz, 1H), 2.73 – 2.65 (m, 1H), 2.36 (d, *J* = 14.6 Hz, 1H), 2.23 (d, *J* = 17.6 Hz, 1H), 1.93 (s, 1H), 1.27 (d, *J* = 9.0 Hz, 2H), 1.05 (s, 3H), 0.74 (s, 3H).

The presented spectral data is in accordance with the literature.[51]



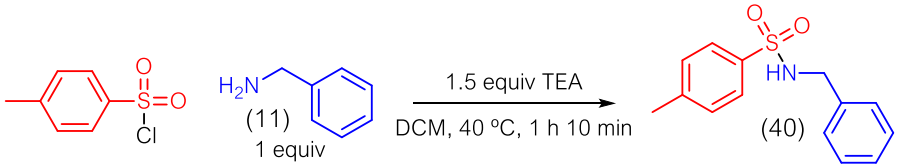
(2)

^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35 (d, *J* = 7.8 Hz, 2H, H2), 7.11 (d, *J* = 7.6 Hz, 2H, H3), 2.28 (s, 3H, H5').

The presented spectral data is in accordance with the literature.[53]

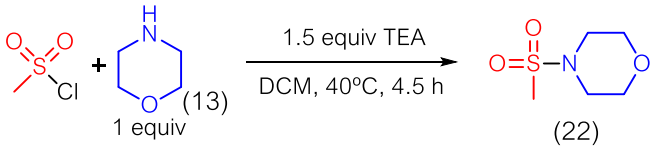
3.3 SYNTHESIS OF STANDARD COMPOUNDS FOR CONTROL EXPERIMENTS

3.3.1 Synthesis of *N*-benzyl-4-methylbenzenesulfonamide (40)

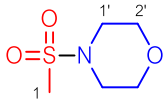


A round-bottom flask was charged with 4-methylbenzenesulfonyl chloride (179.5 mg, 0.94 mmol), benzylamine (11) (0.1 mL, 0.92 mmol) and triethylamine (0.2 mL, 1.43 mmol) dissolved in 5 mL of dichloromethane. The reaction stirred at 40 °C for 1 h 10 min. The crude was washed with water. The resulting organic phase was concentrated under vacuum and precipitated using petrol ether. No evidence of the product (40) was found. The solid was dried and stored.

3.3.2 Reaction of methanesulfonyl chloride with morpholine – synthesis of (methylsulfonyl)morpholine (22)



A dried round-bottom flask was charged with methanesulfonyl chloride (34 µL, 438 µmol), morpholine (13) (42 µL, 487 µmol) and triethylamine (100 µL, 717 µmol) dissolved in 2.5 mL of dichloromethane. The flask stirred at 40 °C for 4.5 h. The crude was washed with water, ammonium chloride and brine. The resulting organic phase was dried with sodium sulfate, filtered and concentrated under vacuum. The product (22) was separated using preparative thin layer chromatography as 7.3 mg, but not completely purified.

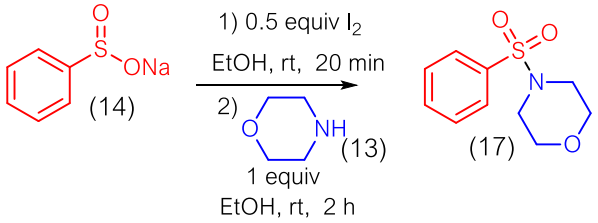


(22)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 – 3.76 (m, 4H, H2'), 3.25 – 3.18 (m, 4H, H1'), 2.79 (s, 3H, H1).

The presented spectral data is in accordance with the literature.[54]

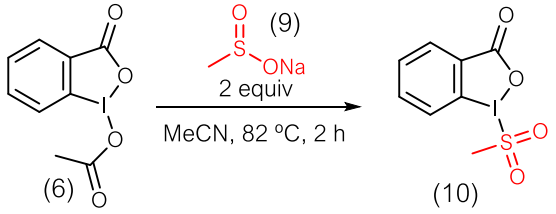
3.3.3 Control reaction of morpholine with sodium phenylsulfinate[4]



A round-bottom flask was charged with sodium phenylsulfinate (14) (206 mg, 1.3 mmol) and diiodine (171 mg, 0.67 mmol). After stirred at room temperature for 20 min, morpholine (13) (54 µmL, 0.63 mmol) dissolved in 0.5 mL of ethanol were charged. The reaction stirred at room temperature for 2 h. The crude was extracted with ethyl acetate and washed with a solution of 5% sodium thiosulfate in water. The resulting organic phase was concentrated under vacuum and stored in a glass vial. No evidence of sulfonamide (17) was found.

3.4 OXOBENZIODOXOLYL ACETATE ASSAYS

3.4.1 Synthesis of 1-(methylsulfonyl)benziodoxolone



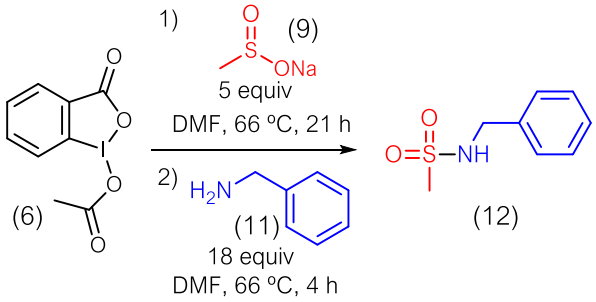
A round-bottom flask with a side-arm was charged with oxobenziodoxolyl acetate (6) (100 mg, 0.33 mmol), sodium methylsulfinate (9) (70.0 mg, 0.69 mmol) and 2.6 mL of acetonitrile. The flask stirred at 82 °C for 2 h. After cooled to room temperature, the crude was concentrated under vacuum and purified using a chromatographic column with hexane:ethyl acetate from 4:1 to 0:1. No evidence of product (10) was found.

The following table summarises the assays based on the previous protocol.

Table 3-4 – Resume of the attempts of synthesise 1-(methylsulfonyl)benziodoxolone using oxobenziodoxolyl acetate

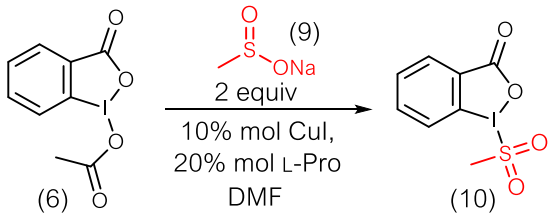
Entry	(6) (mmol)	Observations
1	0.33	No product found.
2	0.68	No product found.

3.4.2 One-pot synthesis of *N*-benzylmethanesulfonamide (12)



A round-bottom flask was charged with oxobenziodoxolyl acetate (6) (108 mg, 0.35 mmol) and sodium methylsulfinate (9) (88.6 mg, 0.87 mmol) dissolved in 2.6 mL of DMF. The flask stirred at room temperature for 2 h. The temperature was raised to 66 °C and the flask stirred for another 19 h. More sodium methylsulfinate (80.0 mg, 0.79 mmol) was added and the flask stirred at the same temperature for another 4 h. The flask was taken of the heating and, when cooled, benzylamine (11) (0.7 mL, 6.4 mmol) was charged. Lastly, after stirring at 66 °C for 3 h 20 min, the crude was concentrated under vacuum and stored in glass vials. No evidence of sulfonamide was found.

3.4.3 Copper catalysed synthesis of methylsulfonylbenziodoxolone (10)[8]



A round-bottom flask was charged with copper(I) iodide (4.3 mg, 0.023 mmol), oxobenziodoxolyl acetate (6) (52.0 mg, 0.17 mmol), L-Proline (5.0 mg, 0.043 mmol) and sodium methylsulfinate (9) (35.9 mg, 0.35 mmol) dissolved in 1.3 mL of DMF. The flask stirred. The content of the flask was concentrated under vacuum and stored in glass vials.

The following table summarises the assays based on the previous protocol.

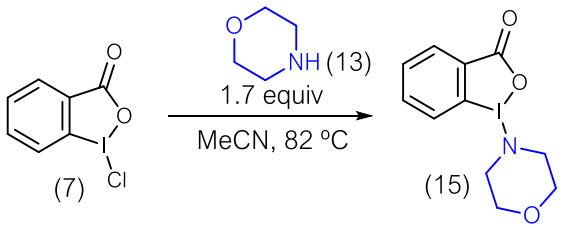
Table 3-5 – Resume of the attempts of synthesise 1-(methylsulfonyl)benziodoxolone using oxobenziodoxolyl acetate and copper catalysis

Entry	(6) (mmol)	(9) (mmol)	Temp (°C)	Time (h)	Observations
1*	0.36	0.80	rt to 80	23.5	Complex mixture at rt and 80 °C
2*	0.34	--	rt to 80	23.5	Single small spot at rt that evolved to a complex mixture
3	0.17	0.35	80	2.3	Single dragging spot
4	0.17	--	80	2.3	Complex mixture

*The first 17.5 h of this experiment were conducted at rt, the last 6 h were at 80 °C

3.5 MORPHOLINE BENZIODOXOLONE APPROACH

3.5.1 Synthesis of (morpholine)benziodoxolone (15)



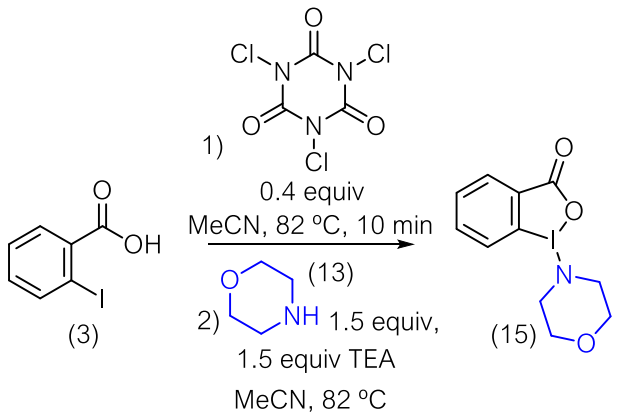
A round-bottom flask was charged with chloro benziodoxolone (7) (107 mg, 0.38 mmol) dissolved in 0.75 mL of acetonitrile. The flask stirred at 82 °C. When the chloro benziodoxolone (7) was completely dissolved, morpholine (13) (54 µL, 0.63 mmol) was charged. The flask stirred at 82 °C for 2 h. The reaction was stopped and the crude was resuspended, concentrated under vacuum and stored in glass vials. No evidence of sulfonamide was found.

The following table summarises the assays based on the previous protocol.

Table 3-6 – Resume of the attempts of synthesise (methylsulfonyl)benziodoxolone using chloro benziodoxolone

Entry	(7) (mmol)	(13) (mmol)	Time (h)	Observations
1	0.38	0.63	2	A faint spot of R_f = 0.8 and 0.3 evolved to a dragging spot
2	0.37	0.63	5.5	Dragging spot and a very faint spot of R_f = 0.9. The crude was separated using chromatographic column with hexane:ethyl acetate from 1:0 to 1:1. No compound (15) was found

3.5.2 General One-pot procedure for morpholine benziodoxolone starting in 2-iodo benzoic acid (3)



A round-bottom flask was charged with 2-iodobenzoic acid (3) (219 mg, 0.88 mmol) and 1.5 mL of acetonitrile. The mixture stirred at 82 °C for 5 min. A vail was charged with TCICA (77 mg, 0.33 mmol) dissolved in 0.5 mL of acetonitrile and slowly charged into the flask. After stirring for 10 min, the heating was stopped. When the reaction was cooled to room temperature, morpholine (13) (0.1 mL, 1.2 mmol) and triethylamine (0.2 mL, 1.4 mmol) were charged into the flask. The flask stirred at 82 °C for 1 h. The resulting mixture was filtered through cellite and concentrated under vacuum.

The following table resumes the collection of time variation assays.

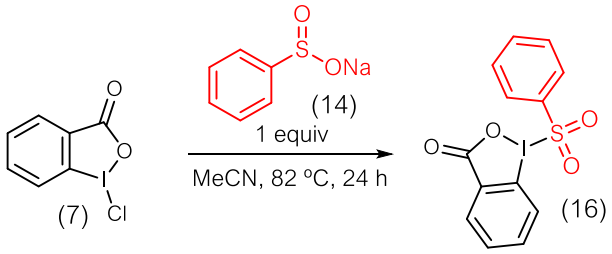
The following table summarises the assays based on the previous protocol.

Table 3-7 – Resume of the attempts of synthesise (methylsulfonyl)benziodoxolone using chloro benziodoxolone in a one-pot procedure

Entry	(3) (mmol)	TEA (mmol)	Time (h)	Observations
1	0.82	--	2.5	Single dragging spot
2	0.88	1.4	1	Single dragging spot
3	0.85	1.4	3	Complex mixture

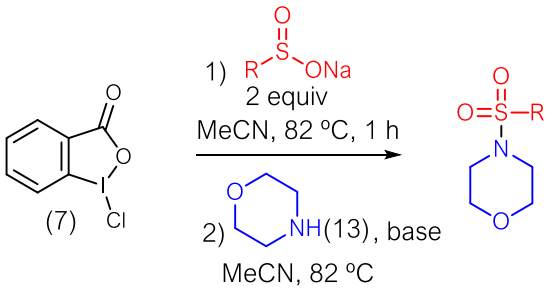
3.6 PHENYLSULFONYL BENZIODOXOLONE APPROACH

3.6.1 Synthesis of (phenylsulfonyl)benziodoxolone



A round-bottom flask was charged with chloro benziodoxolone (7) (107 mg, 0.38 mmol) and sodium phenylsulfinate (14) (66 mg, 0.40 mmol) dissolved 1 mL of acetonitrile. The reaction stirred at 82 °C for 24 h. The crude was resuspended in ethyl acetate. The mixture was washed with of water and brine. The resulting organic phase was dried with sodium sulfate, filtered and concentrated under vacuum. The crude was stored in a glass vial. No evidence of the hypervalent compound (16) was found.

3.6.2 Different approaches of sulfonylation using one-pot procedure

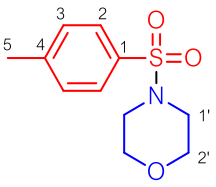


A round-bottom flask was charged with chloro benziodoxolone (7) (158 mg, 0.56 mmol) dissolved in 7.5 mL acetonitrile. The solution stirred at 82 °C for 5 min. The flask was charged with sodium 4-(methylphenyl)sulfinate (9) (175 mg, 0.98 mmol). After stirring for 1 hour, morpholine (13) (0.14 mL, 1.6 mmol) and, when used, base were charged. The reaction stirred at 82 °C for 16 h. The crude was filtered through cellite and concentrated under vacuum.

The following table summarises the assays based on the previous protocol.

Table 3-8 – Resume of the attempts of synthesise sulfonamide using chloro benziodoxolone in a one-pot procedure

Entry	(7) (mmol)	R (mmol)	(13) (mmol)	Base (mmol)	Time (h)	Observations
1	0.56	Tosyl (0.98)	1.62	--	16	Purified using a chromatographic column with hexane:ethyl acetate from 4:1 to 1:1 η= 40% (53.3 mg)
2	0.53	Methyl (0.93)	1.62	--	16	No visible nor revealed compounds
3	0.72	Methyl (1.3)	2.32	--	6.5	The morpholine was added after 9h30 min
4	0.71	Methyl (1.3)	2.32	TEA (0.72)	16	Complex mixture
5	0.72	Phenyl (1.3)	2.32	TEA (1.1)	16	Complex mixture
6	0.73	Phenyl (1.3)	1.16	KCO_3 (0.81)	16	Purified using a chromatographic column with hexane:ethyl acetate from 4:1 to 1:1 η=36% (60.3 mg)
7	0.73	Phenyl (1.1)	1.16	$CsCO_3$ (0.80)	16	TLC showed (17) in low quantity



(18)

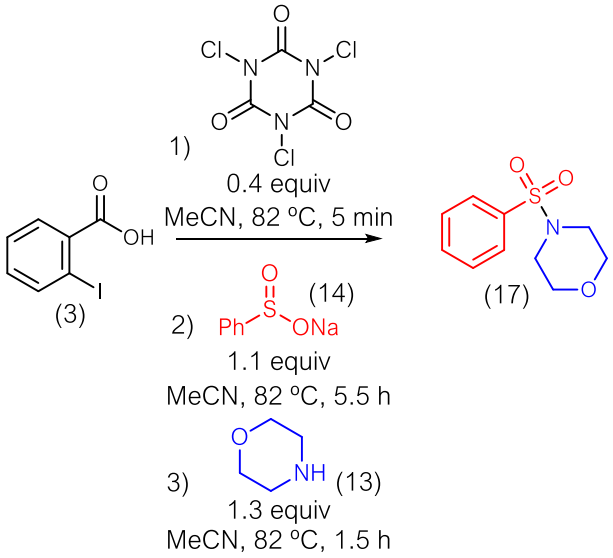
1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.2 Hz, 1H, H2), 7.37 (d, J = 7.9 Hz, 1H, H3), 3.79 – 3.74 (m, 2H, H2'), 3.03 – 2.97 (m, 2H, H1'), 2.47 (s, 3H, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1 (s, C1), 132.2 (s, C4), 129.9 (s, C3), 128.1 (s, C2), 66.3 (s, C2'), 46.0 (s, C1'), 21.70 (s, C5).

IV (KBr) ν_{max} (cm^{-1}): 3053 (w, C-H aromatics), 2974-2853 (m, C-H aliphatics), 1346 (s, S=O), 1114 (s, S=O), 1114 (s, C-O-C)

The presented spectral data is in accordance with the literature.[10]

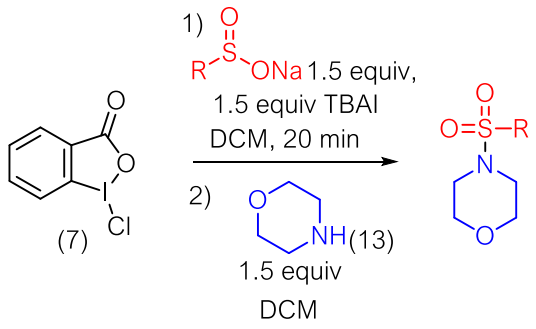
3.7 One-pot procedure from 2-iodobenzoic acid (3) to sulfonamide (17)



A round-bottom flask was charged with 2-iodobenzoic acid (3) (0.10 g, 0.40 mmol) dissolved in 0.75 mL of acetonitrile. The mixture stirred at 80 °C for 5 min. Then, TCICA (0.38 g, 0.16 mmol) dissolved in 0.2 mL of acetonitrile was slowly charged to the flask. The mixture stirred at 80 °C for another 7 min. Sodium phenylsulfinate (14) (0.10 g, 0.43 mmol) was charged to the flask. The reaction stirred at 80 °C for 5.5 h. Morpholine (13) (53 µL, 0.53 mmol) was charged to the flask. Lastly, the reaction stirred at 80 °C for 1.5 h. After cooled room temperature, the crude was filtered through a pad of cellite in a hirsch funnel and washed with ethyl acetate. The resulting solution was concentrated under vacuum and stored in a glass vial. No evidence of sulfonamide (17) was found.

3.8 TBAI-MEDIATED ASSAYS

3.8.1 TBAI-mediated sulfonylation



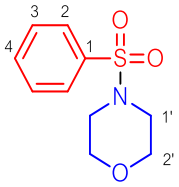
A round-bottom flask was charged with chloro benziodoxolone (7) (156 mg, 0.55 mmol), sodium camphorsulfinate (34) (191 mg, 0.80 mmol) and tetrabuthylamonium iodide (297 mg, 0.80 mmol) dissolved in 3.8 mL of dichloromethane. The reaction stirred at 40 °C for 20 min before the morpholine (13) (70 µL, 0.81 mmol) was charged. The reaction continued stirring at the same temperature for another 16 h. The solution was washed with hydrochloridric acid, water and brine solution. The resulting organic phase was evaporated and the crude purified through chromatographic column.

The following table summarises the assays based on the previous protocol.

Table 3-9 – Resume of the attempts of synthesise of 4-(methylsulfonyl)morpholine using TBAI in a one-pot procedure

Entry	(7) (mmol)	R (mmol)	Temp (°C)	Time (h)	Product (g)	η (%)	Obs
1	0.55	Camphor (0.80)	40	16	--	--	Complex mixture
2	0.74	Methyl (1.1)	40	16	--	--	Complex mixture
3	0.72	Tosyl (1.1)	40	16	--	--	Main spot of R_f = 0.66; complex mixture after work-up
4	0.71	Phenyl (1.1)	-78	3	--	--	Main spot of R_f = 0.71; Chromatographic column; No product
5*	0.73	Phenyl (1.1)	-78	2.5	(17) 0.14	(17) 82.7	No isolation process was needed

*Different work-up: washed only with water and brine.



(17)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.5 Hz, 2H, H2), 7.63 (t, *J* = 7.1 Hz, 1H, H4), 7.56 (t, *J* = 7.6 Hz, 2H, H3), 3.78 – 3.70 (m, 4H, H2'), 3.05 – 2.96 (m, 4H, H1').

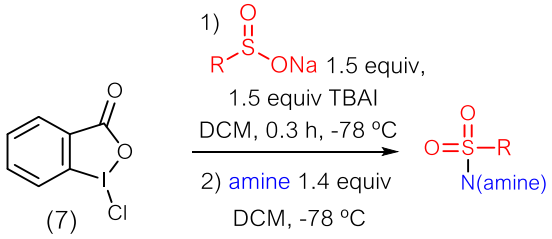
^{13}C NMR (101 MHz, $CDCl_3$) δ 135.3 (s, C1), 133.2 (s, C4), 129.3 (s, C2), 128.0 (s, C3), 66.2 (s, C2'), 46.1 (s, C1').

IV (KBr) ν_{max} (cm^{-1}): 3468 (w, N-S), 3059 (s, C-H aromatics), 2978-2853 (m, C-H aliphatics), 1348(s, S=O)

Mp: 104 – 107 °C

The presented spectral data is in accordance with the literature.[24,55]

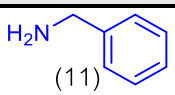
3.8.2 TBAI-mediated synthesis of different sulfonamides



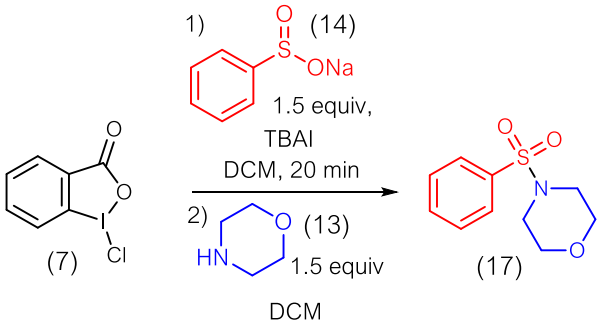
A round-bottom flask was charged with chloro benziodoxolone (7) (201 mg, 0.71 mmol), sodium phenylsulfinate (14) (178 mg, 1.1 mmol) and tetrabuthylamonium iodide (401 mg, 1.1 mmol) dissolved in 3.8 mL of dichloromethane. After the reaction stirred at -78 °C for 20 min benzylamine (11) (0.1 mL, 0.92 mmol) was charged. The reaction stirred at the same temperature for another 2 h. The solution was washed with water and brine solution. The resulting organic phase was concentrated under vacuum. The crude was purified filtering through a pad of silica.

The following table summarises the assays based on the previous protocol.

Table 3-10 – Resume of the attempts to synthesise sulfonamides using TBAI

Entry	(7) (mmol)	R (mmol)	Amine (mmol)	Time (h)	η (%)	Observations
1	0.71	Phenyl (1.1)	 (11) (0.92)	2	--	Complex mixture; no isolation
2	0.72	Methyl (1.1)	 (13) (1.2)	1	--	No product found

3.8.3 Time and stoichiometry optimization of TBAI-mediated sulfonilation



A round-bottom flask was charged with chloro benziodoxolone (7) (51.4 mg, 0.18 mmol), sodium phenylsulfinate (14) (47.2 mg, 0.29 mmol) and TBAI (32.7 mg, 89 µmol) dissolved in 1 mL of dichloromethane. The reaction stirred at -40 °C for 20 min before the amine was charged. The reaction stirred for 16 h before being quenched. The solution was washed with water and brine solution. The resulting organic phase was concentrated under vacuum. The crude was purified filtering through a pad of silica.

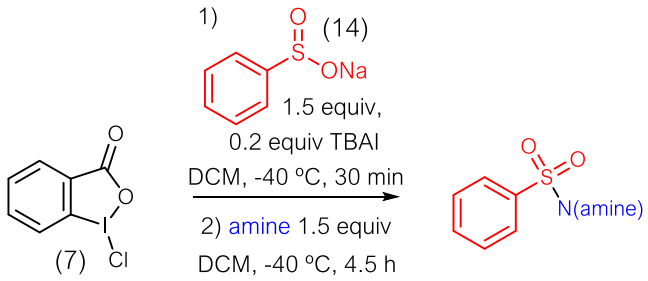
The following table summarises the assays based on the previous protocol.

Table 3-11 – Resume of the protocol's optimization

Entry	(7) (mmol)	TBAI (µmol)	Temp (°C)	Time (h)	(17) (mg)	(17) η (%)	Observations
1	0.18	89	-40	16	34.8	84.1	Pure product after work-up
2	0.18	97	0	3	--	--	No product found
3	0.18	37	-15	1.5	--	--	No product found
4	0.18	37	-40	2.5	36.5	88.0	Pure product after work-up

3.9 SCOPE OF THE REACTION

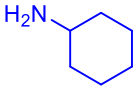
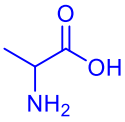
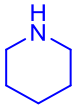
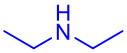
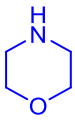
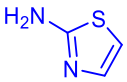
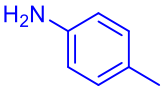
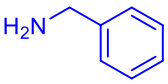
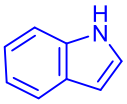
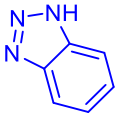
3.9.1 Different amines with sodium phenylsulfinate

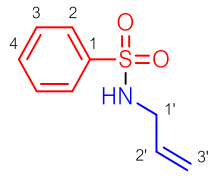


A round-bottom flask was charged with chloro benziodoxolone (7) (51.2 mg, 0.18 mmol), sodium phenylsulfinate (14) (43.7 mg, 0.27 mmol) and tetrabuthylamonium iodine (15.3 mg, 41.4 µmol) dissolved in 1 mL of dichloromethane. The reaction stirred at -40 °C for 30 min. Allylamine (21 L, 0.28 mmol) was added to the reaction. The flask stirred at -40 °C for 4.5 h. When completed, the reaction was let to warm to room temperature and washed with water and brine. The resulting organic phase was dried with sodium sulfate, filtrated and concentrated under vacuum. The crude was purified using preparative thin layer chromatography.

The following table summarises the assays with different nucleophilic amines.

Table 3-12 – Resume of the scope: different amines

Entry	Amine (mmol)	Time (h)	Product (mg)	η (%)	Observations
1	 (0.28)	4.5	(23) 5.5	(23) 15.4	Yellow oil
2	 (0.27)	3	--	--	Complex mixture
3	 (0.31)	2	(25) 16.0	(25) 37.6	Yellow oil
4	 (0.27)	2.5	--	--	Complex mixture
5	 (0.30)	2.5	(27) 27.2	(27) 67.1	Yellow solid
6	 (0.27)	2	(28) 22.5	(28) 58.8	Yellow oil
7	 (0.27)	2	(29) 27.3	(29) 72.6	Yellow solid
8	 (0.27)	2.5	(17) 35.1	(17) 83.6	White solid
9	 (0.27)	2	--	--	Complex mixture
10	 (0.25)	2.5	--	--	Complex mixture
11	 (0.32)	2.5	(20) 29.4	(20) 64.6	White solid
12	 (0.27)	2.5	--	--	Complex mixture
13	 (0.30)	16	(33) 12.5	(33) 26.4	Pale yellow solid



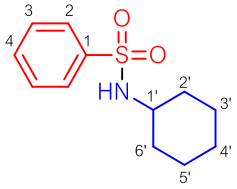
#1 (23)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.4 Hz, 2H, H2), 7.62 – 7.56 (m, 1H, H4), 7.53 (t, *J* = 7.3 Hz, 2H, H3), 5.72 (m, 1H, H2'), 5.17 (d, J = 17.2 Hz, 1H, H3'), 5.10 (d, J = 10.2 Hz, 1H, H3'), 4.48 (s, 1H, N-H), 3.62 (t, J = 5.2 Hz, 2H, H1').

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1 (s, C1), 133.1 (s, C2'), 132.9 (s, C4), 129.3 (s, C2), 127.2 (s, C3), 118.0 (s, C3'), 46.0 (s, C1').

IV (KBr) ν_{max} (cm^{-1}): 3290 (s, N-H), 3067 (s, C-H aromatics), 2923 (s, C-H aliphatics), 2854 (s, C-H aliphatics), 1646 (m, C=C), 1326 (s, S=O), 1159 (s, S=O)

The presented spectral data is in accordance with the literature. [10]



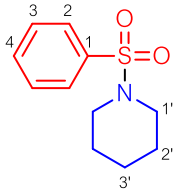
#3 (25)

^{1}H NMR (400 MHz, $CDCl_3$-d_3) δ 7.89 (d, *J* = 7.4 Hz, 2H, H2), 7.60 – 7.53 (m, 1H, H4), 7.50 (t, *J* = 7.3 Hz, 2H, H3), 4.61 (d, *J* = 6.5 Hz, 1H, N-H), 3.21 – 3.06 (m, 1H), 1.82 – 1.70 (m, 2H), 1.62 (d, *J* = 12.4 Hz, 2H), 1.49 (t, *J* = 15.9 Hz, 1H), 1.32 – 1.03 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$-d_3) δ 141.6 (s, C1), 132.5 (s, C4), 129.2 (s, C2), 127.0 (s, C3), 52.8 (s, C1'), 34.1 (s, C2' C6'), 25.3 (s, C4'), 24.7 (s, C3' and C5').

IV (KBr) ν_{max} (cm^{-1}): 3281 (s, N-H), 3065 (s, C-H aromatics), 2932-2855 (s, C-H aliphatics), 1435 (s, S-N), 1324 (s, S=O), 1161 (s, S=O)

The presented spectral data is in accordance with the literature.[24]



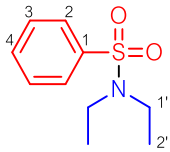
#5 (27)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.3 Hz, 2H, H2), 7.59 (t, *J* = 7.2 Hz, 1H, H4), 7.52 (t, *J* = 7.3 Hz, 2H, H3), 3.04 – 2.92 (m, 4H), 1.64 (dd, *J* = 11.0, 5.7 Hz, 4H), 1.42 (dd, *J* = 11.3, 5.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.4 (s, C1), 132.7 (s, C4), 129.0 (s, C3), 127.7 (s, C2), 47.04 (s, C1'), 25.3 (s, C2'), 23.6 (s, C3').

IV (KBr) ν_{max} (cm^{-1}): 2926 (s, C-H aliphatics), 1446 (m, S-N), 1336 (s, S=O), 1166 (s, S=O)

The presented spectral data is in accordance with the literature.[10]



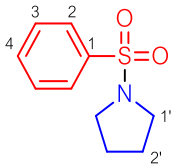
#6 (28)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.4 Hz, 2H, H2), 7.52 – 7.45 (m, 1H, H4), 7.43 (t, J = 7.3 Hz, 2H, H3), 3.18 (q, J = 7.1 Hz, 4H, H1'), 1.06 (t, J = 7.1 Hz, 6H, H2').

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.5 (s, C1), 132.3 (s, C4), 129.1 (s, C3), 127.1 (s, C2), 42.1 (s, C1'), 14.2 (s, C2').

IV (KBr) ν_{max} (cm^{-1}): 2978 (m, C-H aromatics), 2935 (m, C-H aliphatics), 1446 (s, S-N), 1332 (s, S=O), 1154 (s, S=O)

The presented spectral data is in accordance with the literature.[24]



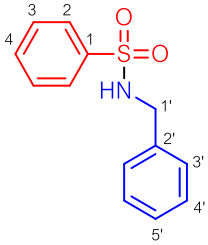
#7 (29)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.5 Hz, 2H, H2), 7.62 – 7.55 (m, 1H, H4), 7.52 (t, *J* = 7.4 Hz, 2H, H3), 3.24 (t, *J* = 6.3 Hz, 4H, H1'), 1.74 (t, *J* = 6.4 Hz, 4H, H2').

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.07 (s, C1), 132.67 (s, C4), 129.11 (s, C2), 127.59 (s, C3), 48.04 (s, C1'), 25.34 (s, C2').

IV (KBr) ν_{max} (cm^{-1}): 3064 (m, C-H aromatics), 2924 (s, C-H aliphatic), 1446 (m, S-N), 1335 (s, S=O), 1161 (s, S=O)

The presented spectral data is in accordance with the literature.[55]



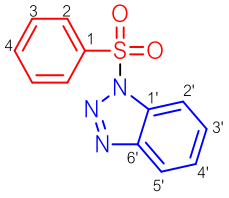
#11 (20)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.7 Hz, 2H, H2), 7.60 (t, *J* = 7.1 Hz, 1H, H4), 7.52 (t, *J* = 7.5 Hz, 2H, H3), 7.28 (d, *J* = 6.1 Hz, 3H, H3' and H5'), 7.21 (d, *J* = 6.8 Hz, 2H, H4'), 4.16 (d, *J* = 6.0 Hz, 2H, H1')

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.98 (s, C1), 136.33 (s, C2'), 132.76 (s, C4), 129.20 (s, C2), 128.73 (s, C3), 127.94 (s, C3', C5'), 127.16 (s, C4'), 47.30 (s, C1').

IV (KBr) ν_{max} (cm^{-1}): 3333 (s, N-H), 3066 (m, C-H aromatics), 2930 (s, C-H aliphatic), 1448 (m, S-N), 1326 (s, S=O), 1152 (s, S=O)

The presented spectral data is in accordance with the literature.[10]



(33)

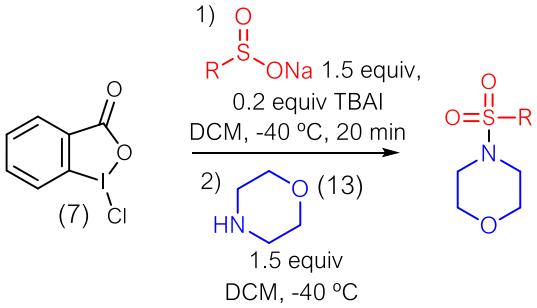
#13

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.8 Hz, 3H, H2 and H2'), 8.08 (d, *J* = 8.4 Hz, 1H, H4), 7.66 (dd, *J* = 14.0, 7.1 Hz, 2H, H3), 7.51 (m, *J* = 20.7, 7.6 Hz, 3H, H3', H4' and H5').

IV (KBr) ν_{max} (cm^{-1}): 3079 (m, C-H aromatics), 1448 (m, S-N), 1326 (s, S=O), 1152 (s, S=O)

The presented spectral data is in accordance with the literature.[56]

3.9.2 Scope of sodium salts – reaction with morpholine



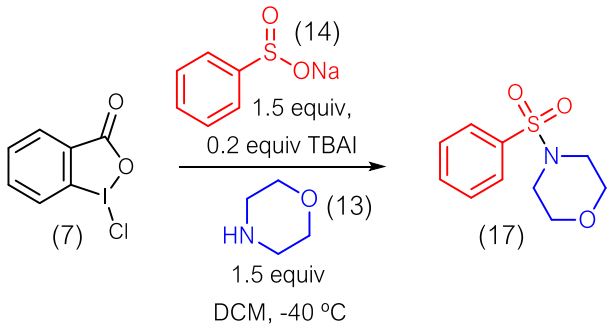
A round-bottom flask was charged with chloro benziodoxolone (36.9 mg, 0.13 mmol), sodium 4-methylbenzenesulfinate (33.4 mg, 0.19 mmol) and tetrabuthylamonium iodine (9.39 mg, 25.4 µmol) dissolved in 1 mL of dichloromethane. The reaction stirred at -40 °C for 30 min. Morpholine (17 µL, 197 µmol) was added. The reaction stirred at -40 °C for 1 hour. When completed, the reaction was let to heat until room temperature and washed with water and brine. The organic phase was dried with sodium sulfate, filtrated and concentrated under vacuum. The crude was purified using preparative thin layer chromatography.

The following table summarises the assays with different sulfinic salts.

Table 3-13 – Resume of the scope: different sodium sulfinic acid salts

Entry	(7) (mmol)	R (mmol)	Product (mg)	η (%)	Observations
1	0.13	Tosyl (0.19)	(18) 12.1	(18) 38.4	Single TLC spot
2	0.18	Camphor (0.28)	--	--	Complex mixture
3	0.18	Methyl (0.28)	--	--	Faint spot R_f = 0.87, no spots revieled

3.9.3 Cascade approach

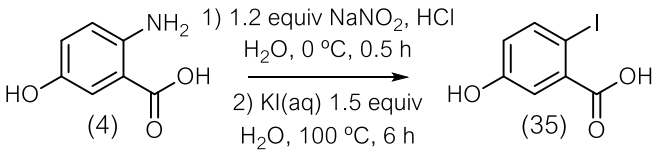


A round-bottom flask was charged with chloro benziodoxolone (7) (53.8 mg, 0.19 mmol), sodium phenylsulfinate (14) (46.8 mg, 0.29 mmol), TBAI (16.0 mg, 0.043 mmol) and morpholine (13) (23 µL, 0.27 mmol) dissolved in 1 mL of dichloromethane. The reaction stirred at -40 °C for 1 h. The crude was washed with water and brine solution. The solution was filtered through a pad of silica. 37.2 mg of the sulfonamide (17) was obtained as a white solid with 85.9% yield.

3.10 POLYMER-SUPPORTED APPROACH

3.10.1 Synthesis of intermediates (5) and (35)

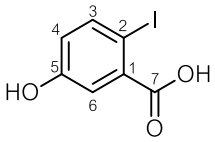
3.10.1.1 Synthesis of 5-hydroxy-2-iodobenzoic acid (35)[46,47]



A round-bottom flask was charged with sodium nitrite (550 mg, 7.97 mmol). Concentrated hydrochloric acid (5 mL, 61.95 mmol) and a solution of 2-amin-5-hydroxybenzoic acid (4) (1.00 g, 6.53 mmol) in 10 mL of water were slowly added while the flask stirred at 0 °C. The reaction stirred at 0 °C for 30 min. A solution of potassium iodide (1.65 g, 9.96 mmol) in 2.5 mL of water was slowly added to the reaction. The flask stirred at 100 °C for 6 h. The crude was extracted with ethyl acetate and the combining organic phases were washed with water and thiosulfate, dried with sodium sulfate, filtered and concentrated under vacuum. The following table summarises the assays based on the previous protocol.

Table 3-14 – Resume of the synthesis of 5-hydroxy-2-iodobenzoic acid

Entry	(4) (mmol)	Time (h)	(35) (g)	(35) η (%)	Observations
1	6.5	6	--	--	No product was found
2	6.6	2	1.6	90.3	There was not a 30min stirring period and the reagents were added sequentially.

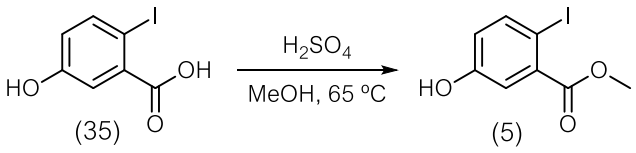


(35)

^{1}H NMR (400 MHz, MeOD) δ 7.73 (d, *J* = 8.6 Hz, 1H, H3), 7.23 (d, *J* = 2.9 Hz, 1H, H6), 6.68 (dd, *J* = 8.6, 2.9 Hz, 1H, H4).

The presented spectral data is in accordance with the literature.[46]

3.10.1.2 Synthesis of methyl 5-hydroxy-2-iodobenzoate (35)[47,46]

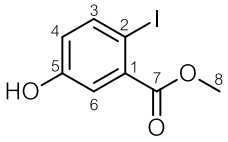


A round-bottom flask was charged with 5-hydroxy-2-iodobenzoic (5) (3.6 mg ,13.5 mmol) dissolved in 64 mL of methanol. While the flask stirred, hydrosulfuric acid (0.5 mL, 9.4 mmol) was added drop by drop. The reaction stirred at 65 °C. The crude was concentrated under vacuum and extracted with ethyl acetate. The resulting organic phases were washed with brine solution, dried with sodium sulfate, filtered and evaporated under vacuum.

The following table summarises the assays based on the previous protocol.

Table 3-15 – Resume of the synthesis methyl 5-hydroxu-2-iodobenzoate

Entry	(5) (mmol)	Time (h)	(35) (g)	(35) η (%)	Observations
1	13.5	41	--	--	Posterior finding of poorly synthesised 5-hydroxy-2-iodobenzoic
2	5.9	18	1.5	93.0	No complications



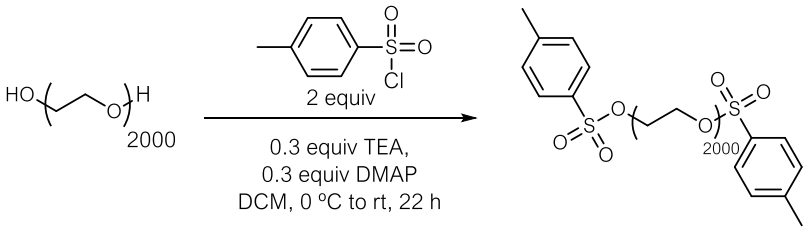
(35)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.6 Hz, 1H, H3), 7.32 (d, *J* = 2.7 Hz, 1H, H6), 6.72 (dd, *J* = 8.5, 2.7 Hz, 1H, H4), 3.91 (s, 3H, H8).

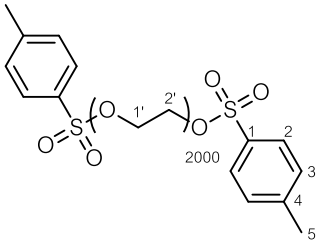
IV (KBr) ν_{max} (cm^{-1}): 3330 (b, OH), 1713 (s, C=O), 1293 (s, C-O)

The presented spectral data is in accordance with the literature.[57]

3.10.1.3 Synthesis of PEG-(OTs)[58]

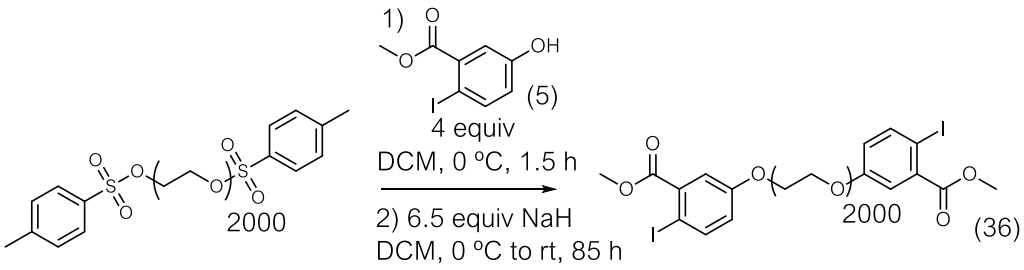


A round-bottom flask was charged with PEG-(OH) (3.11 g, 1.59 mmol). The vessel was evacuated under vacuum, filled with nitrogen, and charged with 30 mL of dichloromethane and dry triethylamine (650 µL, 46.7 µmol). While the flask stirred in a bath of ice, tosyl chloride (582.4 mg, 3.07 mmol) and DMAP (59.3 mg, 0.49 mmol) were added through a nitrogen flow. The reaction stirred for 22 h while slowly warmed to room temperature. The crude was washed with ammonium chloride, water and BRINE. The resulting organic phase was dried with sodium sulfate, filtered and concentrated under vacuum. The tosilated PEG was precipitated using ethyl ether. 2.75 g were obtained as a white solid with 78.9 % yield.

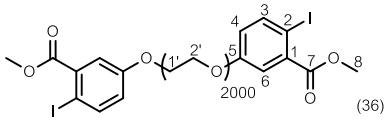


^{1}H NMR (400 MHz, $CDCl_3$-d_3) δ 7.79 (d, *J* = 8.1 Hz, 2H, H3), 7.33 (d, *J* = 8.0 Hz, 2H, H2), 2.44 (s, 3H, H5).

3.10.2 Synthesis of 5-hydroxy-2-iodobenzoate coupled to PEG



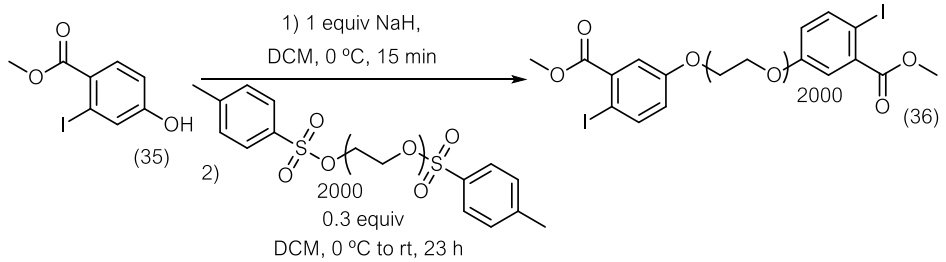
A round-bottom flask was charged with PEG-(OTs) (220.4 mg, 97.4 µmol) and 5-hydroxy-2-iodobenzoate (108.3 mg, 390 mmol) and evacuated under vacuum and filled with nitrogen. The flask was then charged with 0.4 mL of dichloromethane. The reaction stirred at 0 °C for 1.5 h. Then, NaH (15.6 mg, 650 mmol) was added in three portions, 5 min apart. After stirring at room temperature for 24 h, 5 mL of dichloromethane were charged. The reaction was let to stir over weekend. The crude was washed with water, sodium carbonate saturated solution and BRINE solution. After drying the organic phase with sodium sulfate and filtering it, the crude was concentrated under vacuum and the product precipitated with ethyl ether. 139 mg of the product were obtained as a white solid with 50.7% yield.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.7 Hz, 1H, C3-H), 7.37 (d, *J* = 2.6 Hz, 1H, C6-H), 6.81 – 6.74 (m, 1H, C4-H), 3.92 (s, 3H, C8-H_3).

IV (KBr) ν_{max} (cm^{-1}): 3436 (b, O-H), 2872 (s, C-H aliphatics), 1731 (w, C=O), 1296 (m, C-O ester), 1106 (s, C-O ether)

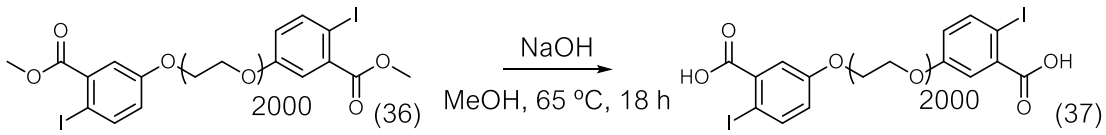
3.10.2.1 Synthesis of 5-hydroxy-2-iodobenzoate coupled to PEG (different order of addition of the reagents)



A round-bottom flask was charged with methyl 5-hydroxy-2-iodobenzoate (474 mg, 1.7 mmol) and sodium hydride (41 mg, 1.7 mmol). The flask was evacuated under vacuum, filled with nitrogen, placed in an ice bath and charged with 1 mL of dichloromethane. A vial was charged with PEG-(OTS) (1.0 g, 0.46 mmol). The vial was evacuated under vacuum, filled with nitrogen and charged with 1 mL of dichloromethane. The

PEG-(OTs) solution was added to the flask. The reaction stirred at 0 °C to room temperature for 23 h. The crude was washed with water, sodium carbonate and brine. The resulting aqueous phase was extracted with dichloromethane. The combined organic phase was dried with sodium sulfate, filtered and concentrated under vacuum. The product was precipitated with ethyl ether. The reaction wasn't complete. 649 mg of the product were obtained as a white solid with 57.5% yield.

3.10.2.2 Synthesis of 5-hydroxy-2-iodobenzoic acid coupled to PEG

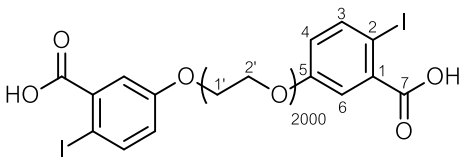


A round-bottom flask was charged with PEG-(5-hydroxy-2-iodobenzoate) (137 mg, 49 µmol) and 0.5 mL of sodium hydroxide 1M dissolved in methanol. The reaction stirred at 65 °C. The crude was extracted with dichloromethane. The organic phase was dried with sodium sulfate, filtrated and concentrated under vacuum. The product was precipitated with ethyl ether.

The following table summarises the assays based on the previous protocol.

Table 3-16 – Resume of the coupling of 5-hydroxy-2-iodobenzoic acid to PEG

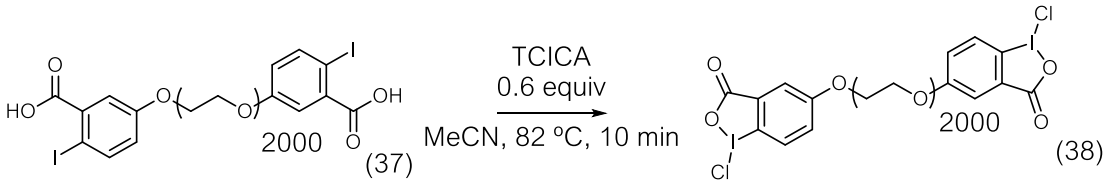
Entry	(36) (µmol)	Time (h)	Product (g)	η (%)	Observations
1	49.4	18.5	0.14	63.6	The reaction was neutralized with hydrochloric acid
2	262	1	0.65	69.6	The reaction was acidified with 5.4 mL of hydrochloric acid 1M



(37)

^{1}H NMR (400 MHz, $CDCl_3$-d_3) δ 7.74 (s, 1H, H3), 7.44 (s, 1H, H6), 6.66 (s, 1H, H4).

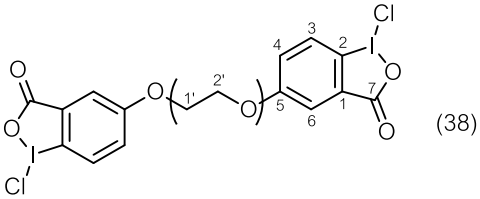
3.10.3 Synthesis of PEG-(chloro 5-hydroxy-benziodoxolone)



A round-bottom flask was charged with PEG-(5-hydroxy-2-iodobenzoic acid) (37) (73.4 mg, 27.5 µmol) dissolved in 0.4 mL acetonitrile. The reaction stirred at 82 °C until fully dissolution. Then, a solution of TCICA (4.76 mg, 18.3 µmol) in 0.1mL acetonitrile was slowly added to the flask. The reaction continued stirring for 10 min. The resulting crude was filtered through a pad of cellite while hot and washed with hot acetonitrile. The product was precipitated with ethyl ether. A white solid was obtained with 35.6% yield.
The following table summarises the assays based on the previous protocol.

Table 3-17 – Resume of the synthesis of PEG-(chloro 5-hydroxy-benziodoxolone)

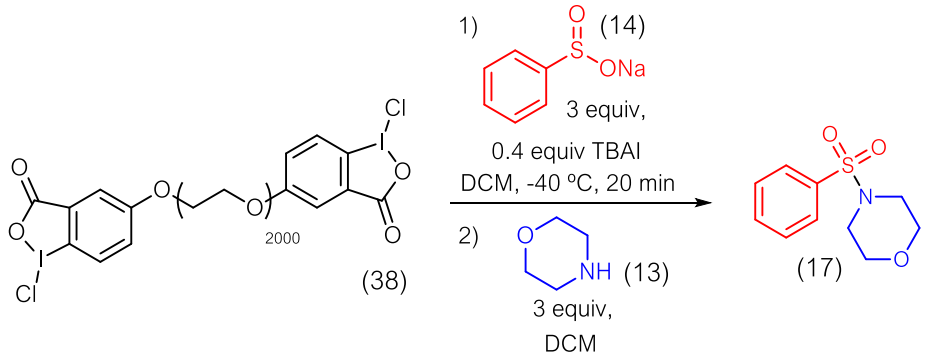
Entry	(37) (µmol)	Product (mg)	η (%)	Observations
1	27.5	24.6	35.6	Difficult filtration
2	149	223	59.4	Cold DCM was used in the filtering process
3	61.6	121	77.9	Cold DCM was used in the filtering process



^{1}H NMR (400 MHz, $CDCl_3$-d_3) δ 7.83 (d, *J* = 8.6 Hz, 1H, H3), 7.56 (s, 1H, H6), 6.78 (d, *J* = 8.7 Hz, 1H, H4).

IV (KBr) ν_{max} (cm^{-1}): 2882 (s, C-H aliphatics), 1727 (m, C=O), 1114 (s, C-O ether)

3.10.4 Synthesis of 4-(phenylsulfonyl)morpholine using PEG coupled reagent



A round-bottom flask was charged with PEG-(chloro 5-hydrhydroxybenziodoxolone) (24.6 mg, 9.78 µmol), TBAI (0.7 mg, 5.5 µmol) and sodium phenylsulfinate (5.04 mg, 30.7 µmol) dissolved in 0.05mL of dichloromethane. The reaction stirred at -78 °C for 20 min. Morpholine (3 µL, 34.8 µmol) was added. The reaction stirred at -78 °C to rt for 21 h. The crude was washed with water and brine solution. The organic phase was dried under sodium sulfate, filtered and concentrated under vacuum.

The following table summarises the assays based on the previous protocol.

Table 3-18 – Resume of the polymer-supported sulfonilation assays

Entry	(38) (µmol)	Time (h)	(17) (mg)	(17) (%)	(37) (mg)	(37) (%)	Observations
1	9.78	21	--	--	--	--	No sulfonamide produced
2	88.8	0.67*	7.8	38.8	151	69.6	Precipitated with ethyl ether and filtered to remove polymer (37). The supernatant was filtered through a pad of silica.
3	48.0	0.67*	6.1	56.0**	2.5	2.13	The crude was filtered through a pad of silica to remove sulfonamide (17) (SA) and washed with DCM to remove polymer (37) (PEG)

*0.67 h ~ 40 min

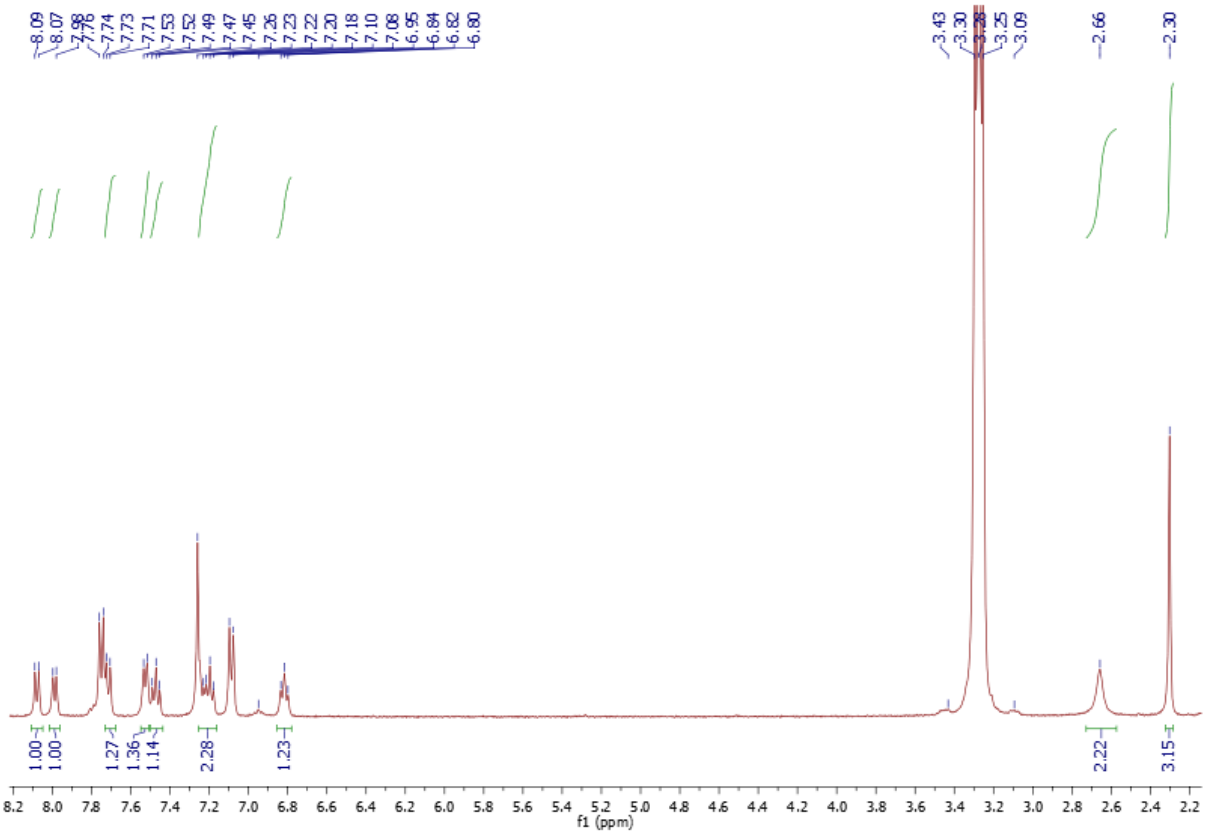
** the NMR analysis showed the presence of compound (37)

BIBLIOGRAPHY

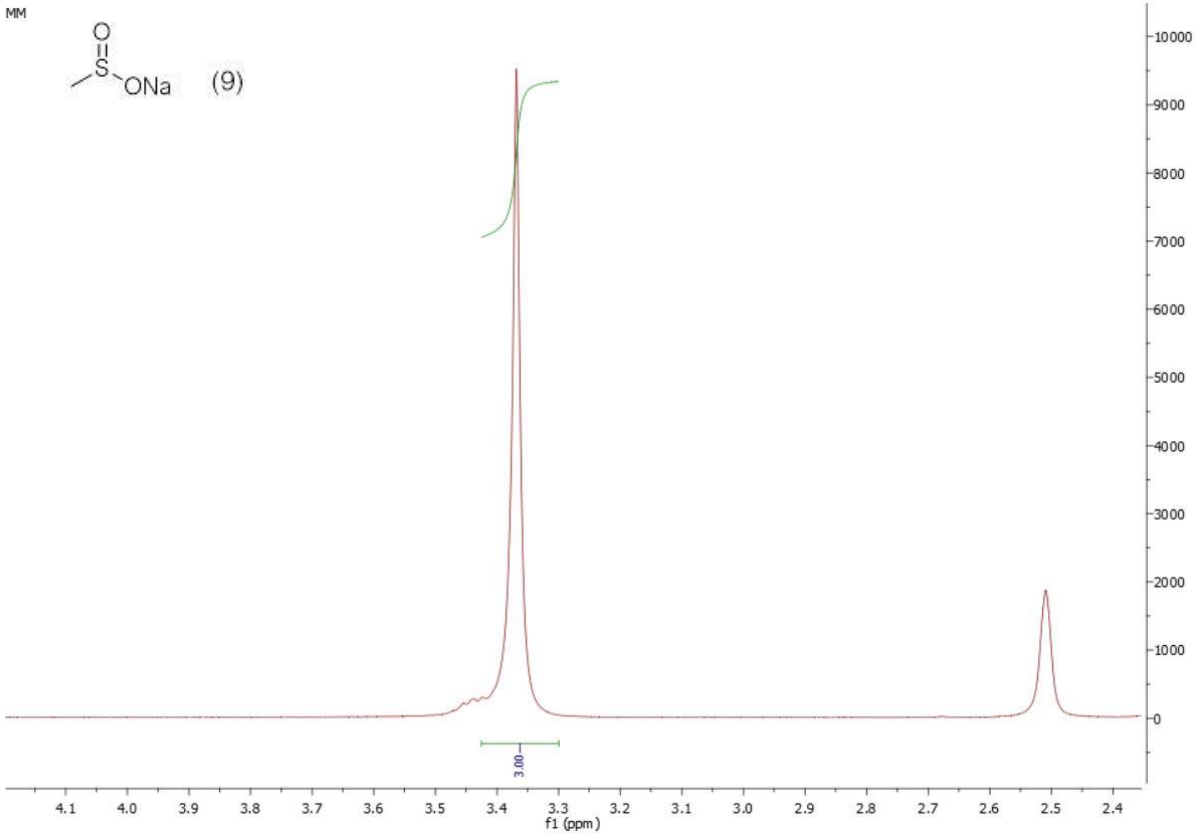
1. Greenwood, N. N.; Earnshaw, A. *Chemistry of the elements*, 2nd ed.; Butterworth-Heinemann: Oxford, 1997.
2. Deeming, A. S.; Emmett, E. J.; Richards-Taylor, C. S.; Willis, M. C. *Synthesis-Stuttgart* **2014,** *46*, 2701-2710.
3. Emmett, E. J.; Willis, M. C. *Asian Journal of Organic Chemistry* **2015,** *4*, 602-611.
4. Yang, K.; Ke, M. L.; Lin, Y. G.; Song, Q. L. *Green Chemistry* **2015,** *17*, 1395-1399.
5. Rad, M. N. S.; Khalafi-Nezhad, A.; Asrari, Z.; Behrouz, S.; Amini, Z.; Behrouz, M. *Synthesis-Stuttgart* **2009**, 3983-3988.
6. Pan, X. J.; Gao, J.; Liu, J.; Lai, J. Y.; Jiang, H. F.; Yuan, G. Q. *Green Chemistry* **2015,** *17*, 1400-1403.
7. Zhu, M. H.; Wei, W.; Yang, D. S.; Cui, H. H.; Wang, L. L.; Meng, G. Q.; Wang, H. *Organic & Biomolecular Chemistry* **2017,** *15*, 4789-4793.
8. Zhu, W.; Ma, D. W. *Journal of Organic Chemistry* **2005,** *70*, 2696-2700.
9. Sridhar, R.; Srinivas, B.; Kumar, V. P.; Narender, M.; Rao, K. R. *Advanced Synthesis & Catalysis* **2007,** *349*, 1873-1876.
10. De Luca, L.; Giacomelli, G. *Journal of Organic Chemistry* **2008,** *73*, 3967-3969.
11. Yotphan, S.; Sumunnee, L.; Beukeaw, D.; Buathongjan, C.; Reutrakul, V. *Organic & Biomolecular Chemistry* **2016,** *14*, 590-597.
12. Zhao, J. W.; Xu, J. X.; Chen, J. X.; Wang, X. Q.; He, M. H. *Rsc Advances* **2014,** *4*, 64698-64701.
13. Moon, S. Y.; Kim, W. S. *Abstracts of Papers of the American Chemical Society* **2014,** *248*, 1.
14. Leontiev, A. V.; Dias, H. V. R.; Rudkevich, D. M. *Chemical Communications* **2006**, 2887-2889.
15. Zheng, D.; Wu, J. In *Sulfur Dioxide Insertion Reactions for Organic Synthesis*; Springer Singapore, 2017; pp. 7 - 9.
16. Kaneko, C.; Hayashi, R.; Fujii, H.; Yamamoto, A. *Chemical & Pharmaceutical Bulletin* **1978,** *26*, 3582-3584.
17. Hogan, P. J.; Cox, B. G. *Organic Process Research & Development* **2009,** *13*, 875-879.
18. Santos, P. S.; Mello, M. T. S. *Journal of Molecular Structure* **1988,** *178*, 121-133.
19. Nguyen, B.; Emmett, E. J.; Willis, M. C. *Journal of the American Chemical Society* **2010,** *132*, 16372-16373.
20. Chen, C. C.; Waser, J. *Organic Letters* **2015,** *17*, 736-739.
21. Deeming, A. S.; Russell, C. J.; Willis, M. C. *Angewandte Chemie-International Edition* **2015,** *54*, 1168-1171.
22. Emmett, E. J.; Richards-Taylor, C. S.; Nguyen, B.; Garcia-Rubia, A.; Hayter, B. R.; Willis, M. C. *Organic & Biomolecular Chemistry* **2012,** *10*, 4007-4014.
23. Wang, X. B.; Xue, L. J.; Wang, Z. Y. *Organic Letters* **2014,** *16*, 4056-4058.
24. Wei, W.; Liu, C. L.; Yang, D. S.; Wen, J. W.; You, J. M.; Wang, H. *Advanced Synthesis & Catalysis* **2015,** *357*, 987-992.
25. Stang, P. J.; Zhdankin, V. V. *Chemical Reviews* **1996,** *96*, 1123-1178.
26. Yusubov, M. S.; Zhdankin, V. V. *Current Organic Synthesis* **2012,** *9*, 247-272.
27. Yoshimura, A.; Yusubov, M. S.; Zhdankin, V. V. *Organic & Biomolecular Chemistry* **2016,** *14*, 4771-4781.
28. Zhdankin, V. V. *Current Organic Synthesis* **2005,** *2*, 121-145.
29. Beringer, F. M.; Lillien, I. *Journal of the American Chemical Society* **1960,** *82*, 725-731.
30. Boucher, M.; Macikenas, D.; Ren, T.; Protasiewicz, J. D. *Journal of the American Chemical Society* **1997,** *119*, 9366-9376.
31. Amey, R. L.; Martin, J. C. *Journal of Organic Chemistry* **1979,** *44*, 1779-1784.
32. Li, Y. F.; Hari, D. P.; Vita, M. V.; Waser, J. *Angewandte Chemie-International Edition* **2016,** *55*, 4436-4454.
33. Waser, J. *Topics in current chemistry* **2016,** *373*, 187-222.
34. Shinomoto, Y.; Yoshimura, A.; Shimizu, H.; Yarnazaki, M.; Zhdankin, V. V.; Saito, A. *Organic Letters* **2015,** *17*, 5212-5215.

35. Zoller, T.; Breuilles, P.; Uguen, D.; De Cian, A.; Fischer, J. *Tetrahedron Letters* **1999,** *40*, 6253-6256.
36. Dess, D. B.; Martin, J. C. *Journal of the American Chemical Society* **1991,** *113*, 7277-7287.
37. Charpentier, J.; Fruh, N.; Togni, A. *Chemical Reviews* **2015,** *115*, 650-682.
38. Matousek, V.; Pietrasiak, E.; Schwenk, R.; Togni, A. *Journal of Organic Chemistry* **2013,** *78*, 6763-6768.
39. Koller, R.; Huchet, Q.; Battaglia, P.; Welch, J. M.; Togni, A. *Chemical Communications* **2009**, 5993-5995.
40. Sorg, G.; Mengel, A.; Jung, G.; Rademann, J. *Angewandte Chemie-International Edition* **2001,** *40*, 4395-+.
41. Ley, S. V.; Thomas, A. W.; Finch, H. *Journal of the Chemical Society-Perkin Transactions 1* **1999**, 669-671.
42. Togo, H.; Sakuratani, K. *Synlett* **2002**, 1966-1975.
43. Egami, H.; Yoneda, T.; Uku, M.; Ide, T.; Kawato, Y.; Hamashima, Y. *Journal of Organic Chemistry* **2016,** *81*, 4020-4030.
44. Pires, M. J. D.; Purificacao, S. I.; Santos, A. S.; Marques, M. M. B. *Synthesis-Stuttgart* **2017,** *49*, 2337-2350.
45. Carvalho, L. C. R.; Pires, M. J. D.; Fernandes, E.; Marques, M. M. B. *Rsc Advances* **2013,** *3*, 25711-25715.
46. Murata, C.; Ogura, T.; Narita, S.; Kondo, A. P.; Iwasaki, N.; Saito, T.; Usuki, T. *Bioorganic & Medicinal Chemistry Letters* **2016,** *26*, 1428-1433.
47. Koguchi, S.; Mihoya, A.; Mimura, M. *Tetrahedron* **2016,** *72*, 7633-7637.
48. Eckschlager, K. *Chemicke Listy* **1967,** *61*, 272-+.
49. Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J. *Organic Letters* **2013,** *15*, 112-115.
50. Iinuma, M.; Moriyama, K.; Togo, H. *Synlett* **2012**, 2663-2666.
51. Lacour, J.; Monchaud, D.; Mareda, J.; Favarger, F.; Bernardinelli, G. *Helvetica Chimica Acta* **2003,** *86*, 65-81.
52. : Spectral Database for Organic Compounds.
53. Kargina, O. I.; Gornostaev, L. M.; Nefedov, A. A. *Russian Journal of Organic Chemistry* **2013,** *49*, 70-77.
54. Zhou, G.; Ting, P.; Aslanian, R.; Piwinski, J. J. *Organic Letters* **2008,** *10*, 2517-2520.
55. Shyam, P. K.; Jang, H. Y. *Journal of Organic Chemistry* **2017,** *82*, 1761-1767.
56. Singh, D.; Silakari, O. *European Journal of Medicinal Chemistry* **2017,** *126*, 183-189.
57. Ueberschaar, N.; Heine, D.; Hertweck, C. *Synlett* **2016,** *27*, 1794-1797.
58. Ma, Y. Z.; Chen, B. Z.; He, N.; Chen, G. J.; Li, L. W.; Wu, C. *Macromolecular Bioscience* **2014,** *14*, 1807-1815.

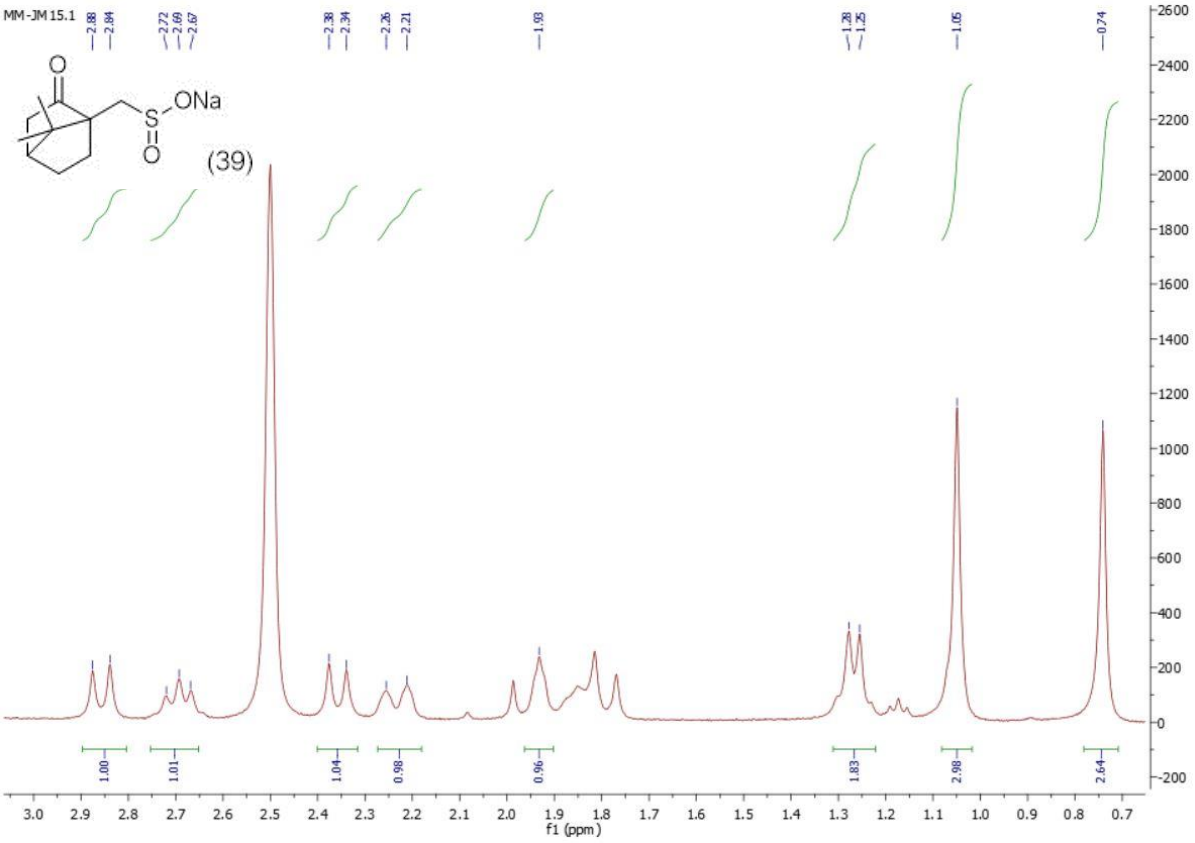
4 APPENDIX



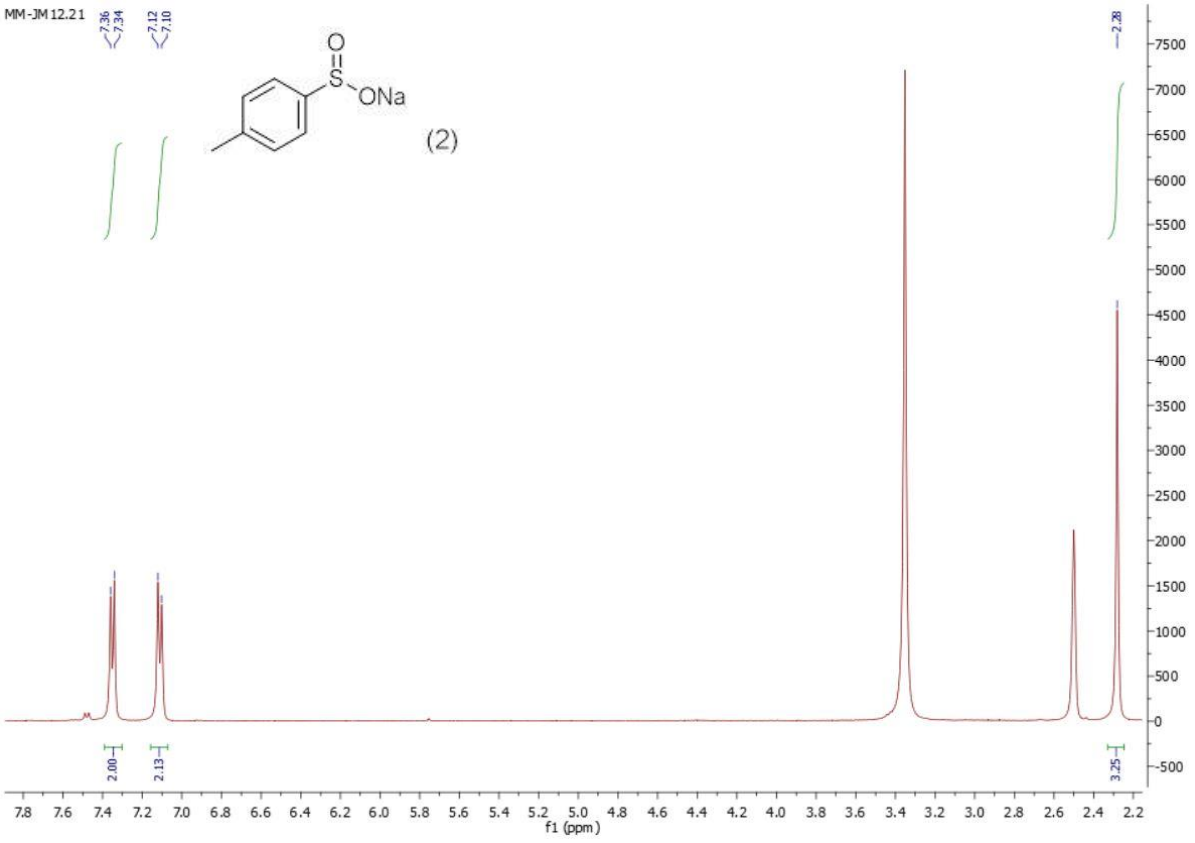
Spectrum 4-1 – ^{1}H NMR sample spectrum of kinetic experience



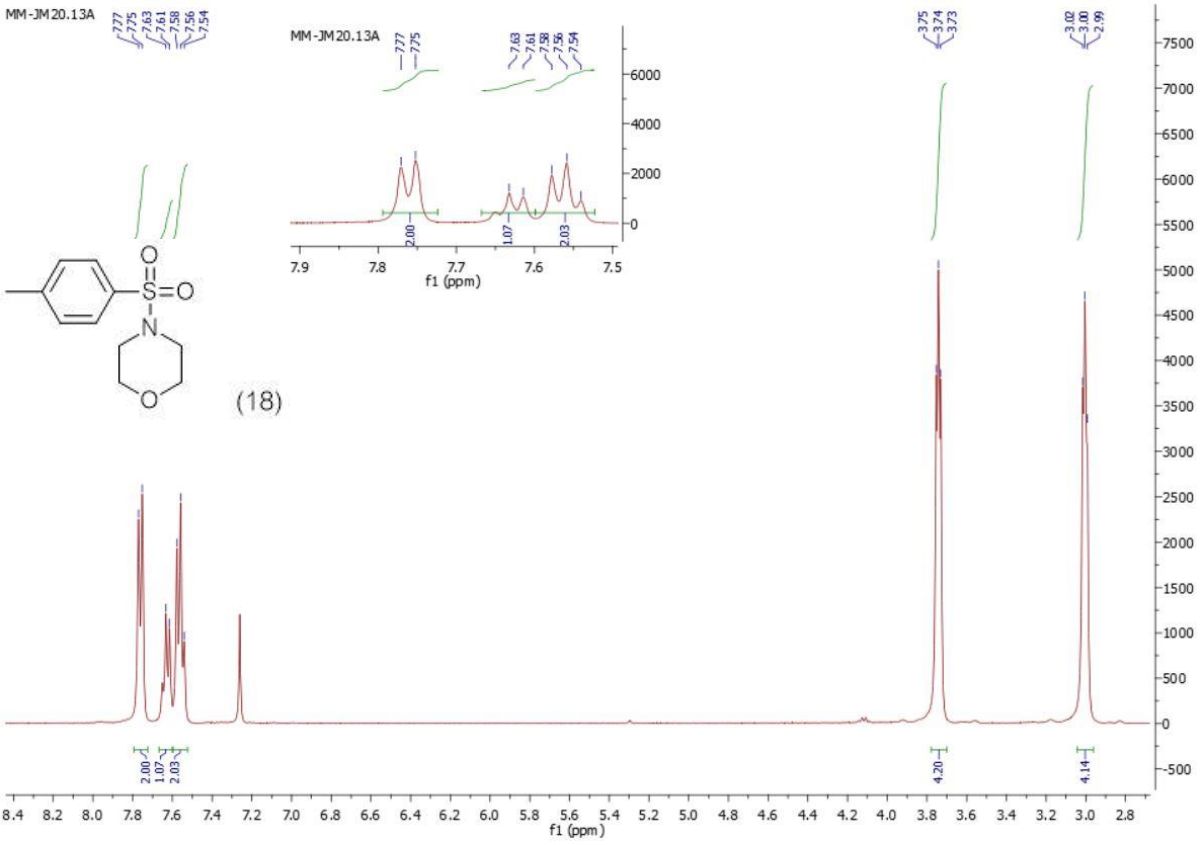
Spectrum 4-2 – ^{1}H NMR spectrum of sodium methylsulfinate



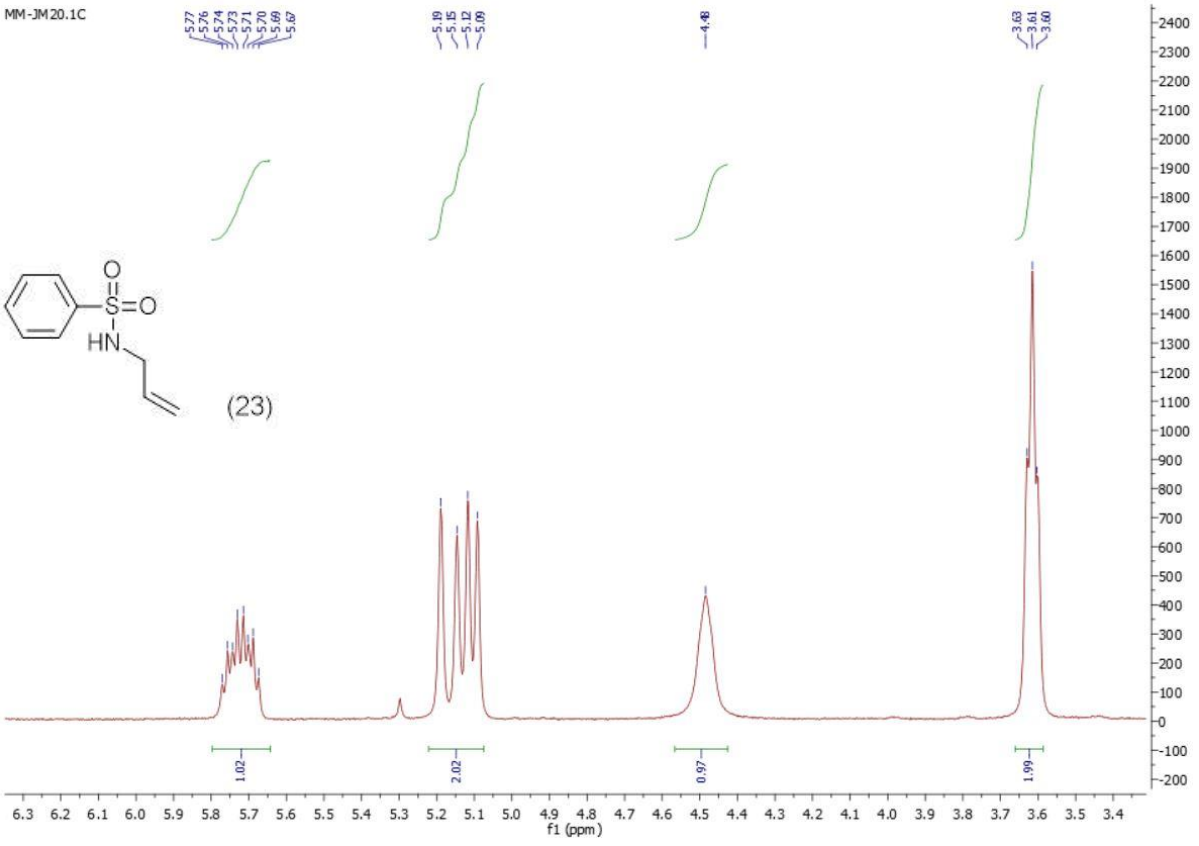
Spectrum 4-3 – ^{1}H NMR spectrum of sodium canphorsulfinate



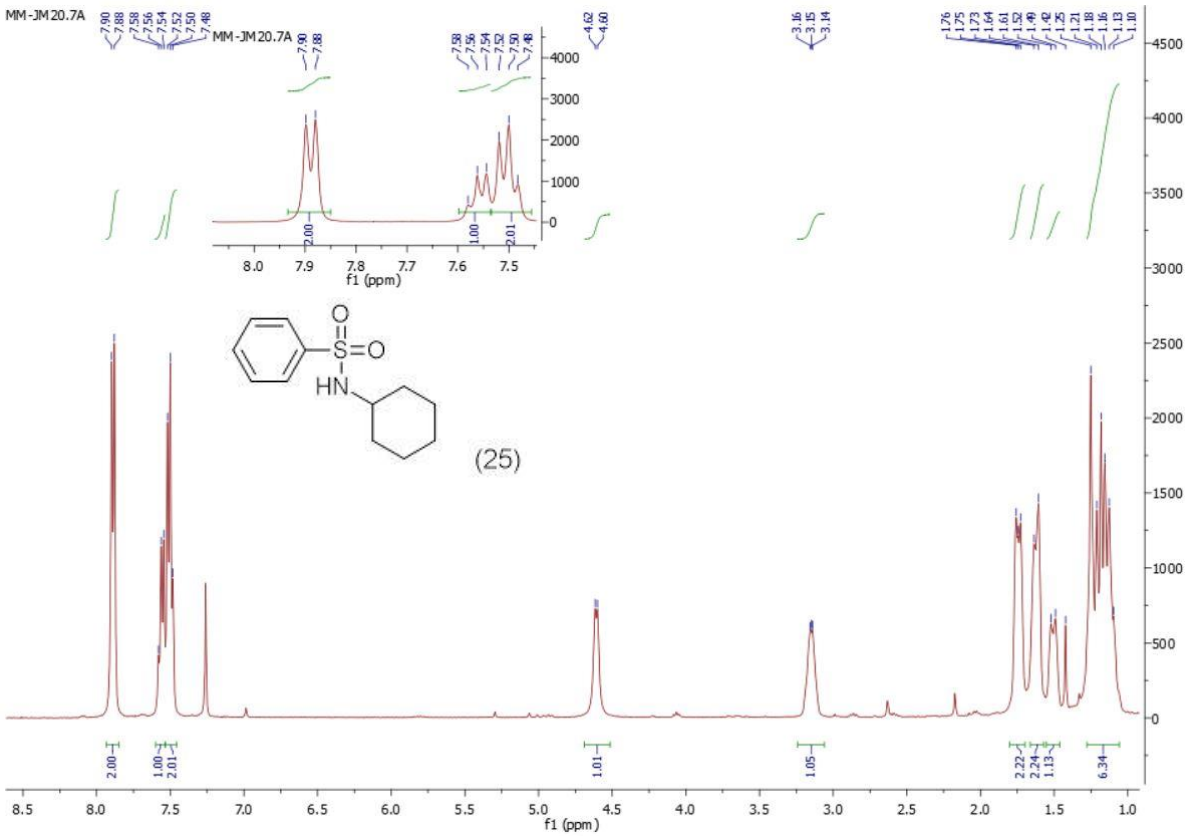
Spectrum 4-4 – ^{1}H NMR spectrum of sodium tosylsulfinate



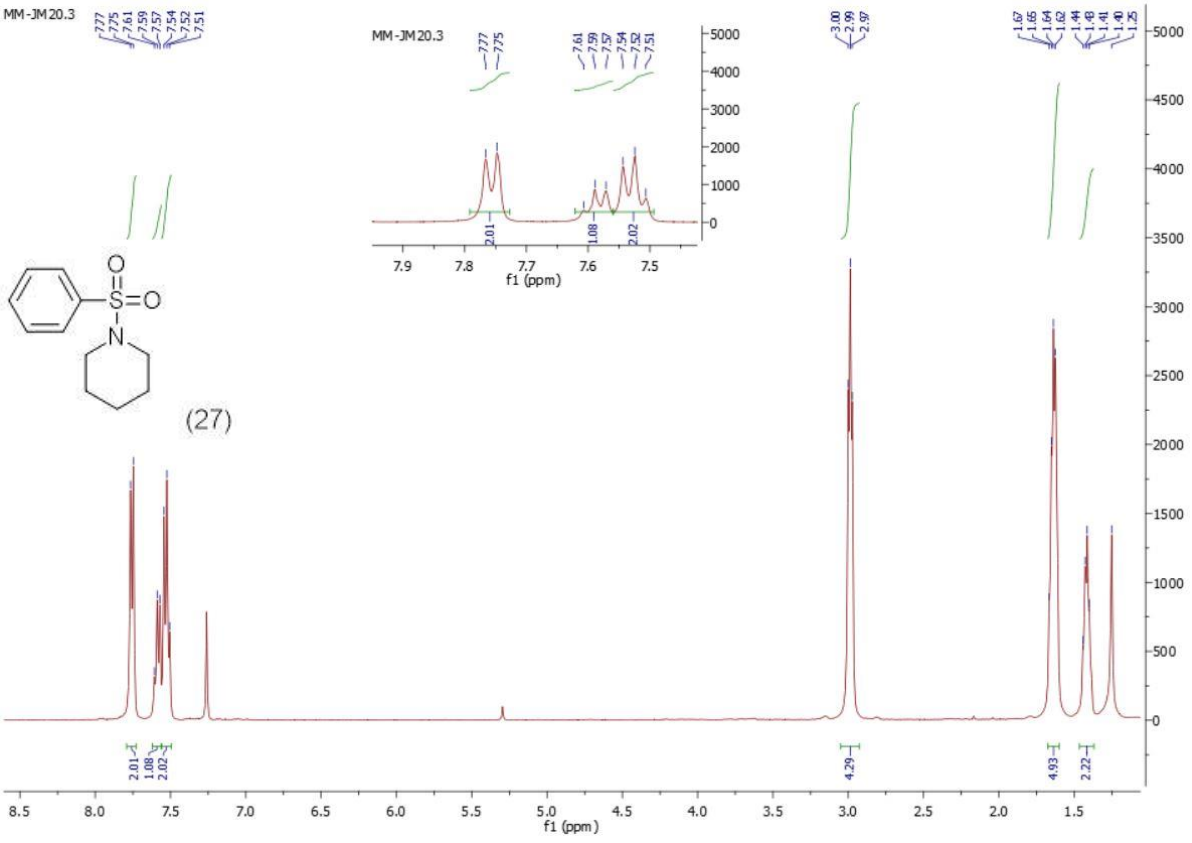
Spectrum 4-5 – ^{1}H NMR spectrum of (phenylsulfonyl)morpholine



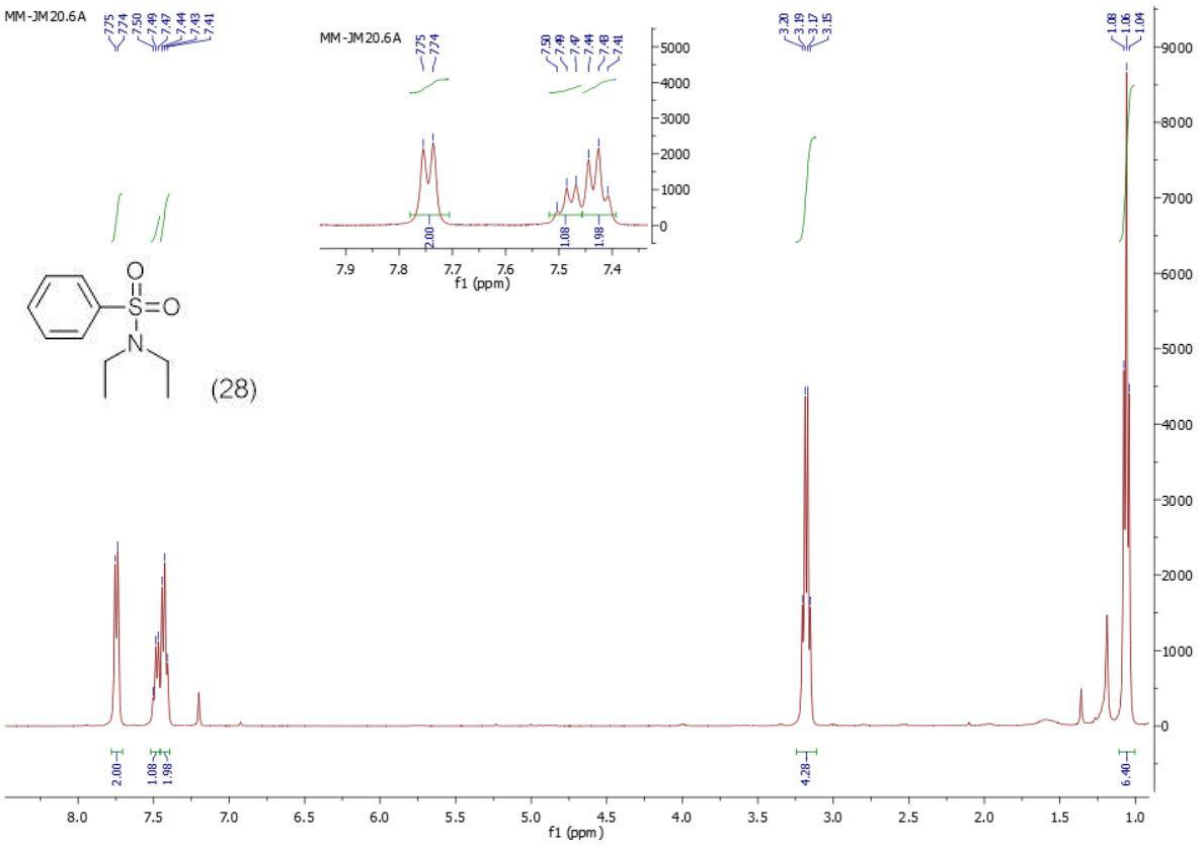
Spectrum 4-6 – ^{1}H NMR spectrum of *N*-allylbenzenesulfonamide



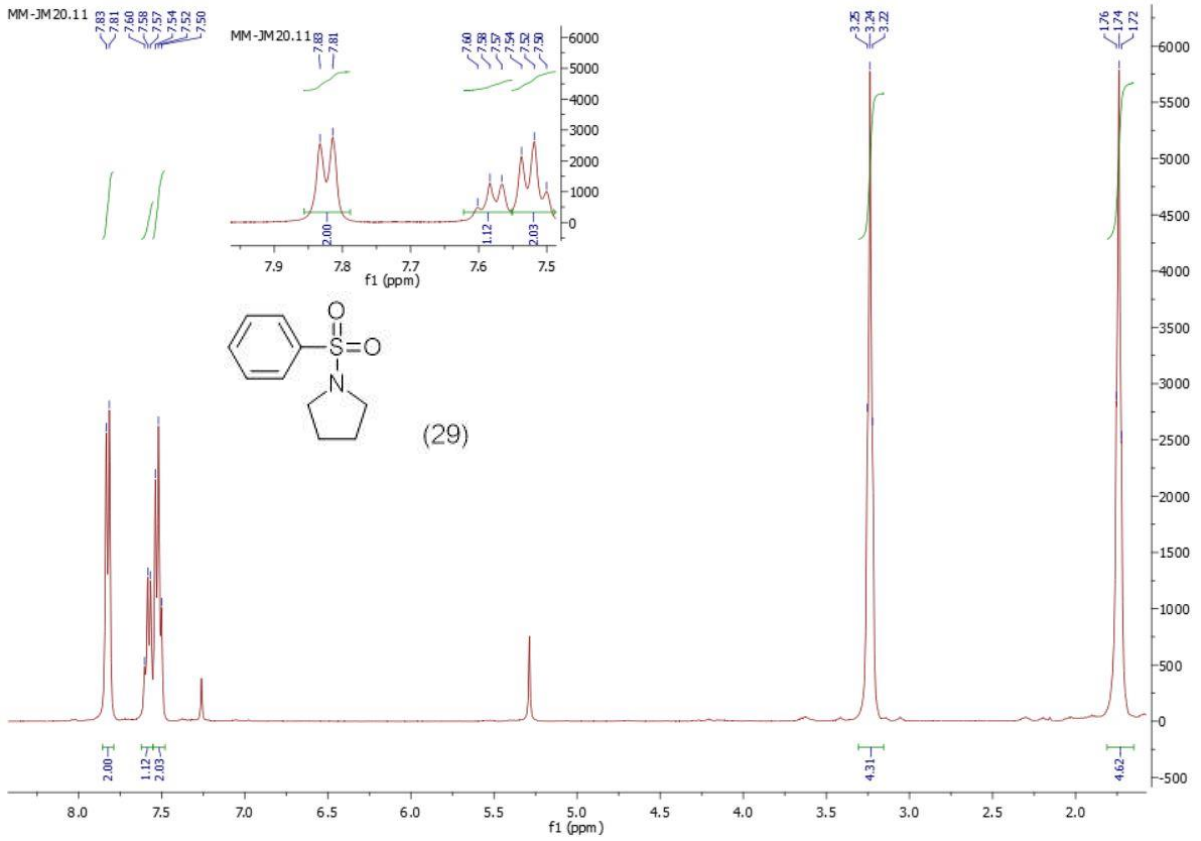
Spectrum 4-7 – ^{1}H NMR spectrum of *N*-cyclohexylbenzenesulfonamide



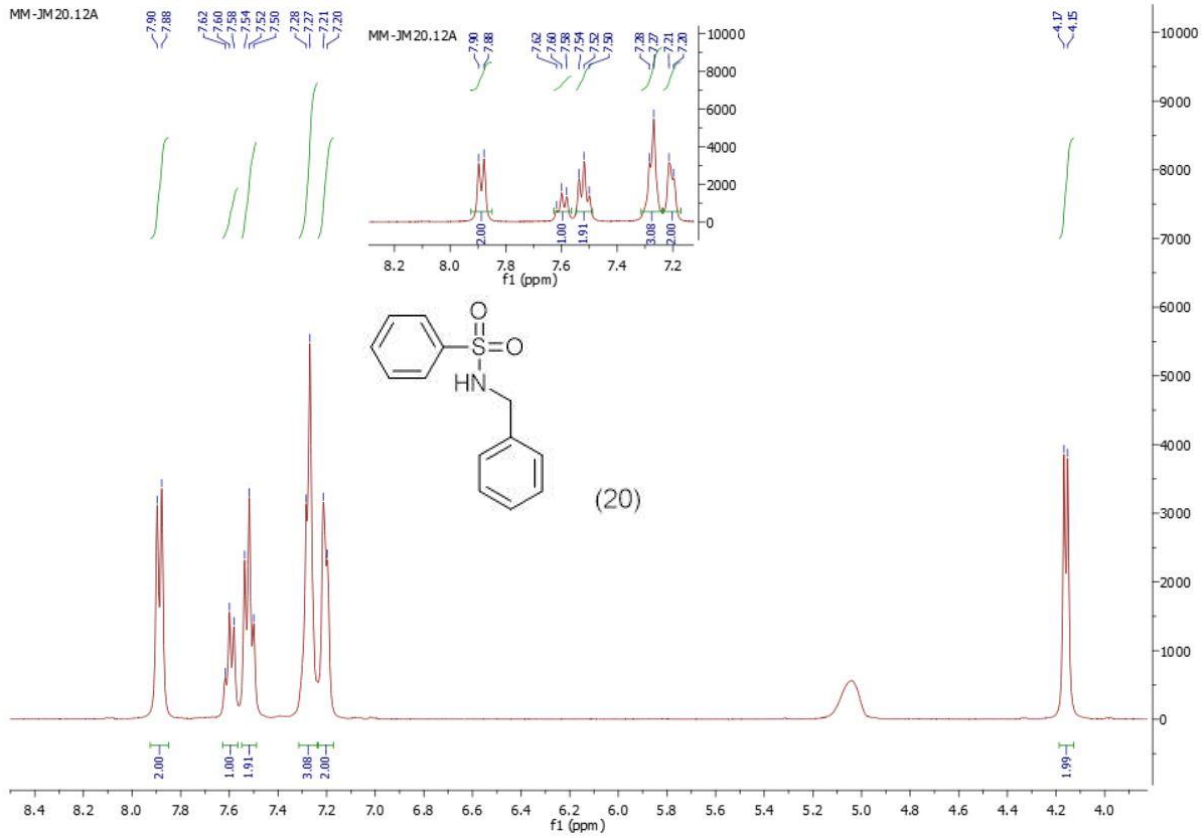
Spectrum 4-8 – ^{1}H NMR spectrum of (phenylsulfonyl)piperidine



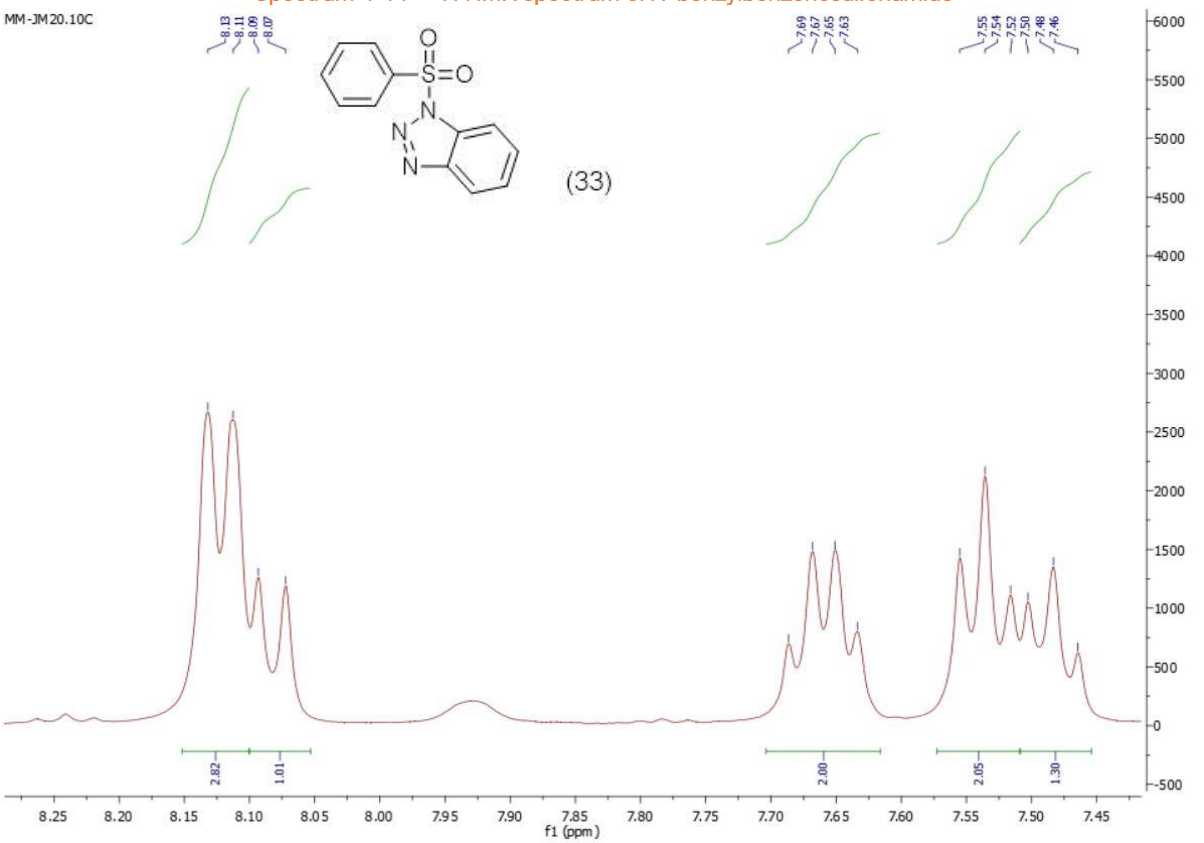
Spectrum 4-9 – ^{1}H NMR spectrum of *N*,*N*-diethylbenzenesulfonamide



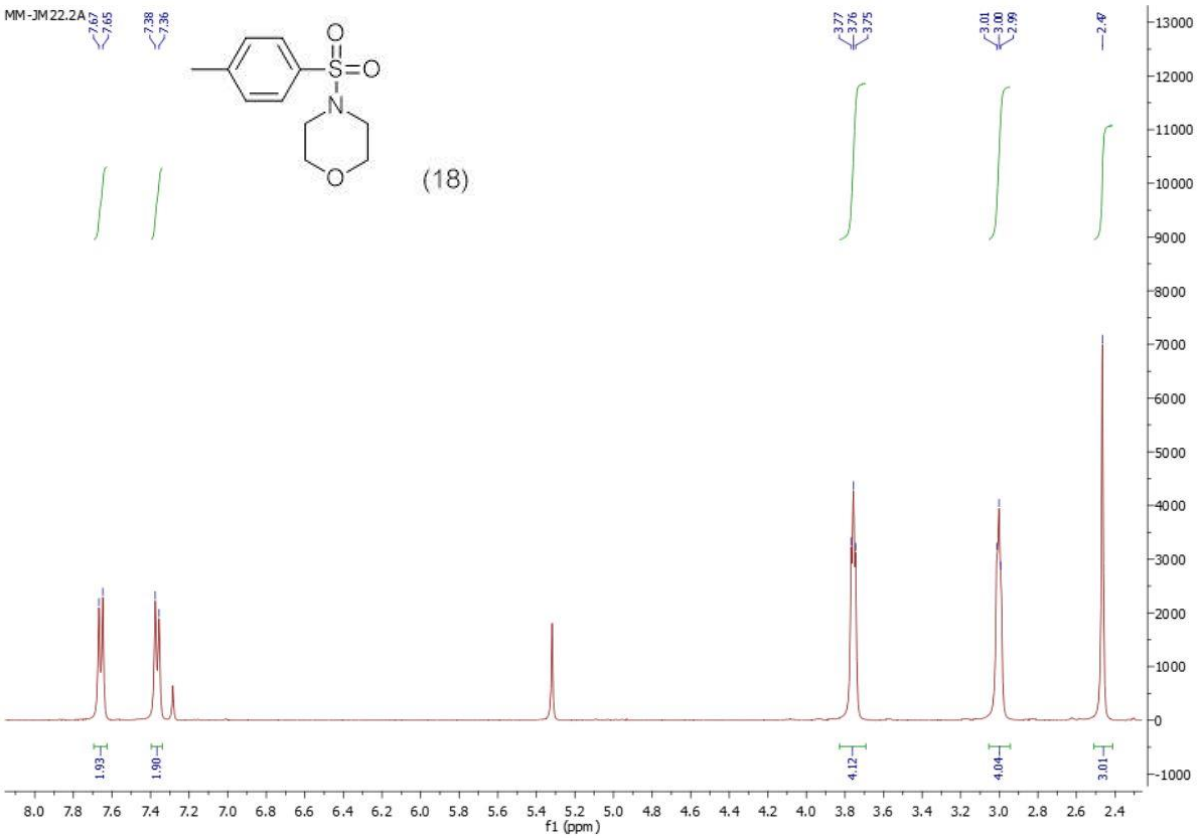
Spectrum 4-10 – ^{1}H NMR spectrum of (phenylsulfonyl)pyrrolidine



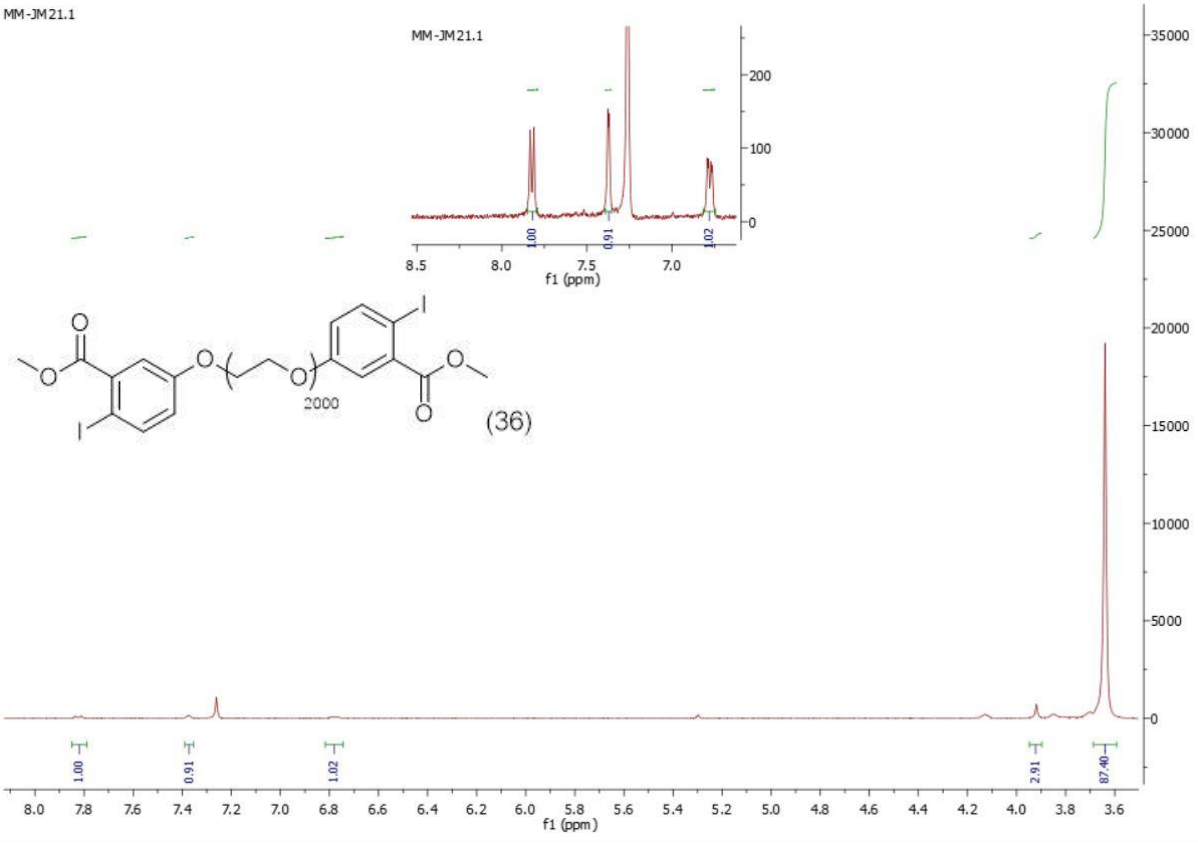
Spectrum 4-11 – ^{1}H NMR spectrum of *N*-benzylbenzenesulfonamide



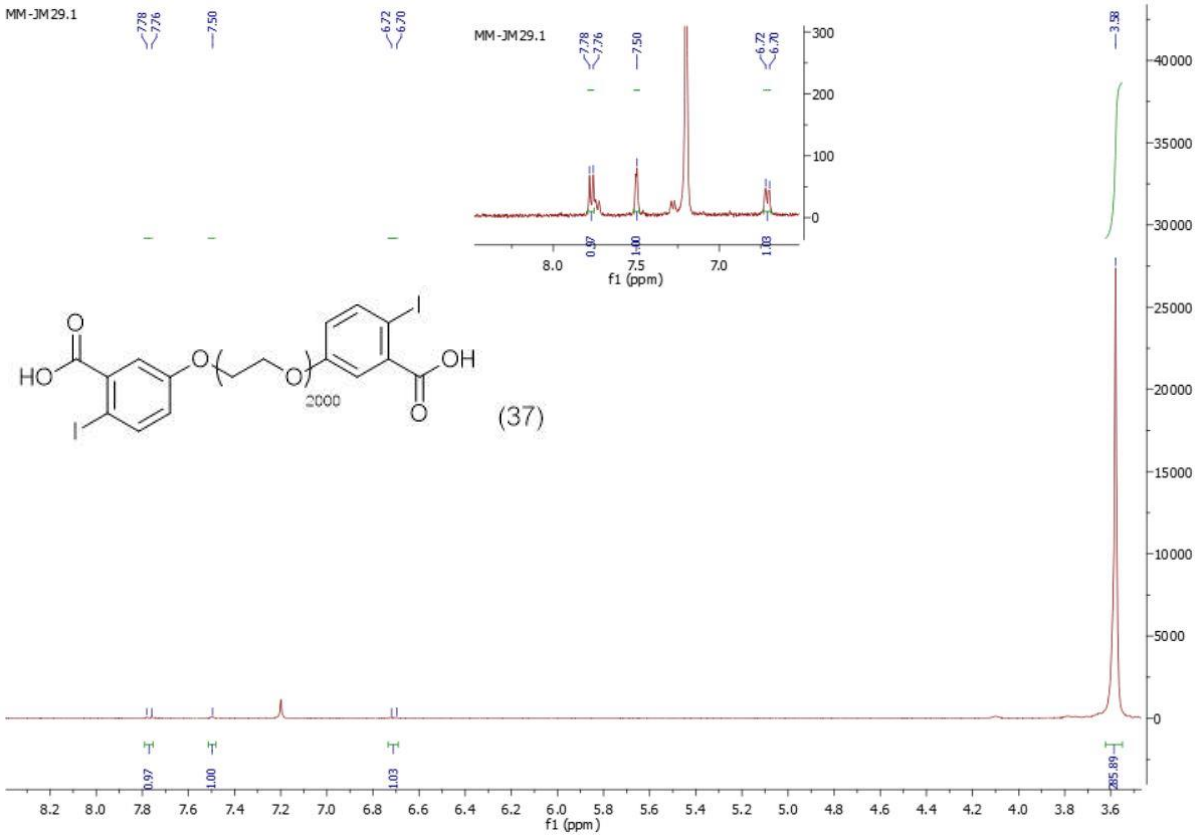
Spectrum 4-12 – ^{1}H NMR spectrum of (phenylsulfonyl)benzotriazole



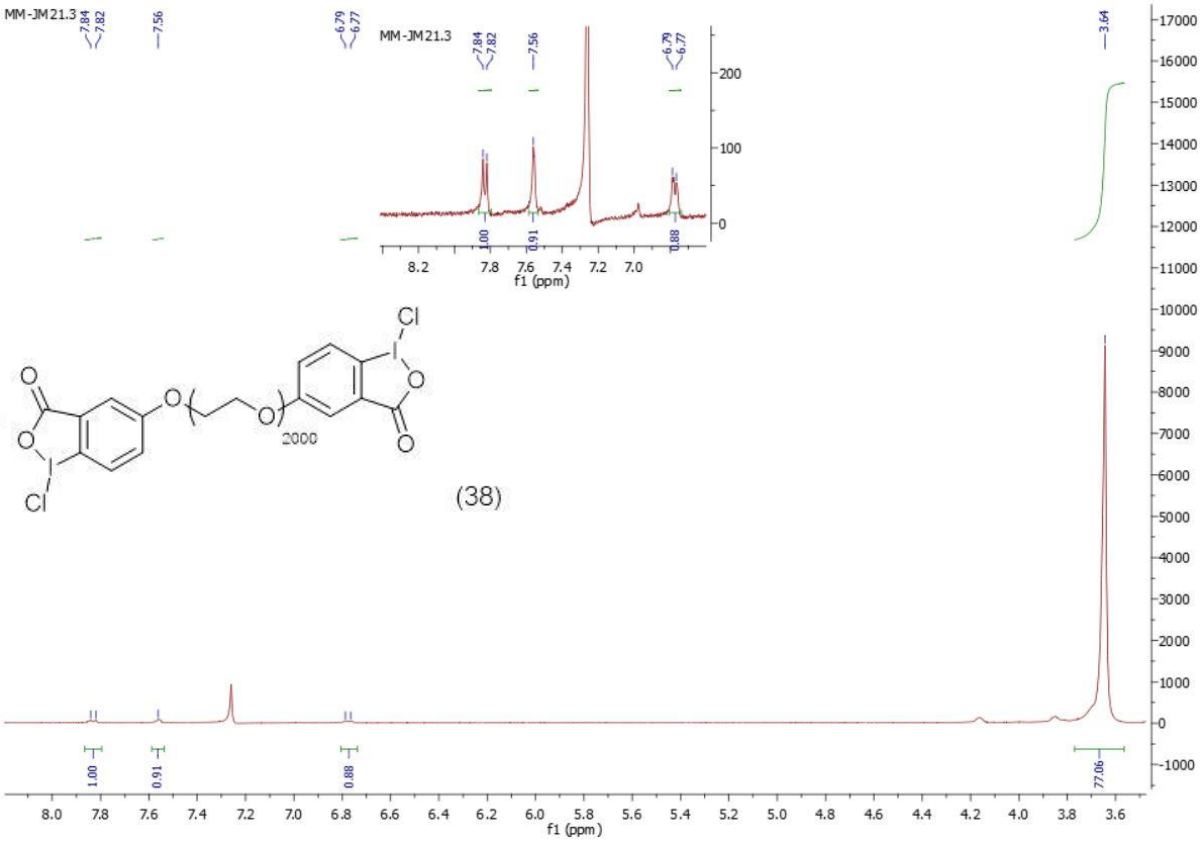
Spectrum 4-13 – ^{1}H NMR spectrum of 4-tosylmorpholine



Spectrum 4-14 – ^{1}H NMR spectrum of pegylated methyl 5-ethoxy-2-iodobenzoate



Spectrum 4-15 – ^{1}H NMR spectrum of pegylated 5-ethoxy-2-iodobenzoic acid



Spectrum 4-16 – ^{1}H NMR spectrum of pegylated chloro benziodoxolone