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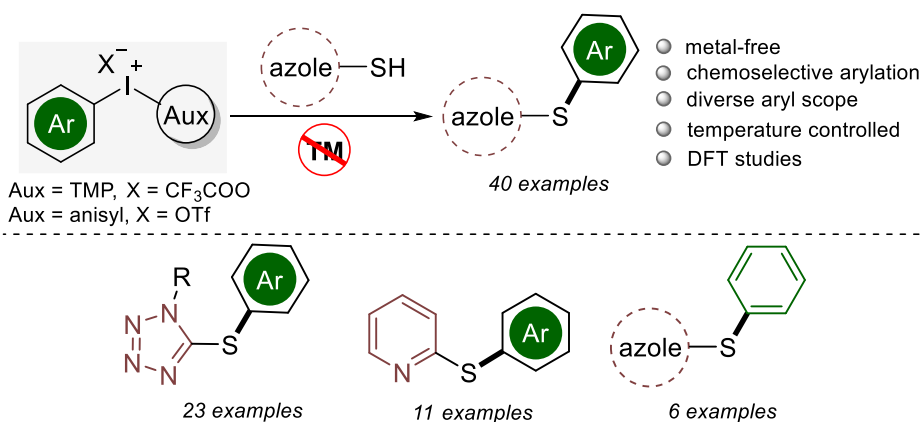
Metal-free *S*-arylation of 5-mercaptotetrazoles and 2-mercaptopyridine with unsymmetrical diaryliodonium salts†

Raktim Abha Saikia,^a Nitumoni Hazarika,^b Nishant Biswakarma,^a
Ramesh Chandra Deka^{id}^a and Ashim Jyoti Thakur^{id}^{*a}

Chapter 3

Metal-Free *S*-arylation of mercaptoazoles

Abstract: This chapter demonstrates the application of unsymmetrical iodonium salts towards *S*-arylation of heterocyclic thiols (especially tetrazole-5-thiols and pyridine-2-thiol) under metal-free condition, affording a diverse range of di(hetero)aryl thioethers in moderate to good yields. Detailed study on the effects of counter-anions and auxiliary of iodonium salts are accomplished. Suitable auxiliary selection of the unsymmetrical iodonium salt offers flexibility for wide range of aryl moieties and its incorporation into *S*-arylation. The DFT study supports the experimental observations of chemoselective arylation.



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3.1 Introduction

3.1.1 Importance of diaryl thioethers or di(hetero)aryl thioethers

S-arylation of aryl or heterocyclic thiols and subsequently, the architecture of privileged diaryl or di(hetero)aryl thioethers **1** have emerged as an important aspect in organic chemistry. These thioethers **2-7** are widely known for their applications in medicinal chemistry (Figure 3.1) [1–2] and design of organic materials [3–4]. Functionalized thioether motifs containing “tetrazole” and “pyridine” ring have exhibited remarkable biological properties [5–6] and have been explored for their utilities in agriculture [7–8], material sciences [9], and inorganic chemistry [10–11].

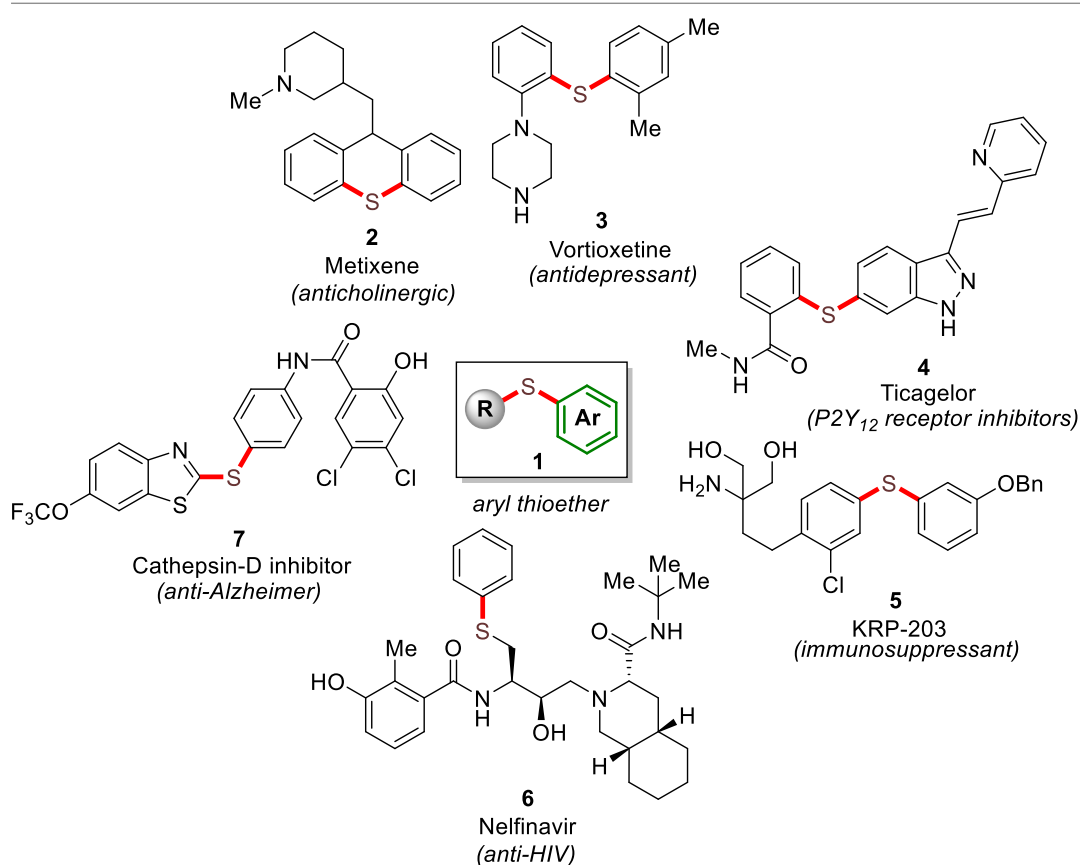


Figure 3.1 Pharmaceutically relevant *S*-arylated thioether scaffolds

Among the subclasses of substituted tetrazole-5-thiols, 1-alkyl-5-alkylthiotetrazoles **8** have been explicitly studied for their potential anti-viral and anti-inflammatory properties (Figure 3.2) [12]. On the other hand, 1-aryl-5-aryl-thiotetrazole **9** has been reported to act as activating agent in RNA synthesis [13]. *S*-arylated compound possessing 3-mercaptopyridine **10** has been reported to be a nicotinic acetylcholine receptor ligand (NARL) [14]. However, it is also to be taken into consideration that

though several methods have been reported to access these pharmaceutically relevant scaffolds, developing a reliable method for *S*-arylation of these heteroaryl thiols is still a challenge for the synthetic community, keeping in mind the diversification required.

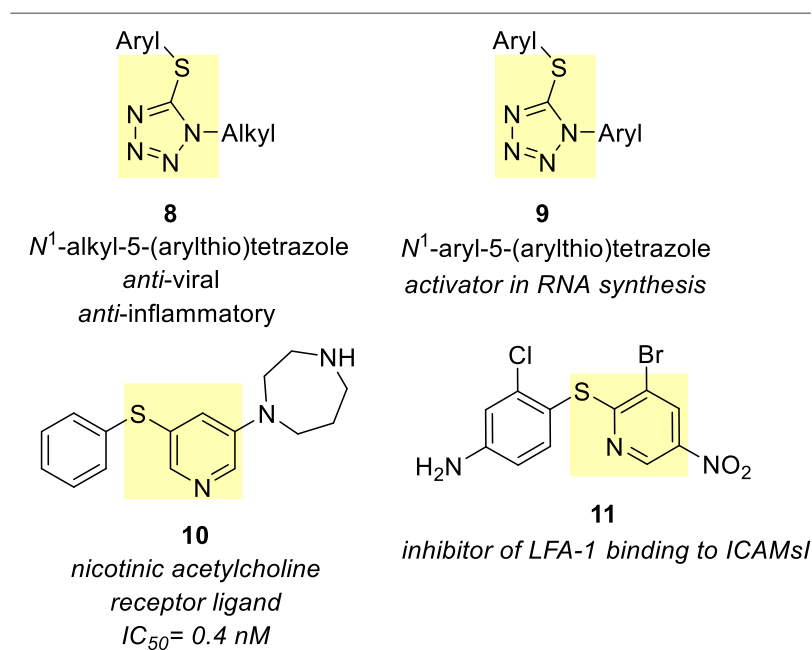
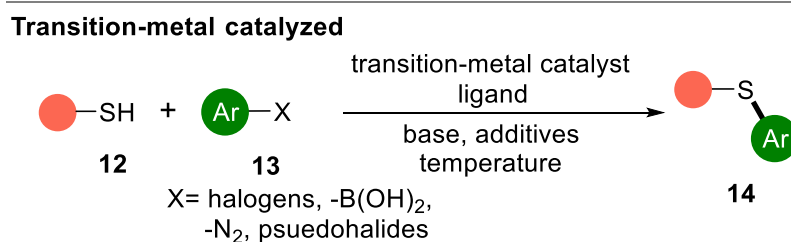


Figure 3.2 Di(hetero)aryl thioether moieties containing tetrazole and pyridine

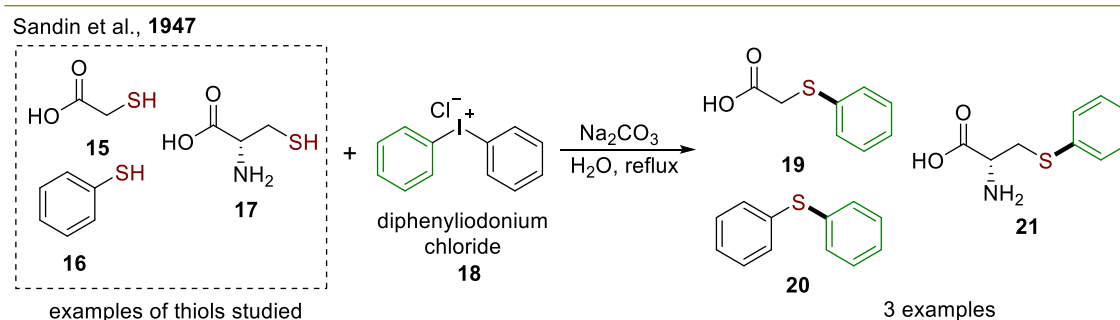
3.1.2 Previous *S*-arylation methods utilizing diaryliodonium salts

To access these *S*-arylated thioethers, the transition-metal catalysed coupling reactions of various aryl electrophiles with thiols is a highly explored approach (Scheme 3.1) [15–23]. Despite its significant contributions, the major drawbacks in those approaches are the toxicity and high cost associated with the designing of transition-metal complexes. Pharmaceutical industries demand synthetic protocols with no use of metals for the synthesis of marketed drugs or organic building blocks.



Scheme 3.1 *S*-arylation of thiols with various arylating partners

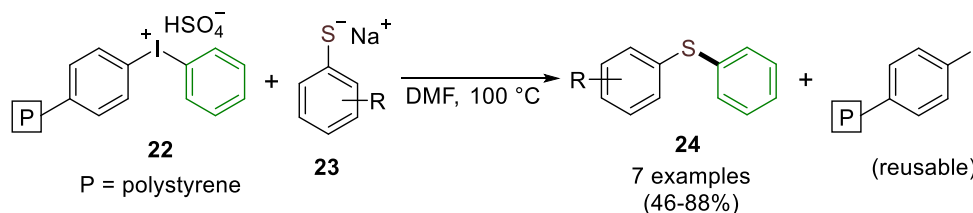
Ever since the first report for metal-free *S*-arylation with diphenyliodonium chloride made as early as in 1947 by Sandin et al. (Scheme 3.2) [24], quite a number of methods have been documented for *S*-arylation of simple alkyl thiols and aryl thiols with diaryliodonium salts later (Scheme 3.3) [25–26]. These early reports highlighted only few examples of symmetrical iodonium salts.



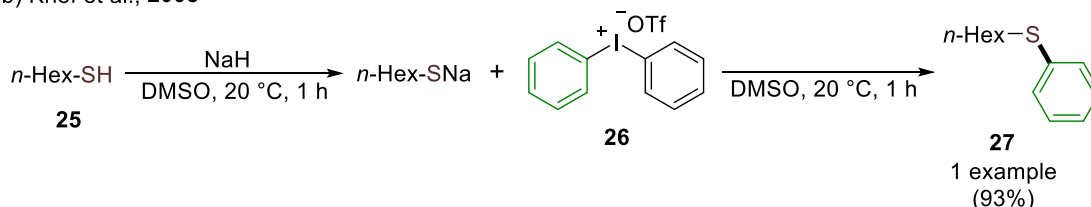
Scheme 3.2 Kirkwood's early method with diphenyliodonium chloride

From pre-functionalized sodium salt of thiols

a) Huang et al., 2001

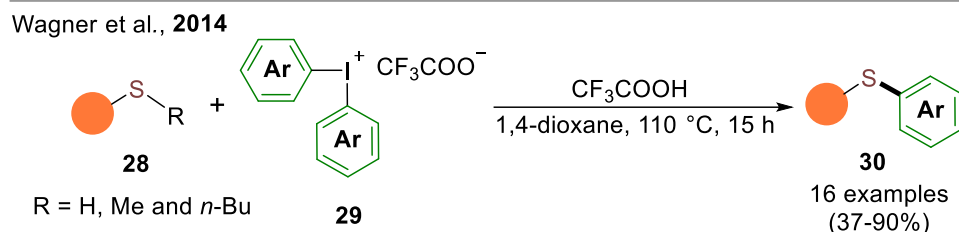


b) Krief et al., 2005



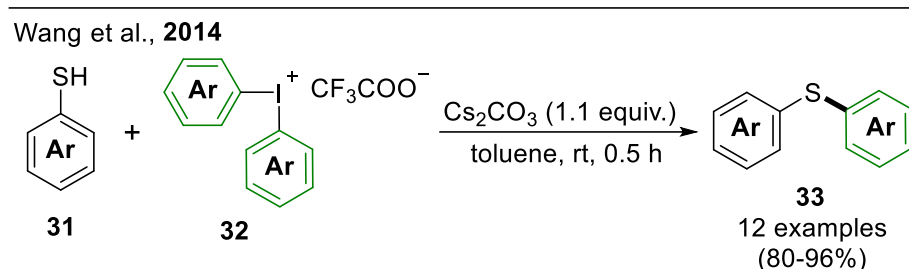
Scheme 3.3 *S*-arylation reaction with sodium thiolates

Of late, the trifluoroacetic acid-mediated method was explored with diverse thiols and thioethers **28** and symmetrical iodonium salts **29** (Scheme 3.4) [27]. However, electron-withdrawing functionalized aryl groups were not mentioned in their method. The mechanistic study of the reaction between *n*-butyl phenyl sulfide and diphenyliodonium trifluoroacetate suggested the generation of short-lived sulfonium salt intermediate followed by the formation of the *S*-arylated product. Under GC-MS analysis, the formation of *n*-butyl trifluoroacetate was observed.



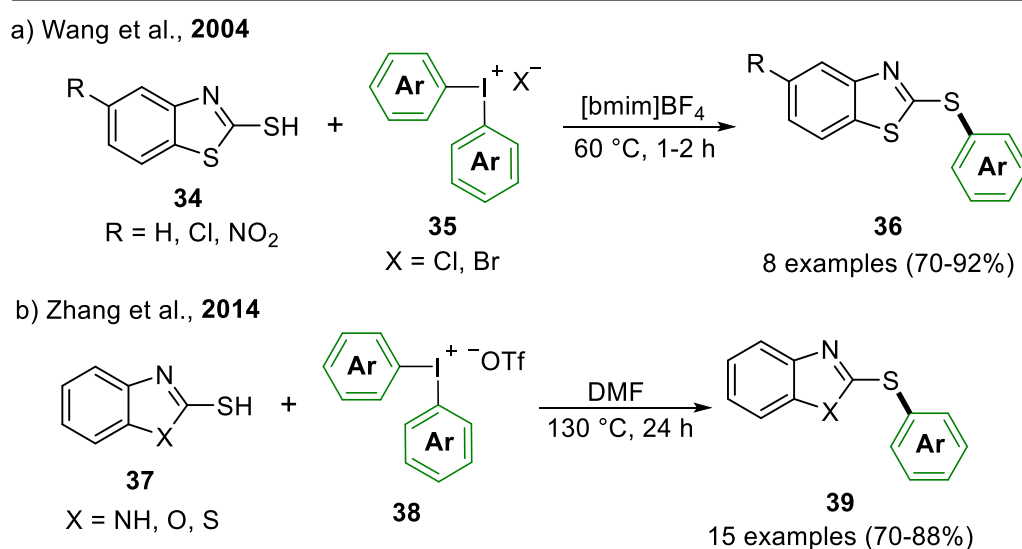
Scheme 3.4 Acid-mediated S-arylation with thiols and thioethers

Shortly after, a similar symmetrical iodonium based S-arylation method was developed under basic-medium (Scheme 3.5). However, the discussion on the arylation scope was limited due to the utilization of symmetrical iodonium salts [28].



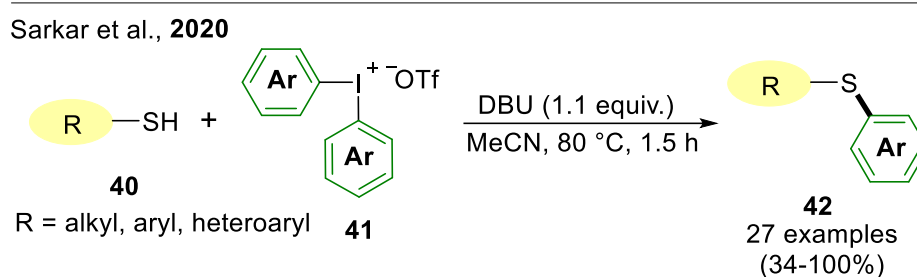
Scheme 3.5 Base-mediated S-arylation with symmetrical iodonium salts

Arylation of heterocyclic thiols (mostly 2-mercaptobenzimidazoles) were also reported with ionic-liquid mediated (Scheme 3.6a) [29] or base-free protocols (Scheme 3.6b) [30]. Their studies on the substrate scope were concluded with limited examples of symmetrical iodonium salts, and neither method mentioned about the application for EW aryl moiety.



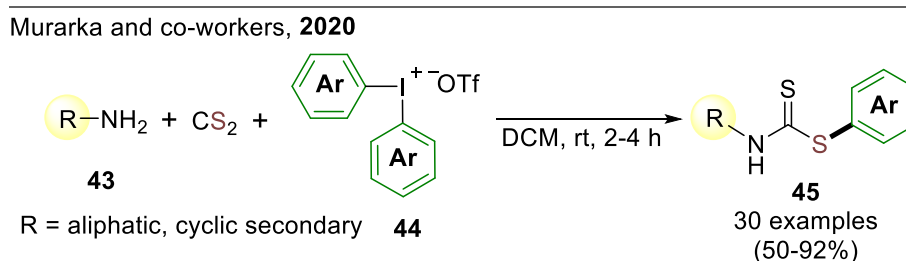
Scheme 3.6 S-arylation with heterocyclic thiols

A recent development in this area was achieved by Kalek and co-workers, offering a broad range of aryl sulfide products, but the range of functionalized aryl group employed were of symmetrical type only (Scheme 3.7) [31]. These known literatures were established exclusively with symmetrical iodonium salts and therefore, deluded the discussion on the broad spectrum of functionalized aryl groups; the accessibility of unsymmetrical iodonium salts remained unexplored. In addition, cyclic iodonium salts were another emerging class in iodonium salt chemistry where quite important sulphur nucleophiles have been utilized and they delivered fascinating biaryl sulfide frameworks [32-34].



Scheme 3.7 Recent report on *S*-arylation of thiols with diaryliodonium salts

Ever since the metal-free *S*-arylation reactions with diaryliodonium salts have been emerged for their remarkable applicability, very recently Murarka and co-workers devised an effective and applicable metal-free protocol for the synthesis of valuable *S*-aryl-dithiocarbamate scaffolds using diaryliodonium salts at room temperature (Scheme 3.8) [35].



Scheme 3.8 One-pot synthesis of *S*-aryl-dithiocarbamates

Inspired by the above-mentioned developments on unsymmetrical iodonium salts, we envisioned to study the applications of unsymmetrical iodonium salts on *S*-arylation of previously less-explored heteroaryl thiols e.g., tetrazole-5-thiol and pyridine-2-thiol. Because of using unsymmetrical iodonium salts, this work intends

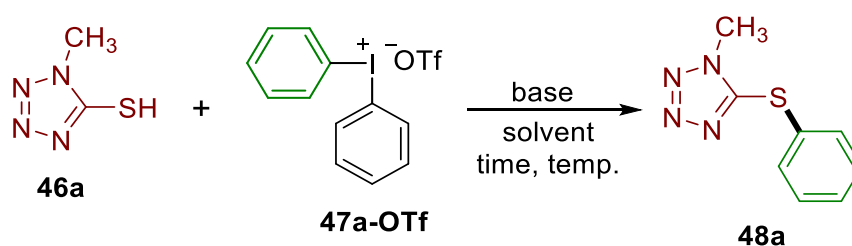
to extend wide scope of functionalized aryl groups into the thiol moiety *via* highly selective arylation and thereby, diverse di(hetero)aryl thioethers can be obtained.

3.2 Optimization

3.2.1 Screening of the reaction conditions

We started our initial optimization of the reaction using model substrates 1-methyl-1*H*-tetrazole-5-thiol (**46a**) as thiol source and diphenyliodonium triflate (**47a-OTf**) as aryl source (Table 3.1). The first positive result on *S*-arylation was observed when **46a** (0.2 mmol) was treated with **47a-OTf** (1 equiv.) and Na₂CO₃ (1.2 equiv.) in toluene and at temperature 60 °C and yielded the product **48a** in 65% yield (entry 7). This optimization indicated the metal-free condition and the essence of a base. It was found that temperature was a crucial factor in this reaction. Optimised temperature being at 80 °C (entry 8), trace amount of arylation was observed at room temperature and below 60 °C (entry 6). In addition, elevating temperature did not change the yield of **48a** (entry 12). Extensive studies of other bases were performed, but no significant change in the yield of **48a** was noticed (entries 13-21). Similarly, other solvents were checked too (entries 22-28). Good conversion was observed in acetonitrile too.

Table 3.1 Optimization between 46a and diphenyliodonium salt 47a-OTf^a



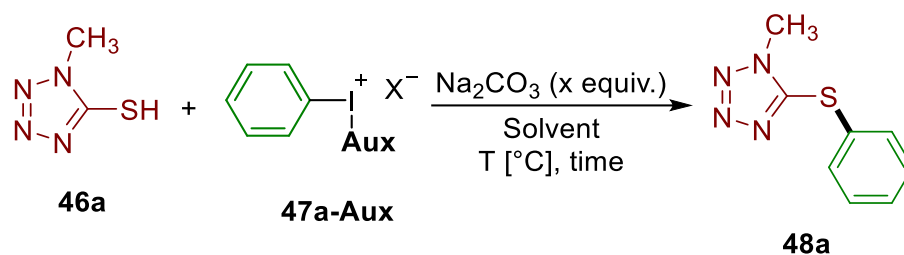
Entry	46a (equiv.)	47a (equiv.)	solvent	base (equiv.)	T (°C)	t (h)	yield ^b (%)
1	1	1	Toluene	-	rt	24	ND
2	1	1	Toluene	-	45	24	ND
3	1	1	Toluene	-	60	24	ND
4	1	1	Toluene	-	100	24	ND
5	1	1	Toluene	Na ₂ CO ₃ (1.1)	rt	24	ND
6	1	1	DCE	Na ₂ CO ₃ (1.1)	45	24	trace
7	1	1	Toluene	Na ₂ CO ₃ (1.1)	60	24	65
8	1	1	Toluene	Na ₂ CO ₃ (1.1)	80	24	72

9	1	1	Toluene	Na ₂ CO ₃ (1.5)	80	24	70
10	1	1.5	Toluene	Na ₂ CO ₃ (1.2)	80	24	71
11	1	1	Toluene	Na₂CO₃ (1.1)	80	10	72
12	1	1	Toluene	Na ₂ CO ₃ (1.1)	100	24	72
13	1	1	Toluene	NaHCO ₃ (1.1)	80	12	60
14	1	1	Toluene	K ₂ CO ₃ (1.1)	80	12	62
15	1	1	Toluene	Et ₃ N (1.1)	80	10	70
16	1	1	Toluene	KO ^t Bu (1.1)	80	12	48
17	1	1	Toluene	DABCO (1.1)	80	12	52
18	1	1	Toluene	DBU (1.1)	80	10	70
19	1	1	Toluene	NaOH (1.1)	80	12	trace
20	1	1	Toluene	Pyridine (1.1)	80	12	50
21	1	1	Toluene	K ₃ PO ₄ (1.1)	80	12	45
22	1	1	1,4-dioxane	Na ₂ CO ₃ (1.1)	80	12	54
23	1	1	DMF	Na ₂ CO ₃ (1.1)	80	12	trace
24	1	1	DMSO	Na ₂ CO ₃ (1.1)	80	12	trace
25	1	1	CH ₃ CN	Na ₂ CO ₃ (1.1)	80	12	70
26	1	1	DCM	Na ₂ CO ₃ (1.1)	80	12	56
27	1	1	DCE	Na ₂ CO ₃ (1.1)	80	12	54
28	1	1	MeOH	Na ₂ CO ₃ (1.1)	80	24	trace

^aReaction conditions: **46a** (0.1 mmol), diphenyliodonium triflate **47a-OTf** (0.1 mmol), base (1.1 equiv.) and solvent (0.1 M) were added to a Schlenk tube. ^bIsolated yields. ND i.e., not detected.

3.2.2 Selection of the auxiliary from the unsymmetrical iodonium salt

As iodonium salts can be synthesized with different counter-anions (such -OTs, -OTf, -BF₄ etc.), the comprehensive studies on counter-anions are an integral part of the arylation chemistry with diaryliodonium salts (Table 3.2, entries 1-4). Both -Br and -BF₄ effected positive conversion of **48a**. The yield of the reaction with **47a-Br** was less in comparison to -OTf, however **47a-BF₄** exhibited comparative conversion like **47a-OTf**. Employing unsymmetrical iodonium salt **47a-TFA-TMP**, we were pleased to observe *S*-arylation product **48a**, with higher isolated yield (82%) than **47a-OTf** salt, and the required reaction time was less (entry 5). Other auxiliary groups such as mesityl (Mes) and anisyl (An) were investigated too; but the comparative chemoselective transfer of **Ph** group to obtain **48a** was found to be superior with TMP as auxiliary (entries 6 and 7). Applying the **46a-TMP-OTs** and **46a-TMP-OTf**, trace amount of **48a** was observed surprisingly and *S*-arylation with TMP (1,3,5-trimethoxyphenyl) part afforded the major product (entries 8 and 9).

Table 3.2 Investigation for unsymmetrical iodonium salt^a

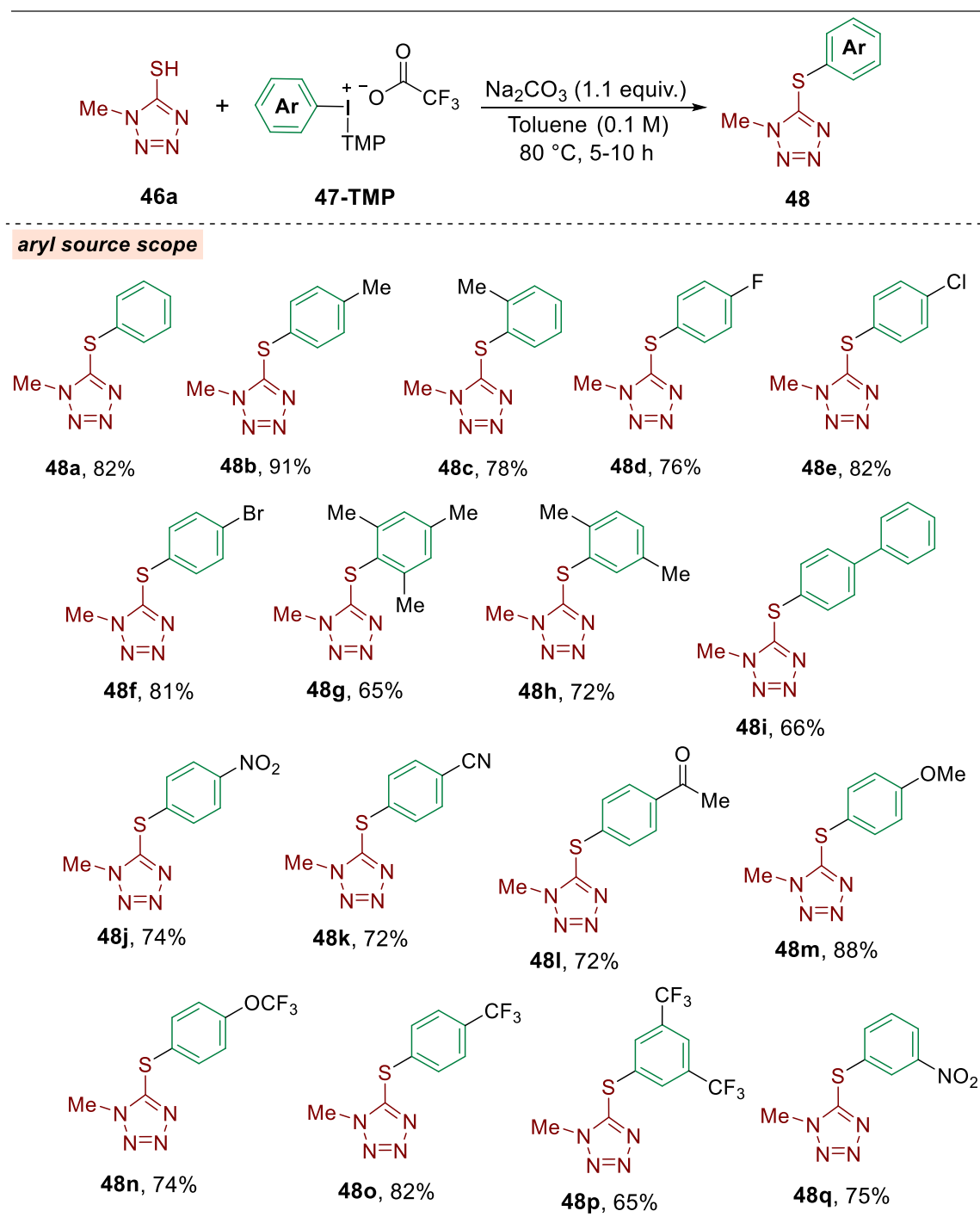
Entry	46a (equiv.)	47a (equiv.)	Aux	X	base (equiv.)	T (°C)	t (h)	yield ^b (%)
1	1	47a-OTf (1.0)	Ph	OTf	Na ₂ CO ₃ (1.1)	80	12	72
2	1	47a-OTs (1.0)	Ph	OTs	Na ₂ CO ₃ (1.1)	80	12	trace
3	1	47a-Br (1.0)	Ph	Br	Na ₂ CO ₃ (1.1)	80	12	56
4	1	47a-BF₄ (1.0)	Ph	BF ₄	Na ₂ CO ₃ (1.1)	80	12	75
5	1	47a-TMP (1.0)	TMP	TFA	Na₂CO₃ (1.1)	80	5	85 (77)^c
6	1	47a-Mes (1.0)	Mes	OTf	Na ₂ CO ₃ (1.1)	80	12	trace
7	1	47a-An (1.0)	Anisyl	OTf	Na ₂ CO ₃ (1.1)	80	12	60
8	1	47a-TMP (1.0)	TMP	OTs	Na ₂ CO ₃ (1.1)	80	24	trace
9	1	47a-TMP (1.0)	TMP	OTf	Na ₂ CO ₃ (1.1)	80	24	trace
10	1	47a-TMP (1.2)	TMP	TFA	Na ₂ CO ₃ (1.1)	80	10	82
11	1	47a-TMP (1.0)	TMP	TFA	Na ₂ CO ₃ (0.5)	80	12	65
12	1	47a-TMP (1.0)	TMP	TFA	Na ₂ CO ₃ (1.5)	80	12	78
13	1.2	47a-TMP (1.0)	TMP	TFA	Na ₂ CO ₃ (1.1)	80	12	75
14	1	47a-TMP (1.0)	TMP	TFA	Na ₂ CO ₃ (1.1)	100	12	80

^aReaction conditions: **46a** (0.1 mmol), **47a-Aux** (0.1 mmol), base (1.1 equiv.) and solvent (0.1 M) were added to a Schlenk tube. ^bIsolated yields. ^cCH₃CN as solvent.

3.3 Substrate scope

3.3.1 Scope of aryl(TMP)iodonium salts

With the metal-free condition in hand, we tested the efficacy of the reaction with various unsymmetrical iodonium salts and thiol **46a** (Table 3.3). Weakly activating –CH₃ containing iodonium salts were proceeded easily, affording the arylated products **48b** and **48c** in yields 91% and 78%, respectively. The *ortho*-methyl substituted TMP-iodonium salt **47c-TMP** offered less yield of **48c** due to the steric factor of the *ortho*-methyl group which finally led to lower chemoselectivity of the iodonium salt. Aryl source with C4-halide substituents such as -F, -Cl, and -Br was selectively transferable and provided the products **48d**, **48e** and **48f** in 76%, 82% and 81% yields, respectively. These substrate scope are highly valuable as other aryl sources (aryl iodine or arylboronic acids) with halide-substituents show difficulty in selective arylation under metal-catalysed protocol. Though yields were moderate, both sterically congested mesityl and *para*-xylyl groups smoothly transferred to products **48g** and **48h** in 65% and 72% yields, respectively. Synthesis of diaryliodonium salt possessing biphenyl group is very difficult either in symmetrical type or with other auxiliaries. Interestingly, when TMP-iodonium salt of biphenyl group was applied with the optimized reaction condition, the biphenyl group (product **48i**) was easily transferred to the thiol nucleophile of the tetrazolic ring. Electron-withdrawing moieties such as –NO₂, -CN, and -acetyl were also tolerated and furnished the products **48j**, **48k**, and **48l** respectively in moderate yields. In the previous *S*-arylation methods with symmetrical iodonium salts, the examples of aryl ring with EW groups were less explored since symmetrical iodonium salts were not suitable precursor for EW aryl moieties. Therefore, the incorporation of EW aryl rings by utilizing TMP-iodonium salts under chemoselective manner was advantageous in this study. Similarly, ED aryl ring such as *p*-methoxy-phenyl group (product **48m**) was equally implementable and inducted into **46a** from iodonium salts **47q-TMP**. Like *p*-methoxyphenyl group, *p*-trifluoromethoxy-phenyl group (product **48n**) was also compatible. As -CF₃ moiety is biologically relevant, iodonium salts with 4-CF₃ and 3,5-bis(trifluoromethyl) were also applied leading to products **48o** and **48p** respectively. The *m*-NO₂-substituted product **48q** was formed in 75% yield from **47p-TMP**. Overall, the TMP-iodonium salts was easily explored for all types of aryl moieties and diverse *S*-arylated thioethers could be obtained.

Table 3.3 Scope of *S*-arylation of the 5-mercaptotetrazole^{a,b}

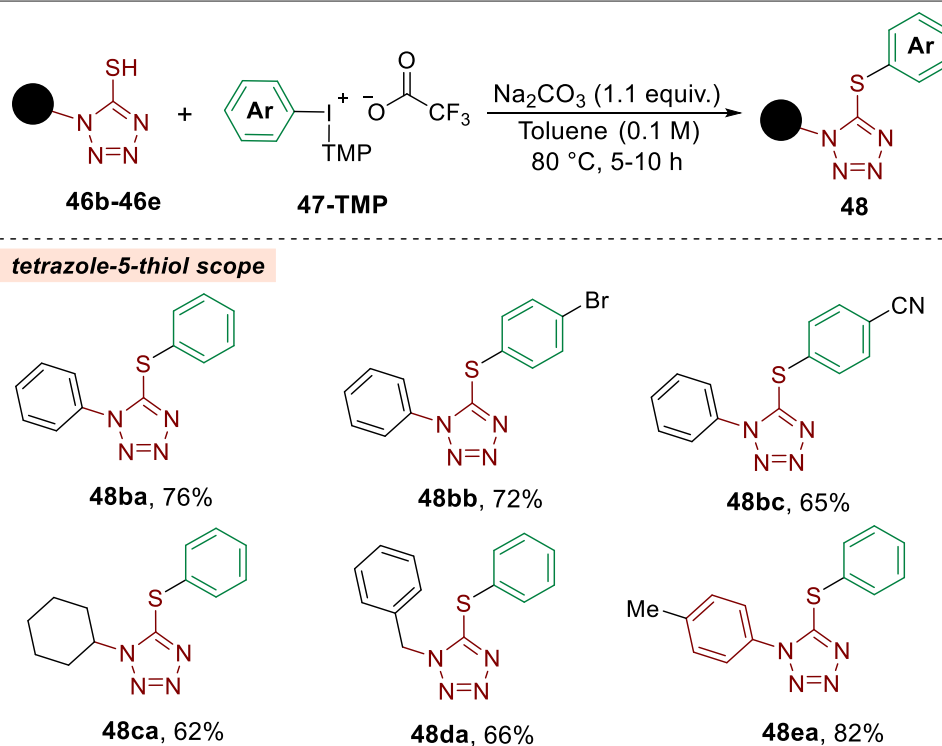
^aReaction conditions: **46a** (0.3 mmol, 1 equiv.), **47-TMP** (1 equiv.), Na₂CO₃ (1.1 equiv.) and toluene (0.1 M) was added to a dry Schlenk tube. ^bIsolated yields.

3.3.2 Scope of substituted tetrazol-5-thiols

Subsequently, the effects of alkyl and aryl groups on the *N*¹-position of tetrazole-5-thiol salts were checked with variable iodonium-TMP (Table 3.4). With phenyl group (**46b**) and *p*-tolyl group (**46e**), the reaction protocol afforded products **48ba** and

48ea respectively. Both 4-Br and 4-CN substituents on aryl part was also subjected to the reaction and furnished the products **48bb** and **48bc** respectively in moderate yields. Alkyl moieties such as cyclohexyl- (**46c**) and benzyl- (**46d**) also worked under the reaction condition and afforded *N*¹-alkyl-*S*⁵-aryl tetrazole-5-thiol products **48ca** and **48da**, respectively.

Table 3.4 Scope of *S*-arylation of the 5-mercaptotetrazole^{a,b}



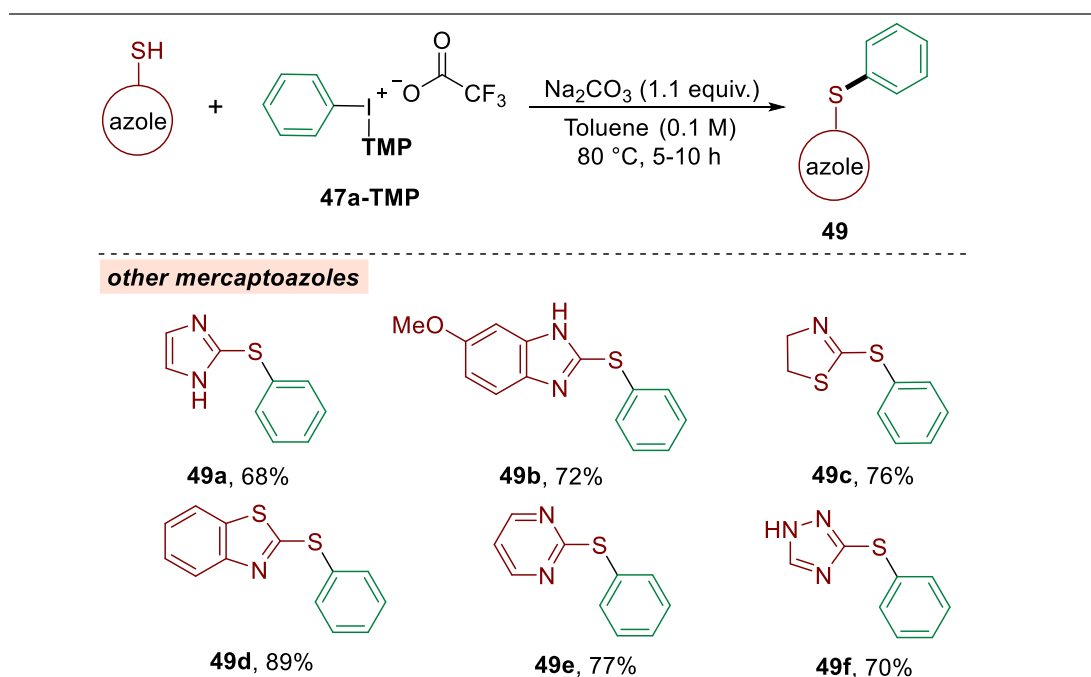
^aReaction conditions: **46b-46e** (0.3 mmol, 1 equiv.), **47-TMP** (1 equiv.), Na₂CO₃ (1.1 equiv.) and toluene (0.1 M) was added to a dry Schlenk tube. ^bIsolated yields.

3.3.3 Scope of other mercaptoazoles

To expand the scope of the thiol group under the developed protocol, the optimized reaction condition of the method was applied to other heteroaryl thiols too; those having diverse azole rings such as imidazole, thiazole, pyrimidine, triazole etc. To our delight, the method exhibited selective phenylation from phenyl(TMP)iodonium salt with these mercaptoazoles too with moderate to good yields (Table 3.5). With thiols containing heterocycles such as imidazole and benzimidazole, we observed no interference of *N*-arylated products due to the presence of free N-H centres in these azole rings and afforded only *S*-arylated products **49a** and **49b** with yields 68% and 72% respectively. Subsequently, other azole rings such as dihydrothiazole (product

49c) and benzo-thiazole (product **49d**) were easily compatible exhibiting good yields. In case of pyrimidine ring too, the *S*-phenylation observed easily and provided the valuable 2-(phenylthio)pyrimidine scaffold, **49e** in 77% yield. The interesting feature of this part was selective *S*-arylation of 1*H*-1,2,4-triazole. Despite the presence of an acidic N-H in the mercaptotriazole moiety, *S*-arylation of the synthetically important moiety was observed and afforded the product **49f** in 70% yield.

Table 3.5 Examples of other mercaptoazoles^{a,b}

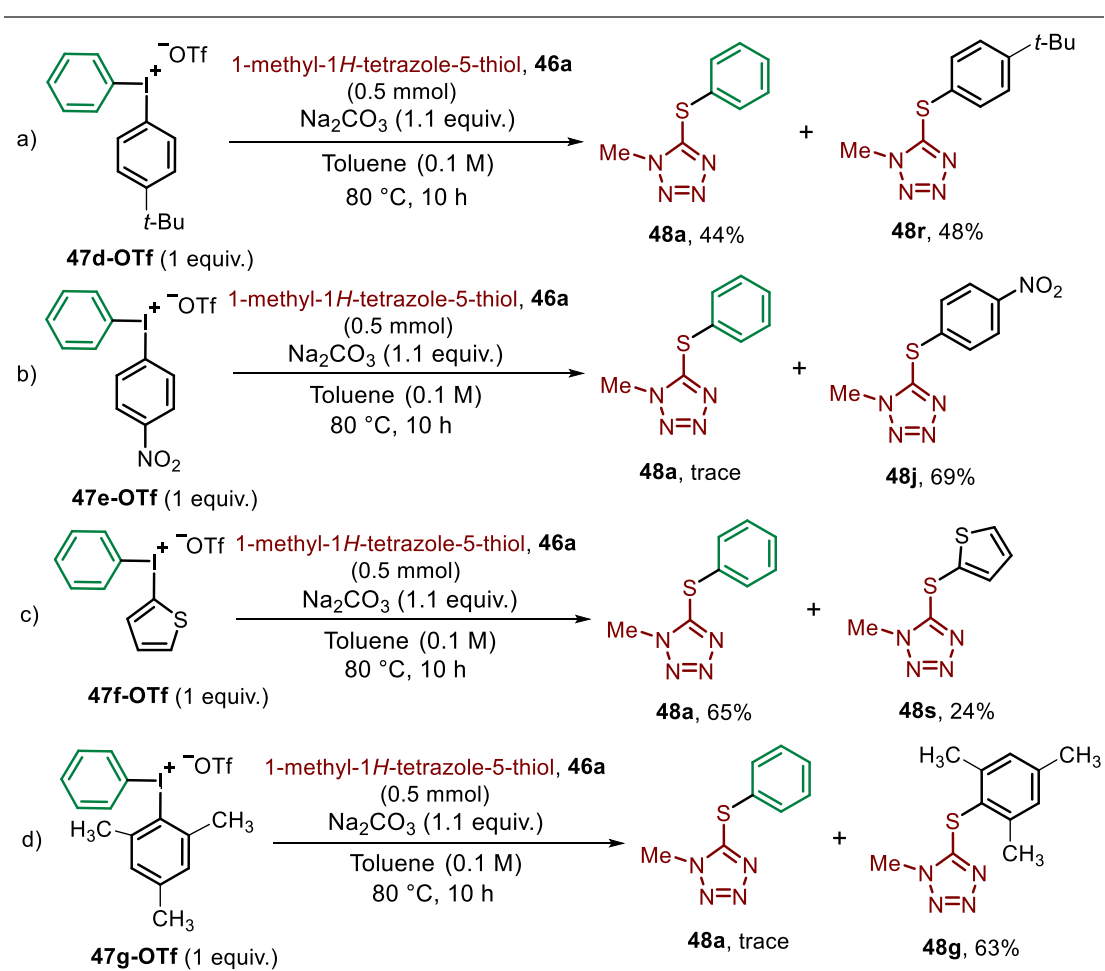


^aReaction conditions: azole (1 equiv.), **47a-TMP** salt (1 equiv.), Na_2CO_3 (1.1 equiv.) and toluene (0.1 M) was added to a dry Schlenk tube. ^bIsolated yields.

3.4 Electronic and steric effect of unsymmetrical iodonium salts

To understand the precise reactivity pattern of the unsymmetrical iodonium salts, we explored the methodology with diverse unsymmetrical iodonium salts (**47d-OTf**, **47e-OTf**, **47f-OTf** and **47g-OTf** possessing electronically and sterically variant aryl groups in the iodonium salts (Scheme 3.9). These selected iodonium salts were reacted with tetrazole-thiol, **46a** under the standard reaction conditions. With iodonium salts possessing comparable electronic factor (Ph and 4-*t*Bu-Ph in case of **47d-OTf**), the selectivity of the iodonium salt for phenylation was less and reaction delivered the arylated products **48a** and **48r** in 44% and 48% yields, respectively

(Scheme 3.9a). In case of iodonium salt **47e-OTf**; the electron-withdrawing part, 4-nitrophenylation product **48j** was obtained preferably in 69% yield and trace amount of phenylated product **48a** was noticed (Scheme 3.9b). Similarly, when the iodonium salt **47g-OTf** was reacted, the sterically hindered mesitylated product **48g** dominated one (Scheme 3.9d). These two observations were in line with previous metal-free arylation chemistry of iodonium salts. Although applying iodonium salt **47f-OTf** containing thienyl group gave phenylation product as the major product; but the thiophene part was transferred too with 24% yield (Scheme 3.9c). In general, thiophene act as a compatible auxiliary like TMP in metal-free reactions. However, the chemoselective of thiophene group was found lesser than TMP in our conditions.

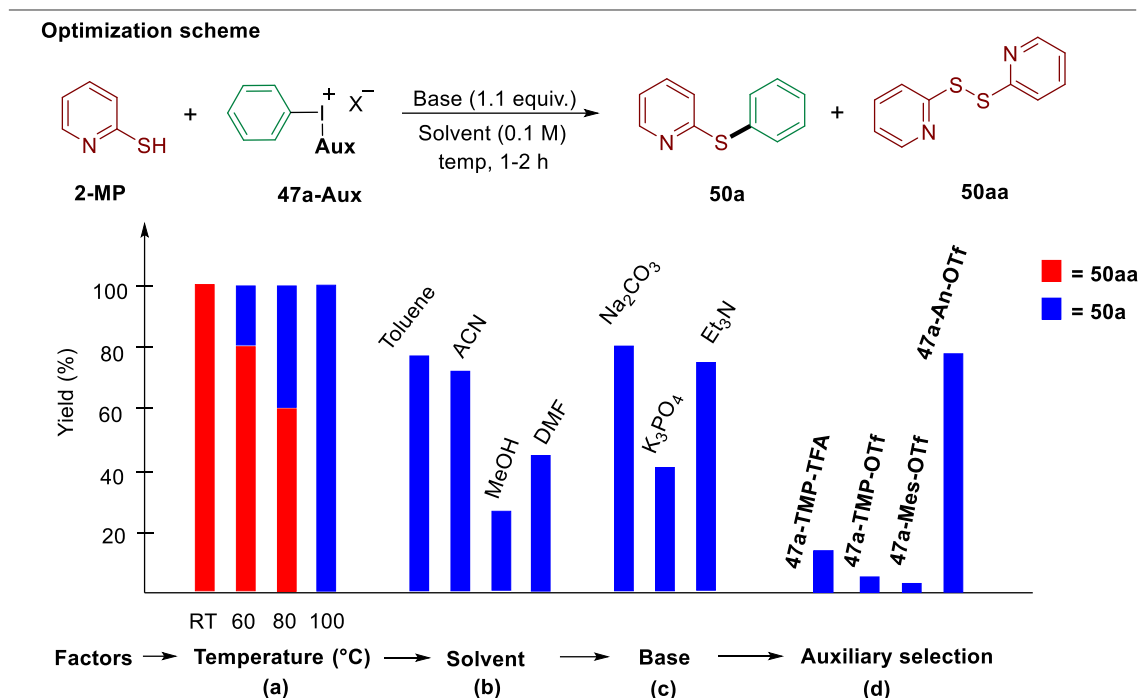


Scheme 3.9 Chemoselectivity Pattern of unsymmetrical iodonium salts. All yields are isolated yields.

3.5 S-arylation of 2-mercaptopyridine

As 2-arylthiopyridine compounds deliver many synthetic utilities in organic chemistry, we extended our metal-free investigations for S-arylation of 2-

mercaptopyridine (Scheme 3.10). When 2-mercaptopyridine (**2-MP**) was subjected to arylation with **47a-TMP** salt under the optimized condition, the formation of disulfide (S-S) bond between **2-MP** i.e., **50aa** was preferred over *S*-arylation. It implied that diaryliodonium salts acted as oxidizing agent under this optimization. While revising the optimized conditions, we found that elevated temperature had played a major role to suppress **50aa**. Gratifyingly, formation of **50aa** was not observed, when the temperature was increased to 100 °C. Solvent and base did not have impact on the yield. The interesting observation was that the yield of **50a** was very low with **47a-TMP** salt. The diaryliodonium salt having anisyl as the auxiliary (**47a-An-OTf**) showed better selectivity than **47a-Mes-OTf** and **47a-TMP-OTf**.

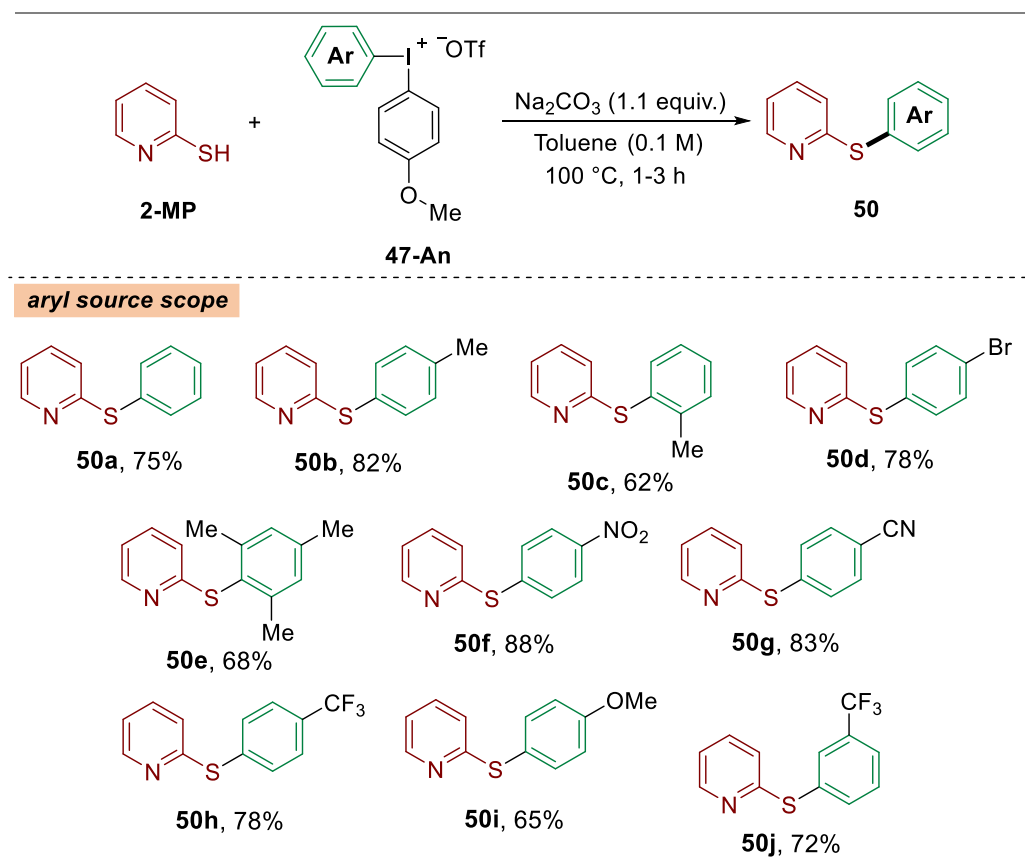


Scheme 3.10 Optimization for *S*-phenylation of 2-mercaptopyridine. a) Relative yields comparison with temperature (isolated yields); b) Solvent screening; c) Screening of bases; d) Chemoselective analysis for iodonium salt with various auxiliary and counter-anions. Toluene was degassed before use.

With the above optimized conditions, reaction could provide easy access *p*-tolyl, *o*-tolyl and 4-Br products **50b**, **50c** and **50d** respectively (Table 3.6). Highly congested mesityl group also showed tolerability in this protocol (product **50e**). Aryl moieties with EW groups -NO₂ and -CN were selectively transferred affording the products **50f** and **50g** in 88% and 83% yields, respectively. The *p*-methoxy group from symmetrical iodonium salt **47i-An** delivered the product **50i** in 65% yield. CF₃-group

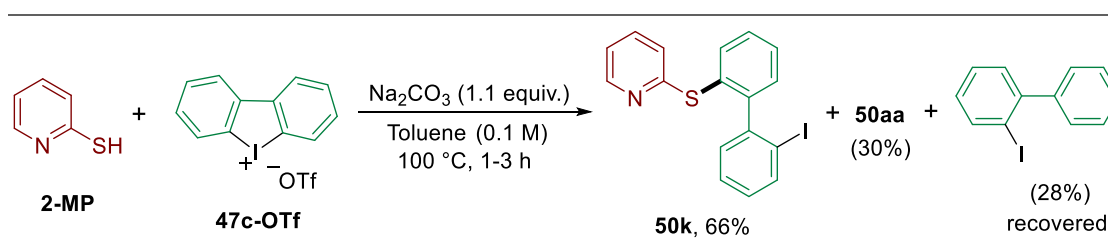
containing iodonium salts on *para*- and *meta*- positions were compatible and afforded the products **50h** and **50j** respectively in moderate yields. Though both aryl substrates having electron donating and electron withdrawing moieties were applicable, substrates with electron withdrawing moieties exhibited better conversion.

Table 3.6 Scope of aryl(anisyl)iodonium salts^{a,b}



^aReaction conditions: **2-MP** (1 equiv.), **47-An** salt (1 equiv.), Na_2CO_3 (1.1 equiv.) and toluene (0.1 M) were added to a dry Schlenk tube. ^bIsolated yields.

Another important scope for *S*-arylation of **2-MP** was induction of 2-iodobiphenyl group into the product **50k**, which was derived from cyclic iodonium



Scheme 3.11 Arylation with cyclic iodonium salt. Reaction conditions: **2-MP** (1 equiv.), **47c-OTf** salt (1 equiv.), Na_2CO_3 (1.1 equiv.) and toluene (0.1 M) were added to a dry Schlenk tube. Isolated yields.

salt **47c-OTf**. In scheme 3.11, applying **47c-OTf** resulted the by-product of starting aryl halide having comparable yield with **50aa**. This implied that formation of **50aa** *via* non-cyclic iodonium salt could break the iodonium salt into aryl halide and arene (starting compounds).

3.6 DFT analysis of the chemoselective arylation between phenyl(anisyl)iodonium triflate with 2-mercaptopyridine

Density Functional Theory (DFT) calculations were performed for *S*-phenylation of **2-MP** and **47a-An** to understand the observed chemoselectivity (Figure 3.3). From the PES calculations [36-37], it was observed that in the presence of **2-MP**, the starting material **47a-An** could easily transform into more stable intermediates **IM1** and **IM2**. From the T-shaped intermediates, though the free energy of **50i** is slightly stabilised than **50a**, the preferential arylation of **Ph** over **anisyl** can be easily realized

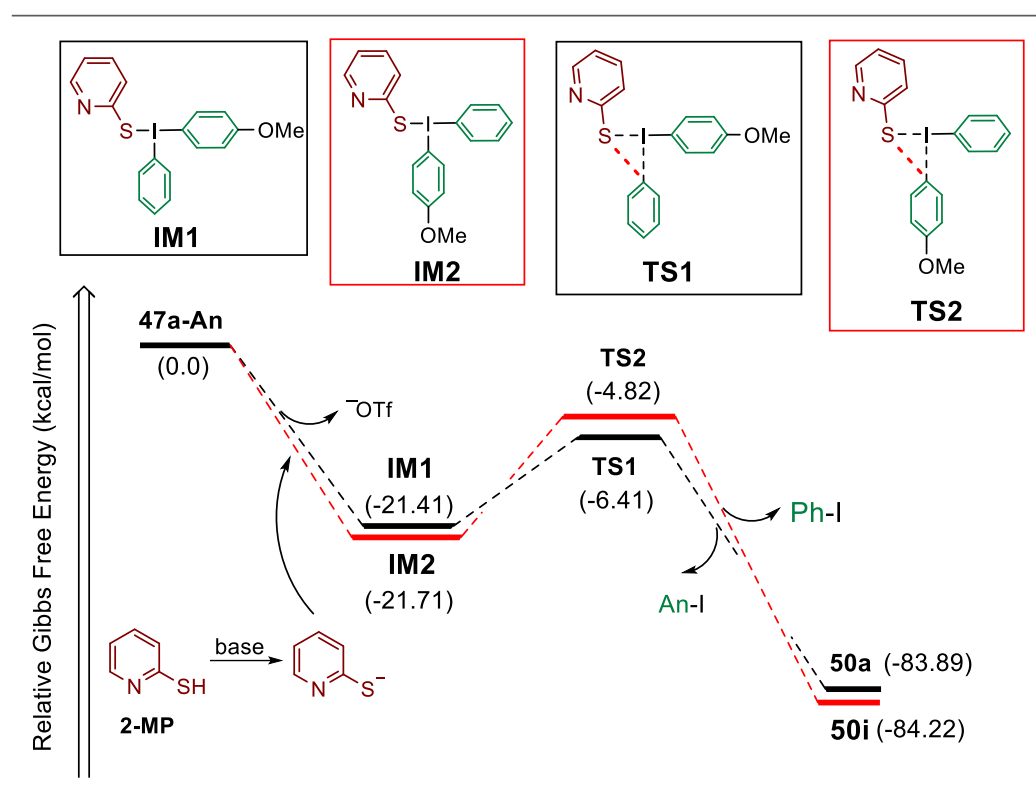


Figure 3.3 Free energy profile (kcal/mol) diagram for chemoselectivity study on arylation

from the transition states. The *S*-phenylation pathway (**TS1**) comprises an energy barrier of 15.01 kcal/mol. On the other hand, arylation of the anisyl group shows the energy barrier of 16.89 kcal/mol. The selective arylation of the Ph group over

anisyl is kinetically controlled and the result matches with experimental observation [38–39].

3.7 Summary of the chapter

In summary, the unsymmetrical iodonium salts with electron-rich auxiliary TMP or anisyl present a transition metal-free route for *S*-arylation of tetrazole-5-thiols and pyridine-2-thiol under basic conditions. This chapter introduces the applicability of unsymmetrical iodonium salts in *S*-arylation. In case of tetrazole-5-thiols, TMP auxiliary is suitable in the unsymmetrical iodonium salts, while anisyl group ensure higher selectivity in case of pyridine-2-thiol. The proper auxiliary choice enables to access diverse functionalized aryl groups including sterically congested aryl groups by providing valuable di(hetero)aryl thioethers in moderate to good yields. The developed protocol can be extended to biologically valuable thiols.

3.8 Experimental section

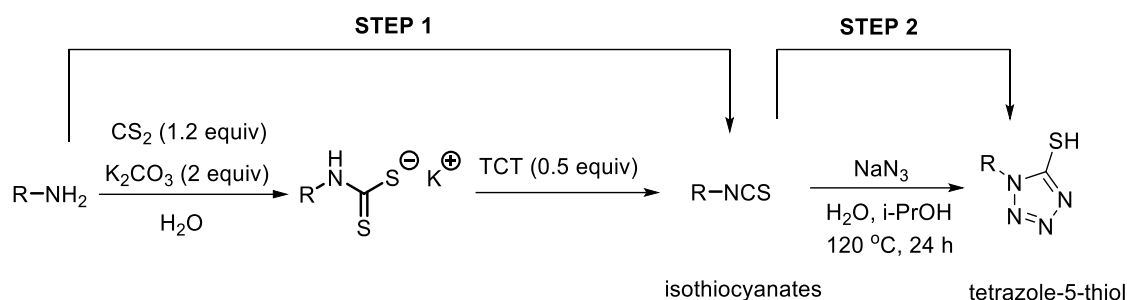
All reactions were performed in oven-dried Schlenk-tubes or round bottom flasks under ambient conditions, unless otherwise stated. Dichloromethane (DCM), 1,2-dichloroethane (DCE) and acetonitrile (ACN) were dried by refluxing over CaH₂ under nitrogen condition and stored over 4Å molecular sieves. Toluene and 1,4-dioxane were dried utilising conventional drying procedures using sodium/benzophenone as indicator and stored over 4Å molecular sieves. All chemicals were purchased from commercial suppliers and used as received unless otherwise is stated. NaOH, Cs₂CO₃, K₃PO₄ and KO^tBu were stored in a desiccator. The diaryliodonium salts were synthesized according to procedures described below. *m*-CPBA (Aldrich, 77% active oxidant) was dried at room temperature over high vacuum for 1 hour and titrated by iodometric titration prior to use in the synthesis of diaryliodonium salts. Thin Layer Chromatography (TLC) analyses were performed on pre-coated Merck silica gel 60F₂₅₄ plates using UV ($\lambda = 254$ nm) light and/or with KMnO₄-stain. Column chromatography was performed on 100-200 mesh silica gel using the gradient system, freshly distilled ethyl acetate-hexane mixture. All NMR data were recorded in a 400 MHz instrument at 298 K using CDCl₃ and DMSO-*d*₆ as solvents. Chemical shifts are given in ppm relative to the residual solvent peak (¹H NMR: CDCl₃ δ 7.26 and sometimes δ 1.56 (CDCl₃-water) and in DMSO-*d*₆ δ 2.50 and δ 3.3 (DMSO-water); ¹³C NMR: CDCl₃ δ 77.16, DMSO-*d*₆ δ 39.52) with multiplicity (bs=

broad singlet, s= singlet, d= doublet, t= triplet, q= quartet, quin= quintet, sex=sextet, sep=septet, m=multiplet, app=apparent), coupling constants (in Hz) and integration.

3.8.1 Synthesis of tetrazole-5-thiols (46a-46e)

1-methyl-1*H*-tetrazole-5-thiol (**46a**) is commercially available but, other tetrazole-5-thiols (**46b-46e**) are known compounds and were prepared by literature procedures [40–41].

General procedure for the alkyl/aryl isothiocyanate and its corresponding tetrazole-5-thiol:

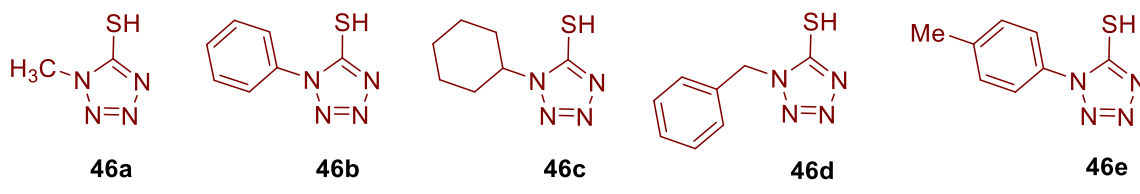


Step 1 [38]: To a mixture of amine (10 mmol) and K_2CO_3 (2.76 g, 20 mmol) in 10 mL of water, 0.914 g of CS_2 (12 mmol) was added dropwise within a period of 20–30 min at room temperature. After the addition was complete, the mixture was stirred for several hours until completion was determined by TLC. Then, the reaction mixture was cooled to 0 °C and a solution of 0.922 g of 2,4,6-trichloro-1,3,5-triazine (TCT) (5 mmol) in 15 mL of CH_2Cl_2 was added dropwise. After the addition was complete, the mixture was stirred for another 0.5 h for reaction completion. The reaction mixture was then basified to pH >11 with 6N NaOH to obtain a clear solution. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 , filtered and the solvent was removed under reduced pressure. The residual reaction mixture was purified by chromatography through a short silica column using petroleum ether as eluent to obtain the isothiocyanates.

Step 2 [39]: To a solution of NaN_3 (325 mg, 5 mmol) and H_2O (5 mL) was added a solution of isothiocyanate (5 mmol) in *i*-PrOH (2.5 mL) at 120 °C using oil bath and the resulting mixture was refluxed for 24 h. The mixture was treated with conc. HCl (1 mL) at 0 °C and then extracted twice with ethyl acetate (10 mL and 5 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to

crude product. Further, the crude product was purified by column chromatography to get the pure product.

Synthesized compounds:

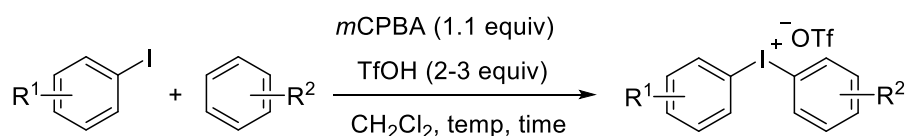


3.8.2 Synthesis of diaryliodonium salts

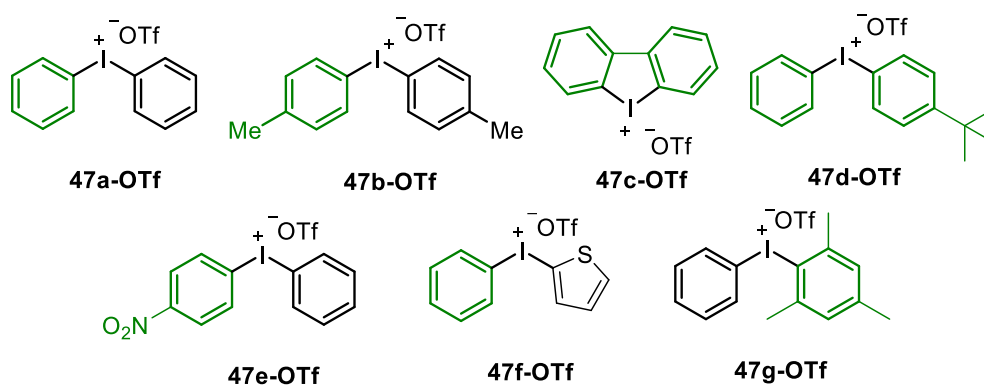
All the diaryliodonium salts are previously well-explored and the analytical data (especially ^1H NMR spectroscopy) synthesized diaryliodonium salts in this work were matched with literature.

Table 3.7 Synthesized diaryliodonium salts in this chapter

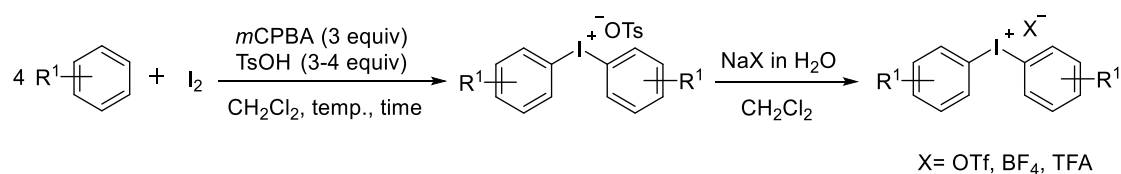
Method I [71, chapter 1]



Synthesized diaryliodonium salts:

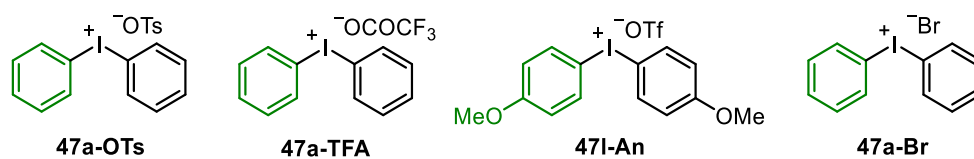


Method II [73, chapter 1]

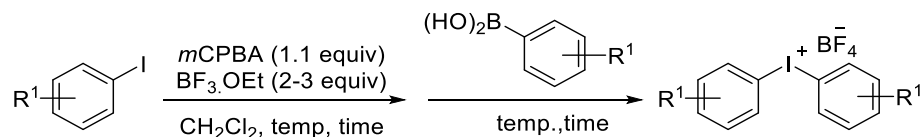


CHAPTER 3

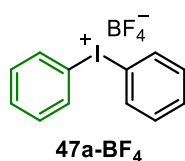
Synthesized diaryliodonium salts:



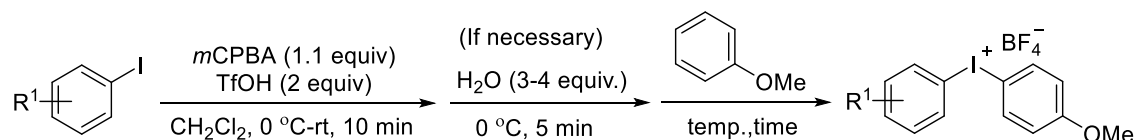
Method III [74, chapter 1]



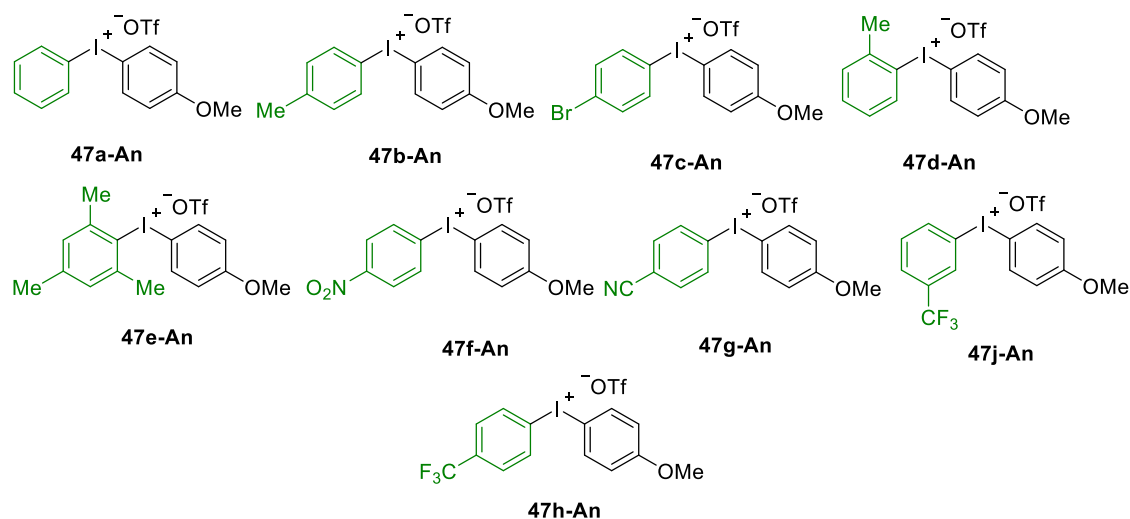
Synthesized diaryliodonium salts:



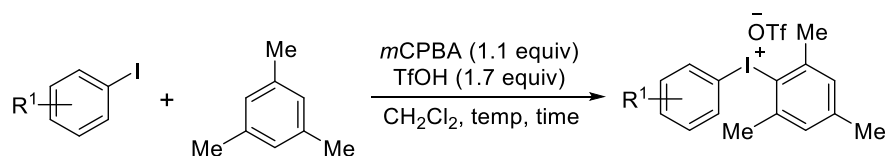
Method IV [45, chapter 1]



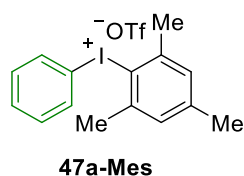
Synthesized diaryliodonium salts:



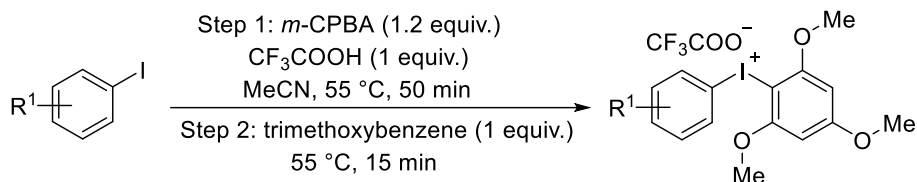
Method V [65, chapter 1]



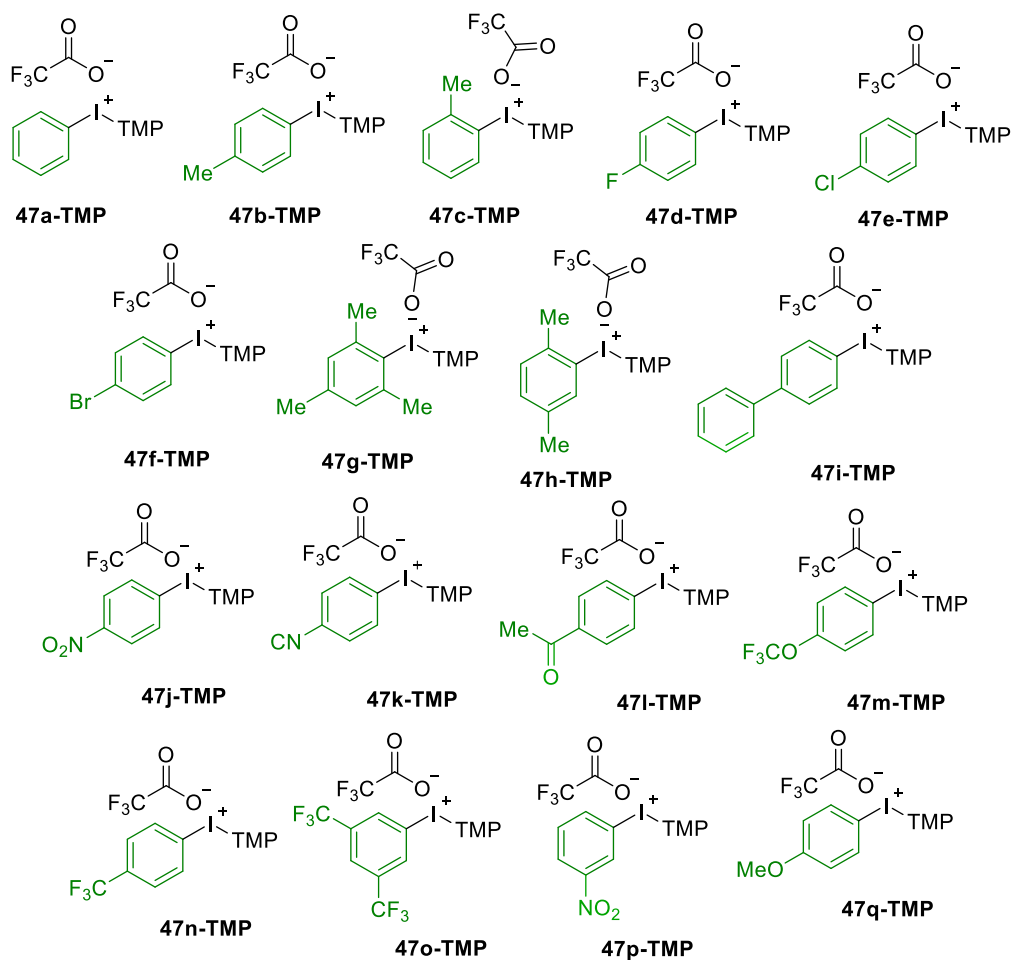
Synthesized diaryliodonium salts:



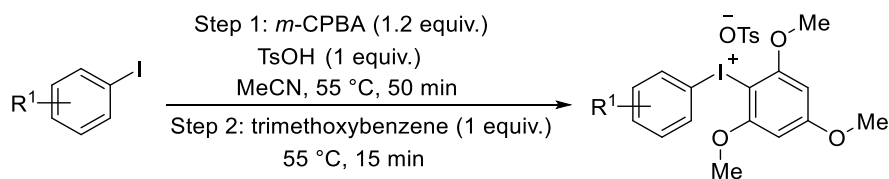
Method VI [79, chapter 1]



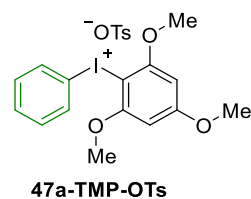
Synthesized diaryliodonium salts:



Method VII [77, chapter 1]

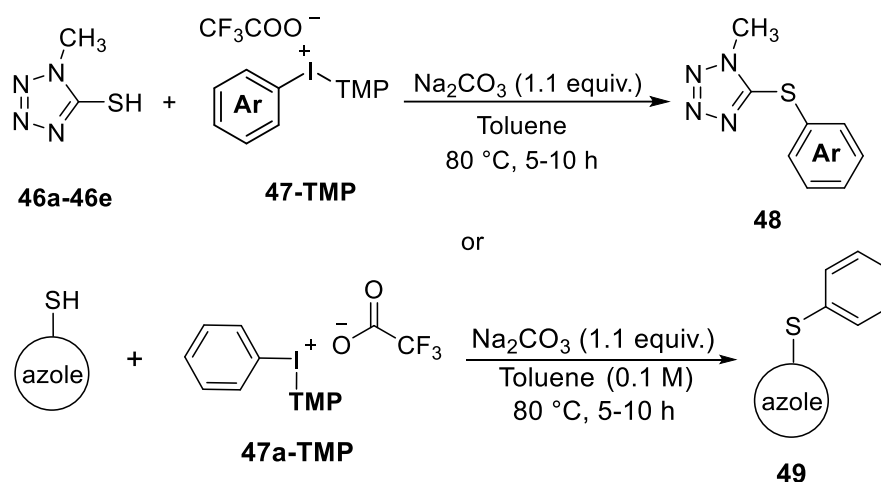


Synthesized diaryliodonium salts:



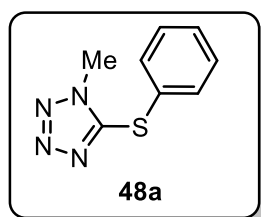
3.9 Synthesis and characterization of *S*-aryl products

3.9.1 General procedure A (GP-A)



To an oven-dried Schlenk-tube, tetrazole-5-thiol (**46**) or azole (0.35 mmol), diaryliodonium salt **47-TMP** (0.35 mmol, 1 equiv.), and Na_2CO_3 (0.385 mmol, 1.1 equiv.) were added. After adding toluene (3.5 mL, 0.1 M), the tube was sealed and placed on a pre-heated oil bath at 80 °C. The reaction mixture was stirred till indicated time. After removing from heat, the reaction was cooled to room temperature and work-up was performed with EtOAc and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then, the crude product was purified using column-chromatography to obtain the desired product **48** or **49**.

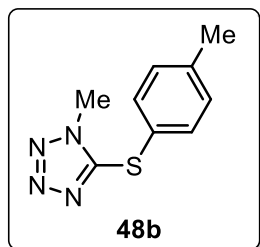
1-methyl-5-(phenylthio)-1H-tetrazole (48a)



Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47a-TMP** (169.5 mg, 0.35 mmol). The reaction was stirred for 5 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48a** (55 mg, 0.285 mmol, 82%) as yellowish liquid. ^1H NMR

(400 MHz, CDCl₃): δ 7.50-7.52 (m, 2H), 7.39-7.41 (m, 3H), 3.96 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 152.4, 132.5, 130, 129.6, 127.8, 34.1. HRMS (ESI) m/z : [M+H]⁺ calculated for C₈H₈N₄S 193.0947; found 193.0939.

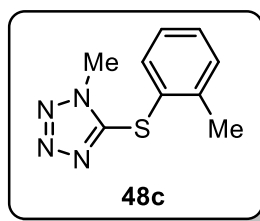
1-methyl-5-(*p*-tolylthio)-1H-tetrazole (48b)



Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47b-TMP** (174.38 mg, 0.35 mmol). The reaction was stirred for 5 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48b** (65 mg, 0.318 mmol, 91%) as colourless liquid.

¹H NMR (400 MHz, CDCl₃): δ 7.40 (d, J = 8 Hz, 2H), 7.18 (d, J = 8 Hz, 2H), 3.95 (s, 3H), 2.36 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 153.0, 140.2, 133.1, 130.7, 123.8, 34.17, 21.34. HRMS (ESI) m/z : [M+H]⁺ calculated for C₉H₁₀N₄S 207.1140; found 207.1145.

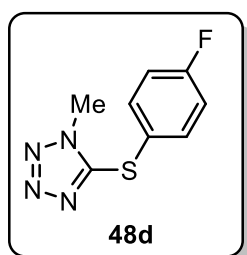
1-methyl-5-(*o*-tolylthio)-1H-tetrazole (48c)



Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47c-TMP** (174.3 mg, 0.35 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48c** (56 mg, 0.35 mmol, 78%) as yellowish oil.

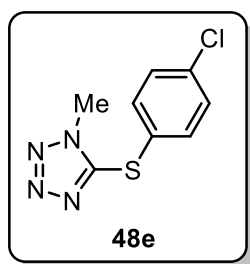
¹H NMR (400 MHz, CDCl₃): δ 7.44 (d, J = 8 Hz, 2H), 7.31-7.36 (m, 2H), 7.20-7.23 (m, 1H), 3.96 (s, 3H), 2.46 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 152.6, 141.3, 134.3, 131.5, 130.4, 127.5, 126.6, 34.0, 20.8. HRMS (ESI) m/z : [M+H]⁺ calculated for C₉H₁₀N₄S 207.0905; found 207.0917.

5-((4-fluorophenyl)thio)-1-methyl-1H-tetrazole (48d)

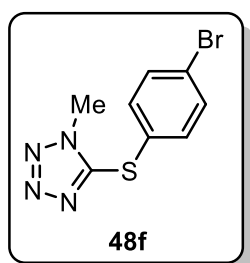


Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47d-TMP** (175.7 mg, 0.35 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48d** (56 mg, 0.26 mmol, 76%) as yellowish oil.

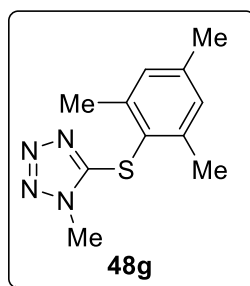
¹H NMR (400 MHz, CDCl₃): δ 7.53-7.56 (m, 2H), 7.08-7.10 (m, 2H), 3.96 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 163.75 (d, J_{C-F} = 250 Hz), 152.95, 135.76, 122.38, 117.3 (d, J_{C-F} = 25 Hz), 34.0. ¹⁹F NMR (376 MHz, CDCl₃): δ -109.7. HRMS (ESI) m/z : [M+H]⁺ calculated for C₈H₇N₄FS 211.0375; found 211.0377.

5-((4-chlorophenyl)thio)-1-methyl-1H-tetrazole (48e)

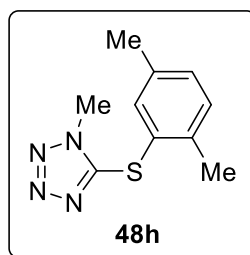
Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47e-TMP** (181.5 mg, 0.35 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48e** (65 mg, 0.28 mmol, 82%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.53 (d, J = 8 Hz, 2H), 7.41 (d, J = 8 Hz, 2H), 3.99 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 152.0, 134.1, 133.1, 126.7, 124.3, 34.1. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_8\text{H}_7\text{N}_4\text{S}\text{Cl}$ 227.0618; found 227.0622.

5-((4-bromophenyl)thio)-1-methyl-1H-tetrazole (48f)

Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47f-TMP** (197 mg, 0.35 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48f** (76 mg, 0.283 mmol, 81%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.44 (d, J = 8 Hz, 2H), 7.33 (d, J = 8 Hz, 2H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 152.2, 136.2, 134.1, 130.1, 125.9, 34.0. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_8\text{H}_7\text{N}_4\text{S}\text{Br}$ 272.9652; found 272.9648.

5-(mesitylthio)-1-methyl-1H-tetrazole (48g)

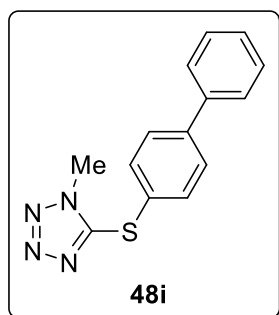
Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47g-TMP** (184 mg, 0.35 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48g** (53 mg, 0.227 mmol, 65%) as yellowish liquid. ^1H NMR (400 MHz, CDCl_3): δ 7.00 (s, 2H), 3.93 (s, 3H), 2.39 (s, 6H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 153.6, 143.2, 141.1, 130.0, 121.6, 33.82, 21.91, 21.16. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{11}\text{H}_{14}\text{N}_4\text{S}$ 235.1008; found 235.1013.

5-((2,5-dimethylphenyl)thio)-1-methyl-1H-tetrazole (48h)

Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47h-TMP** (179 mg, 0.35 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48h** (55 mg, 0.252 mmol, 72%) as white solid. ^1H NMR (400 MHz,

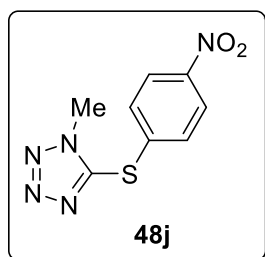
CDCl₃): δ 7.22 (s, 1H), 7.16 (d, J = 8 Hz, 1H), 7.10 (d, J = 8 Hz, 1H), 3.91 (s, 3H), 2.36 (s, 3H), 2.25 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 152.7, 138.0, 137.2, 134.6, 131.1, 126.2, 33.8, 20.8, 20.3. HRMS (ESI) m/z : [M+H]⁺ calculated for C₁₀H₁₂N₄S 221.0860; found 221.0857.

5-([1,1'-biphenyl]-4-ylthio)-1-methyl-1H-tetrazole (48i)



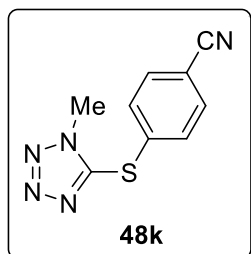
Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47i-TMP** (196 mg, 0.35 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48i** (61.9 mg, 0.231 mmol, 66%) as white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.54-7.61 (m, 6H), 7.43 (t, J = 8 Hz, 2H), 7.36 (t, J = 8 Hz, 2H), 7.10 (d, J = 8 Hz, 1H), 3.97 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 152.5, 142.7, 139.6, 133.0, 129.0, 128.6, 128.1, 127.1, 34.1. HRMS (ESI) m/z : [M+H]⁺ calculated for C₁₄H₁₂N₄S 269.0860; found 269.0859.

1-methyl-5-((4-nitrophenyl)thio)-1H-tetrazole (48j)

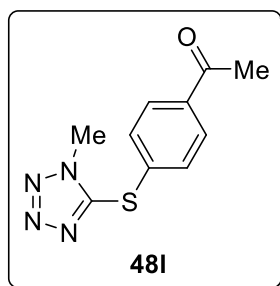


Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47j-TMP** (185 mg, 0.35 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48j** (61.4 mg, 0.259 mmol, 74%) as brownish solid. R_f 0.2 (AcOEt/Hexane: 30/70). ¹H NMR (400 MHz, CDCl₃): δ 8.23 (d, J = 8 Hz, 2H), 7.64 (d, J = 8 Hz, 1H), 4.07 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 150.2, 147.8, 137.0, 131.0, 124.8, 34.2. HRMS (ESI) m/z : [M+H]⁺ calculated for C₈H₇N₅O₂S 238.0390; found 238.0398.

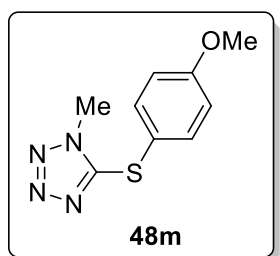
4-((1-methyl-1H-tetrazol-5-yl)thio)benzotrile (48k)



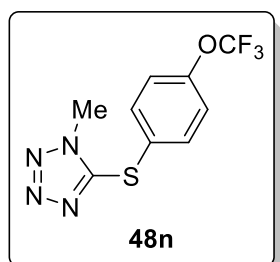
Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47k-TMP** (178 mg, 0.35 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48k** (54.7 mg, 0.252 mmol, 74%) as white solid. ¹H NMR (400 MHz, CDCl₃): δ 7.64 (d, J = 8 Hz, 2H), 7.55 (d, J = 8 Hz, 1H), 4.01 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 150.4, 134.8, 133.3, 131.2, 117.7, 112.8, 34.2. HRMS (ESI) m/z : [M+H]⁺ calculated for C₉H₇N₅S 218.0502; found 218.0499.

1-(4-((1-methyl-1H-tetrazol-5-yl)thio)phenyl)ethan-1-one (48l)

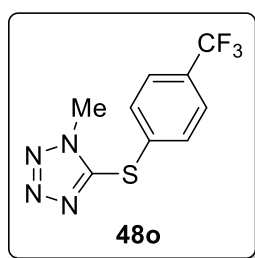
Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47l-TMP** (184 mg, 0.35 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48l** (59 mg, 0.252 mmol, 72%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.91 (d, $J = 8$ Hz, 2H), 7.50 (d, $J = 8$ Hz, 1H), 3.98 (s, 3H), 2.56 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 150.9, 137.2, 134.2, 130.9, 129.6, 34.3, 26.7. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{10}\text{H}_{10}\text{N}_4\text{OS}$ 235.0845; found 235.0835.

5-((4-methoxyphenyl)thio)-1-methyl-1H-tetrazole (48m)

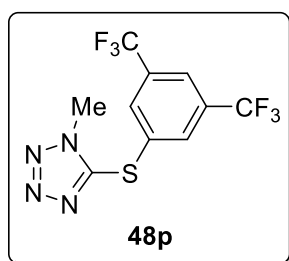
Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47q-TMP** (171 mg, 0.35 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48m** (68.5 mg, 0.308 mmol, 88%) as yellowish liquid. ^1H NMR (400 MHz, CDCl_3): δ 7.48 (d, $J = 8$ Hz, 2H), 6.89 (d, $J = 8$ Hz, 1H), 3.91 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 161.2, 153.8, 135.7, 117.0, 115.6, 55.5, 33.8. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_9\text{H}_{10}\text{N}_4\text{OS}$ 223.0848; found 223.0851.

1-methyl-5-((4-(trifluoromethoxy)phenyl)thio)-1H-tetrazole (48n)

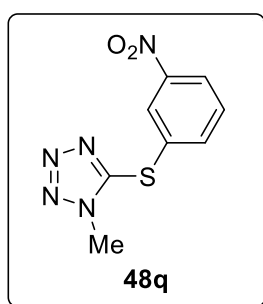
Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47m-An** (198 mg, 0.35 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48n** (71.4 mg, 0.259 mmol, 74%) as colourless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.58 (d, $J = 8$ Hz, 2H), 7.23 (d, $J = 8$ Hz, 1H), 3.99 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 152.2, 150.2, 134.4, 125.9, 122.2, 121.6, 119.0, 34.0. ^{19}F NMR (376 MHz, CDCl_3): δ -58.2. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_9\text{H}_7\text{N}_4\text{OF}_3\text{S}$ 277.0360; found 277.0368.

1-methyl-5-((4-(trifluoromethyl)phenyl)thio)-1H-tetrazole (48o)

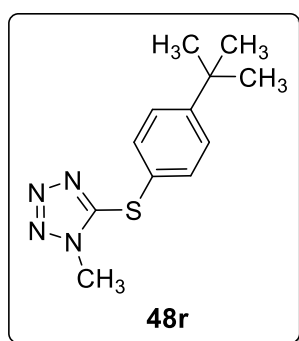
Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47n-An** (193 mg, 0.35 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48o** (74.6 mg, 0.287 mmol, 82%) as colourless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.62 (d, $J = 8$ Hz, 2H), 7.58 (d, $J = 8$ Hz, 1H), 4.00 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 151.1, 132.9, 131.6, 131.5, 127.6, 126.8, 124.9, 122.2, 34.3. ^{19}F NMR (376 MHz, CDCl_3): δ -62.5. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_9\text{H}_7\text{N}_4\text{F}_3\text{S}$ 261.0416; found 261.0419.

5-((3,5-bis(trifluoromethyl)phenyl)thio)-1-methyl-1H-tetrazole (48p)

Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47o-TMP** (217 mg, 0.35 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48p** (75 mg, 0.227 mmol, 65%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 8.02 (s, 2H), 7.90 (s, 1H), 4.07 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 150.8, 133.7, 133.4, 133.0, 132.7, 132.2, 131.1, 126.6, 123.9, 123.4, 121.2, 118.5, 34.1. ^{19}F NMR (376 MHz, CDCl_3): δ -62.9. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{10}\text{H}_6\text{N}_4\text{F}_6\text{S}$ 329.0872; found 329.0878.

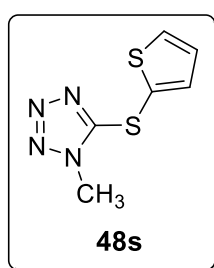
1-methyl-5-((3-nitrophenyl)thio)-1H-tetrazole (48q)

Synthesized following **GP-A** starting from **46a** (40.6 mg, 0.35 mmol) and **47p-TMP** (285 mg, 0.35 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48q** (62 mg, 0.262 mmol, 75%) as yellowish oil. ^1H NMR (400 MHz, CDCl_3): δ 8.38 (t, $J = 2.2$ Hz, 1H), 8.21 (dq, $J = 8$ and 1 Hz, 1H), 7.86 (dq, $J = 8$ and 1 Hz, 1H), 7.60 (t, $J = 8$ Hz, 1H), 4.04 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 151.3, 148.7, 138.2, 130.9, 130.1, 127.0, 124.4, 34.2. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_8\text{H}_7\text{N}_5\text{O}_2\text{S}$ 238.0410; found 238.0401

5-((4-(tert-butyl)phenyl)thio)-1-methyl-1H-tetrazole (48r)

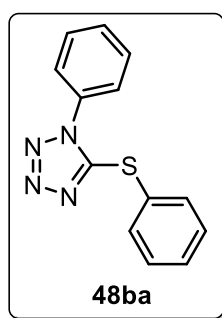
Synthesized following **GP-A** starting from **46a** (58 mg, 0.5 mmol) and **47d-OTf** (244 mg, 0.5 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48r** (59 mg, 0.24 mmol, 48%) as colourless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.47 (d, $J = 8$ Hz, 2H), 7.41 (d, $J = 8$ Hz, 2H), 3.96 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, CDCl_3):

δ 153.2, 152.9, 132.7, 129.5, 127.0, 123.8, 120.2, 115.4, 34.8, 34.1, 31.1. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{12}\text{H}_{16}\text{N}_4\text{S}$ 249.1570; found 249.1565

1-methyl-5-(thiophen-2-ylthio)-1H-tetrazole (48s)

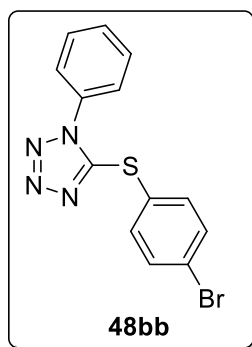
Synthesized following **GP-A** starting from **46a** (58 mg, 0.5 mmol) and **47f-OTf** (218 mg, 0.5 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48s** (24 mg, 0.12 mmol, 24%) as black oil. ^1H NMR (400 MHz, CDCl_3): δ 7.56 (dd, $J = 8$ & 1 Hz, 1H), 7.45 (dd, $J = 8$ & 1 Hz, 1H), 7.10 (dd, $J = 8$ & 1 Hz, 1H), 4.04 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 152.7, 137.5, 133.0, 128.2, 122.9, 115.4, 34.1. HRMS (ESI) m/z :

$[\text{M}+\text{H}]^+$ calculated for $\text{C}_6\text{H}_6\text{N}_4\text{S}_2$ 200.0474; found 200.0472.

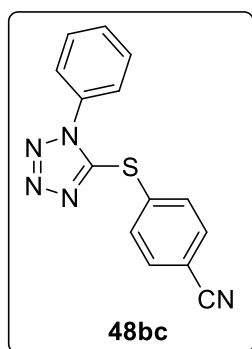
1-phenyl-5-(phenylthio)-1H-tetrazole (48ba)

Synthesized following **GP-A** starting from **46b** (44.5 mg, 0.25 mmol) and **47a-TMP** (121 mg, 0.25 mmol). The reaction was stirred for 6 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48ba** (48 mg, 0.190 mmol, 76%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.54-7.58 (m, 7H), 7.37-7.43 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 153.7, 134.0, 133.6, 130.4, 126.8, 124.5. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated

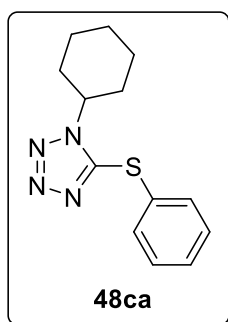
for $\text{C}_{13}\text{H}_{10}\text{N}_4\text{S}$ 255.1225; found 255.1227.

5-((4-bromophenyl)thio)-1-phenyl-1H-tetrazole (48bb)

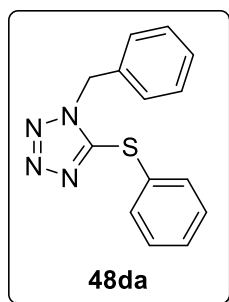
Synthesized following **GP-A** starting from **46b** (44.5 mg, 0.25 mmol) and **47f-TMP** (141 mg, 0.25 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48bb** (59 mg, 0.18 mmol, 72%) as yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 7.50-7.55 (m, 7H), 7.42 (d, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 153.2, 135.6, 133.5, 133.1, 130.6, 129.9, 125.8, 125.0, 124.5. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{13}\text{H}_9\text{N}_4\text{BrS}$ 331.9731; found 332.9808

4-((1-phenyl-1H-tetrazol-5-yl)thio)benzonitrile (48bc)

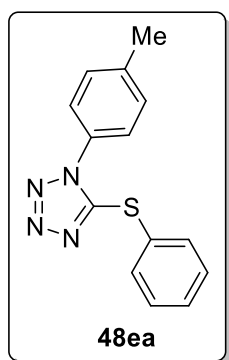
Synthesized following **GP-A** starting from **46b** (44.5 mg, 0.25 mmol) and **47k-TMP** (127 mg, 0.25 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48bc** (45.3 mg, 0.162 mmol, 65%) as off-white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.64 (m, 5H), 7.54-7.58 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 151.6, 133.8, 133.1, 133.0, 130.9, 124.5, 117.8, 113.4. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{14}\text{H}_9\text{N}_5\text{S}$ 280.0679; found 280.0652.

1-cyclohexyl-5-(phenylthio)-1H-tetrazole (48ca)

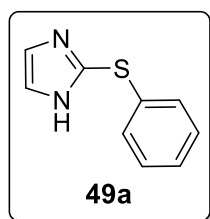
Synthesized following **GP-A** starting from **46c** (46 mg, 0.25 mmol) and **47a-TMP** (121 mg, 0.25 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48ca** (40 mg, 0.155 mmol, 62%) as yellowish liquid. ^1H NMR (400 MHz, CDCl_3): δ 7.51-7.54 (m, 2H), 7.38-7.40 (m, 3H), 1.90-1.93 (m, 6H), 1.28-1.39 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3): δ 151.1, 132.6, 129.9, 129.5, 128.4, 58.6, 32.4, 25.3, 24.8. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{13}\text{H}_{16}\text{N}_4\text{S}$ 261.1114; found 261.1117.

1-benzyl-5-(phenylthio)-1H-tetrazole (48da)

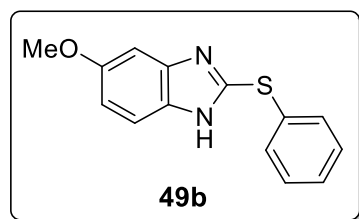
Synthesized following **GP-A** starting from **46d** (48 mg, 0.25 mmol) and **47a-TMP** (121 mg, 0.25 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48da** (44.2 mg, 0.165 mmol, 66%) as yellowish liquid. ^1H NMR (400 MHz, CDCl_3): δ 7.43-7.46 (m, 2H), 7.32-7.35 (m, 6H), 7.22-7.24 (m, 2H), 5.50 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 152.4, 133.0, 132.7, 129.9, 129.6, 129.18, 129.06, 128.1, 127.8, 51.4. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{S}$ 269.0663; found 269.0655.

5-(phenylthio)-1-(p-tolyl)-1H-tetrazole (48ea)

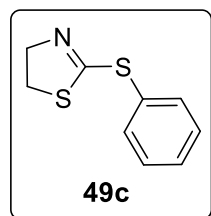
Synthesized following **GP-A** starting from **46e** (48 mg, 0.25 mmol) and **47a-TMP** (121 mg, 0.25 mmol). The reaction was stirred for 8 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **48ea** (55 mg, 0.205 mmol, 82%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 7.57 (d, $J = 8$ Hz, 2H), 7.35-7.43 (m, 7H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 153.6, 140.9, 134.0, 131.1, 130.3, 129.8, 127.0, 21.4. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{12}\text{N}_4\text{S}$ 269.1354; found 269.1367.

2-(phenylthio)-1H-imidazole (49a)

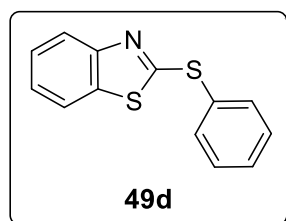
Synthesized following **GP-A** starting from 1H-imidazole-2-thiol (35 mg, 0.35 mmol) and **47a-TMP** (170 mg, 0.35 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **49a** (42 mg, 0.238 mmol, 68%) as white solid. ^1H NMR (600 MHz, $\text{DMSO}-d_6$): δ 7.03 (t, $J = 8$ Hz, 2H), 6.91-6.95 (m, 3H), 6.83 (d, $J = 8$ Hz, 2H). ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$): δ 134.9, 133.6, 128.3, 126.3, 125.4. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_9\text{H}_8\text{N}_2\text{S}$ 177.0858; found 177.0862.

5-methoxy-2-(phenylthio)-1H-benzo[d]imidazole (49b)

Synthesized following **GP-A** starting from 5-methoxy-1H-benzo[d]imidazole-2-thiol (63 mg, 0.35 mmol) and **47a-TMP** (170 mg, 0.35 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **49b** (64 mg, 0.252 mmol, 72%) as yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 7.42-7.45 (m, 2H), 7.38 (d, $J = 8$ Hz, 1H), 7.21-7.23 (m, 3H), 6.76 (d, $J = 4$ Hz, 1H), 6.83 (q, $J = 8$ Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 156.5, 147.1, 139.3, 134.4, 132.2, 131.0, 129.6, 128.5, 115.8, 112.3, 97.1, 55.8. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{OS}$ 257.1179; found 257.1184.

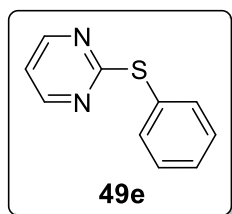
2-(phenylthio)-4,5-dihydrothiazole (49c) [40]

Synthesized following **GP-A** starting from 4,5-dihydrothiazole-2-thiol (38.9 mg, 0.35 mmol) and **47a-TMP** (170 mg, 0.35 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **49c** (52 mg, 0.266 mmol, 76%) as colourless liquid. ^1H NMR (400 MHz, CDCl_3): δ 7.63-7.65 (m, 2H), 7.40-7.44 (m, 3H), 4.26 (t, $J = 8$ Hz, 2H), 3.30 (t, $J = 8$ Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 167.7, 135.6, 130.0, 129.2, 65.4, 35.0. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{11}\text{H}_9\text{NS}$ 196.0706; found 196.0710.

2-(phenylthio)benzo[d]thiazole (49d) [31, 40]

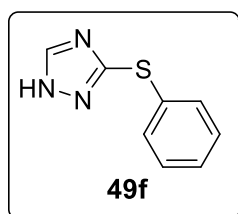
Synthesized following **GP-A** starting from benzo[d]thiazole-2-thiol (58.5 mg, 0.35 mmol) and **47a-TMP** (170 mg, 0.35 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **49d** (75.8 mg, 0.3115 mmol, 89%) as colourless liquid. ^1H NMR (400 MHz, CDCl_3): δ 7.88 (d, $J = 8$ Hz, 1H), 7.73 (d, $J = 8$ Hz, 2H), 7.64 (d, $J = 8$ Hz, 1H), 7.41-7.49 (m, 3H) 7.40 (t, $J = 8$ Hz, 1H), 7.26 (t, $J = 8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 169.7, 153.9, 135.5, 135.4, 130.5, 129.9, 126.2, 124.3, 121.9, 120.8. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{13}\text{H}_9\text{NS}_2$ 244.0624; found 244.0624.

2-(phenylthio)pyrimidine (49e) [31, 40]



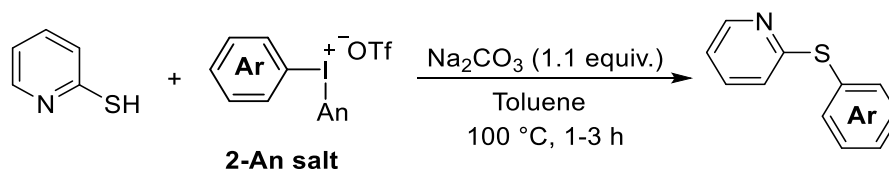
Synthesized following **GP-A** starting from pyrimidine-2-thiol (40 mg, 0.35 mmol) and **47a-TMP** (170 mg, 0.35 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **49e** (50.7 mg, 0.269 mmol, 77%) as yellow liquid. ^1H NMR (400 MHz, CDCl_3): δ 8.48 (d, J = 8 Hz, 2H), 7.62-7.65 (m, 2H), 7.45 (t, J = 4 Hz, 1H), 6.95 (t, J = 4 Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 172.8, 157.6, 135.3, 129.3, 117.0. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{10}\text{H}_8\text{N}_2\text{S}$ 189.0920; found 189.0922.

3-(phenylthio)-1H-1,2,4-triazole (**49f**) [40]



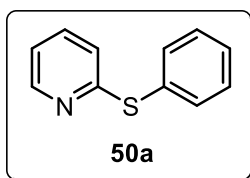
Synthesized following **GP-A** starting from pyrimidine-2-thiol (40 mg, 0.35 mmol) and **47a-TMP** (170 mg, 0.35 mmol). The reaction was stirred for 10 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **49f** (44 mg, 0.245 mmol, 70%) as colourless liquid. ^1H NMR (400 MHz, CDCl_3): δ 8.04 (s, 1H), 7.52-7.53 (m, 2H), 7.34-7.37 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 156.3, 147.4, 132.5, 130.4, 129.6, 128.7, 125.1. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_8\text{H}_7\text{N}_3\text{S}$ 178.0838; found 178.0844.

3.9.2 General procedure B (GP-B): S-arylation of 2-mercaptopyridine



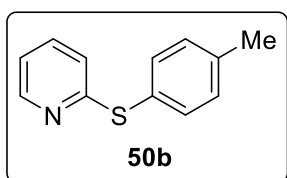
To an oven-dried Schlenck-tube, 2-mercaptopyridine (0.25 mmol), diaryliodonium salt **47-An** (0.25 mmol, 1 equiv.), and Na_2CO_3 (0.275 mmol, 1.1 equiv.) were added. After adding toluene (3.5 mL, 0.1 M), the tube was sealed and placed on a pre-heated oil bath at 100 °C. After removing from heat, the reaction was cooled to room temperature and performed work-up with EtOAc and water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Then, the crude product was purified using column-chromatography to obtain the desired product **50**.

2-(phenylthio)pyridine (**50a**) [27, 40]



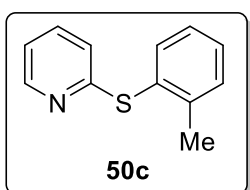
Synthesized following **GP-B** starting from 2-mercaptopyridine (38.9 mg, 0.35 mmol) and **47a-An** (161 mg, 0.35 mmol). The reaction was stirred for 2 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **50a** (49 mg, 0.262 mmol, 75%) as colourless liquid. ^1H NMR (400 MHz, CDCl_3): δ 8.39-8.41 (m, 1H), 7.56-7.59 (m, 2H), 7.39-7.45 (m, 4H), 6.95-6.98 (m, 1H), 6.87 (dt, $J = 8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 61.6, 149.6, 136.8, 135.0, 131.1, 129.7, 129.2, 121.4, 120.02. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{11}\text{H}_9\text{NS}$ 188.0956; found 188.0989.

2-(*p*-tolylthio)pyridine (**50b**) [41]



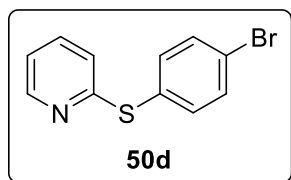
Synthesized following **GP-B** starting from 2-mercaptopyridine (38.9 mg, 0.35 mmol) and **47b-An** (166 mg, 0.35 mmol). The reaction was stirred for 2 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **50b** (57.8 mg, 0.287 mmol, 82%) as white solid. ^1H NMR (400 MHz, CDCl_3): δ 8.40 (d, $J = 8$ Hz, 1H), 7.47 (d, $J = 8$ Hz, 2H), 7.41 (dt, $J = 8$ & 1 Hz, 1H), 7.22 (d, $J = 8$ Hz, 2H), 6.95 (dq, $J = 5$ & 1 Hz, 1H), 6.82 (t, $J = 8$ Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 162.3, 149.6, 139.5, 136.7, 135.3, 130.6, 127.3, 120.9, 119.6, 21.3. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{12}\text{H}_{11}\text{NS}$ 202.0690; found 202.0758.

2-(*o*-tolylthio)pyridine (**50c**) [40]



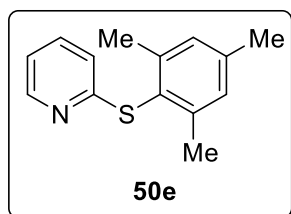
Synthesized following **GP-B** starting from 2-mercaptopyridine (38.9 mg, 0.35 mmol) and **47b-An** (166 mg, 0.35 mmol). The reaction was stirred for 3 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **50c** (57.8 mg, 0.287 mmol, 72%) as colourless liquid. ^1H NMR (400 MHz, CDCl_3): δ 8.40 (d, $J = 8$ Hz, 1H), 7.59 (d, $J = 8$ Hz, 1H), 7.39 (dt, $J = 8$ & 1 Hz, 1H), 7.33-7.34 (m, 2H), 7.21-7.25 (m, 1H), 6.95 (dq, $J = 5$ & 1 Hz, 1H), 6.82 (t, $J = 8$ Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 161.3, 149.7, 142.8, 136.8, 131.1, 129.9, 127.2, 120.4, 119.6, 20.9. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{12}\text{H}_{11}\text{NS}$ 202.0690; found 202.0758.

2-((4-bromophenyl)thio)pyridine (**50d**) [41]



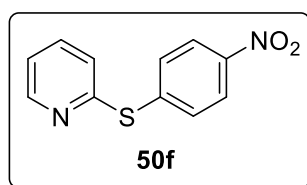
Synthesized following **GP-B** starting from 2-mercaptopyridine (38.9 mg, 0.35 mmol) and **47b-An** (188.6 mg, 0.35 mmol). The reaction was stirred for 3 h. The reaction mixture was purified by column chromatography (30% in ethyl acetate in hexane) to afford **50d** (72.6 mg, 0.273 mmol, 78%) as yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 8.41 (d, $J = 8$ Hz, 1H), 7.42-7.54 (m, 5H), 7.01 (dq, $J = 5$ & 1 Hz, 1H), 6.84 (t, $J = 8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 160.4, 149.8, 136.9, 136.3, 132.8, 130.4, 123.5, 121.8, 120.4. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{11}\text{H}_8\text{NSBr}$ 266.0160; found 266.0168.

2-(mesitylthio)pyridine (50e)



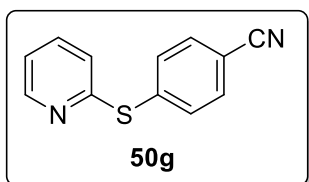
Synthesized following **GP-B** starting from 2-mercaptopyridine (38.9 mg, 0.35 mmol) and **47b-An** (175.8 mg, 0.35 mmol). The reaction was stirred for 3 h. The reaction mixture was purified by column chromatography (5% in ethyl acetate in hexane) to afford **50e** (57.8 mg, 0.287 mmol, 62%) as light-yellow liquid. ^1H NMR (400 MHz, CDCl_3): δ 8.38 (d, $J = 8$ Hz, 1H), 7.33-7.37 (m, 1H), 7.01 (s, 2H), 6.90-6.93 (m, 1H), 6.53 (d, $J = 8$ Hz, 1H), 2.38 (s, 6H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 161.6, 149.6, 143.8, 139.8, 136.7, 129.5, 125.8, 119.0, 21.7, 21.4. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{15}\text{NS}$ 230.0925; found 230.0946.

2-((4-nitrophenyl)thio)pyridine (50f) [40]



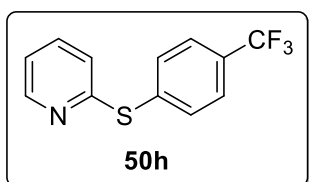
Synthesized following **GP-B** starting from 2-mercaptopyridine (38.9 mg, 0.35 mmol) and **47f-An** (176 mg, 0.35 mmol). The reaction was stirred for 3 h. The reaction mixture was purified by column chromatography (5% in ethyl acetate in hexane) to afford **50f** (71.5 mg, 0.308 mmol, 88%) as yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 8.50 (d, $J = 8$ Hz, 1H), 8.16 (d, $J = 8$ Hz, 2H), 7.58 (d, $J = 8$ Hz, 2H), 7.29 (d, $J = 8$ Hz, 1H), 7.15-7.19 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 156.6, 150.5, 147.0, 142.5, 137.5, 131.9, 125.0, 124.2, 122.1. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{15}\text{NS}$ 233.0454; found 233.0462.

4-(pyridin-2-ylthio)benzotrile (50g) [40]



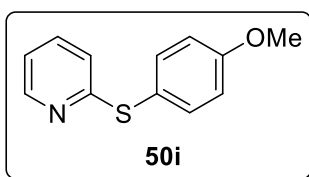
Synthesized following **GP-B** starting from 2-mercaptopyridine (38.9 mg, 0.35 mmol) and **47g-An** (169 mg, 0.35 mmol). The reaction was stirred for 3 h. The reaction mixture was purified by column chromatography (5-10% in ethyl acetate in hexane) to afford **50g** (61.6 mg, 0.308 mmol, 83%) as colourless liquid. ^1H NMR (400 MHz, CDCl_3): δ 8.47 (d, $J = 8$ Hz, 1H), 7.53-7.61 (m, 5H), 7.21 (d, $J = 8$ Hz, 1H), 7.11-7.15 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 150.4, 139.7, 137.4, 132.7, 132.5, 124.5, 121.8, 118.5, 11.3. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{12}\text{H}_8\text{N}_2\text{S}$ 213.0408; found 213.0408.

2-((4-(trifluoromethyl)phenyl)thio)pyridine (**50h**) [41]



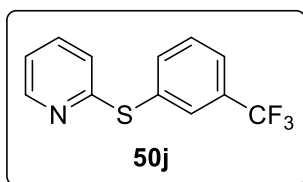
Synthesized following **GP-B** starting from 2-mercaptopyridine (38.9 mg, 0.35 mmol) and **47h-An** (184 mg, 0.35 mmol). The reaction was stirred for 3 h. The reaction mixture was purified by column chromatography (5% in ethyl acetate in hexane) to afford **50h** (69.6 mg, 0.273 mmol, 78%) as colourless liquid. ^1H NMR (400 MHz, CDCl_3): δ 8.45 (d, $J = 8$ Hz, 1H), 7.60-7.65 (m, 4H), 7.53 (t, $J = 8$ Hz, 1H), 7.06-7.10 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 158.8, 150.1, 137.1, 133.6, 130.4 (q, $J_{\text{C-F}} = 40$ Hz), 129.9, 126.2, 125.3, 123.1, 122.6, 121.1. ^{19}F NMR (376 MHz, CDCl_3): δ -61.7. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{12}\text{H}_8\text{NSF}_3$ 258.0258; found 258.0262.

2-((4-methoxyphenyl)thio)pyridine (**50i**) [41]



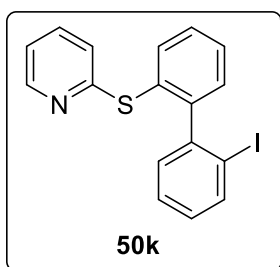
Synthesized following **GP-B** starting from 2-mercaptopyridine (38.9 mg, 0.35 mmol) and **47i-An** (171 mg, 0.35 mmol). The reaction was stirred for 3 h. The reaction mixture was purified by column chromatography (5% in ethyl acetate in hexane) to afford **50i** (49 mg, 0.227 mmol, 65%) as colourless liquid. ^1H NMR (400 MHz, CDCl_3): δ 8.38 (d, $J = 8$ Hz, 1H), 7.52 (d, $J = 8$ Hz, 2H), 7.40 (t, $J = 8$ Hz, 1H), 6.92-6.96 (m, 3H), 6.76 (d, $J = 8$ Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 162.9, 160.7, 149.5, 137.3, 136.6, 121.1, 120.4, 119.5, 115.3, 55.5. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{12}\text{H}_8\text{NSF}_3$ 256.0328; found 256.0330.

2-((3-(trifluoromethyl)phenyl)thio)pyridine (**50j**)



Synthesized following **GP-B** starting from 2-mercaptopyridine (38.9 mg, 0.35 mmol) and **47j-An** (185 mg, 0.35 mmol). The reaction was stirred for 3 h. The reaction mixture was purified by column chromatography (5% in ethyl acetate in hexane) to afford **50j** (64 mg, 0.252 mmol, 72%) as yellow liquid. ^1H NMR (400 MHz, CDCl_3): δ 8.43 (d, $J = 8$ Hz, 1H), 7.82 (s, 1H), 7.73 (d, $J = 8$ Hz, 1H), 7.62 (d, $J = 8$ Hz, 1H), 7.51 (t, $J = 8$ Hz, 2H), 7.03-7.07 (m, 1H), 7.01 (d, $J = 8$ Hz, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 159.4, 150.0, 137.5, 137.1, 133.6, 133.1, 132.4, 132.1, 131.7, 131.4, 130.9, 129.9, 125.5, 125.1, 122.3, 120.7. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{12}\text{H}_8\text{NSF}_3$ 256.0330; found 256.0334.

2-((2'-iodo-[1,1'-biphenyl]-2-yl)thio)pyridine (**50k**)



Synthesized following **GP-B** starting from 2-mercaptopyridine (27.7 mg, 0.25 mmol) and **47c-OTf** (108 mg, 0.25 mmol). The reaction was stirred for 3 h. The reaction mixture was purified by column chromatography (5% in ethyl acetate in hexane) to afford **50k** (64 mg, 0.165 mmol, 66%) as yellow liquid. ^1H NMR (400 MHz, CDCl_3): δ 8.33 (d, $J = 8$ Hz, 1H), 7.55 (dd, $J = 8$ & 1 Hz, 1H), 7.66-7.68 (m, 1H), 7.28 (dd, $J = 8$ & 1 Hz, 1H), 7.21-7.25 (m, 1H), 7.12 (d, $J = 8$ Hz, 1H), 6.91-6.99 (m, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ 160.7, 149.5, 148.2, 145.3, 138.8, 136.5, 135.7, 131.1, 130.1, 128.9, 127.6, 122.5, 120.1, 100.1. HRMS (ESI) m/z : $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{17}\text{H}_{12}\text{NSI}$ 389.9733; found 389.9735.

3.10 Representative ^1H and ^{13}C NMR spectra

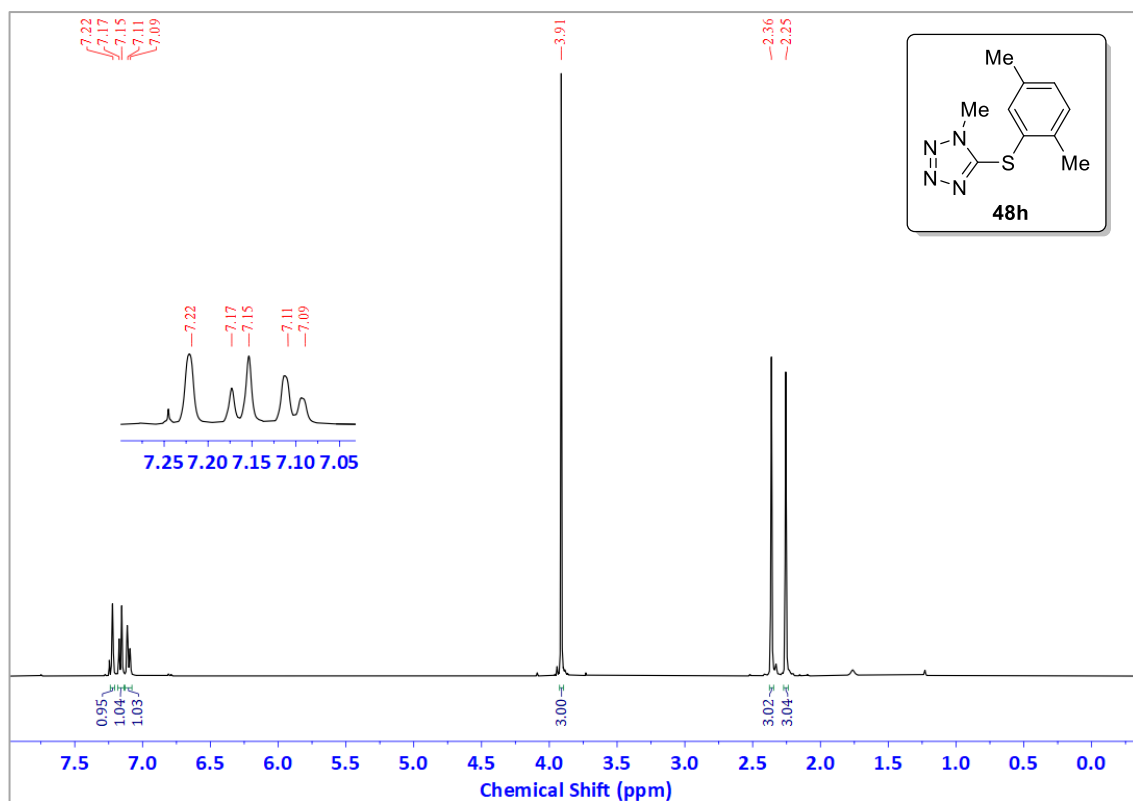


Figure 3.4 ^1H NMR spectrum of **48h** (CDCl_3 , 400 MHz, 298 K)

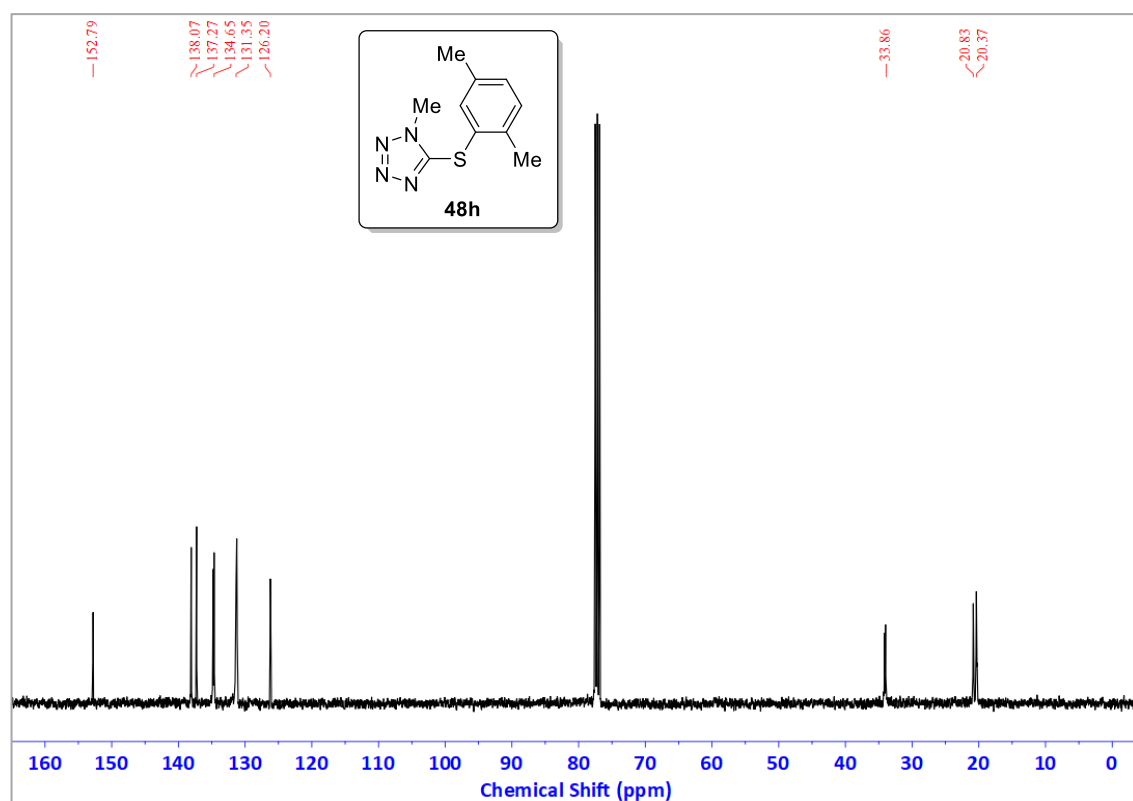


Figure 3.5 ^{13}C NMR spectrum of **48h** (CDCl_3 , 100 MHz, 298 K)

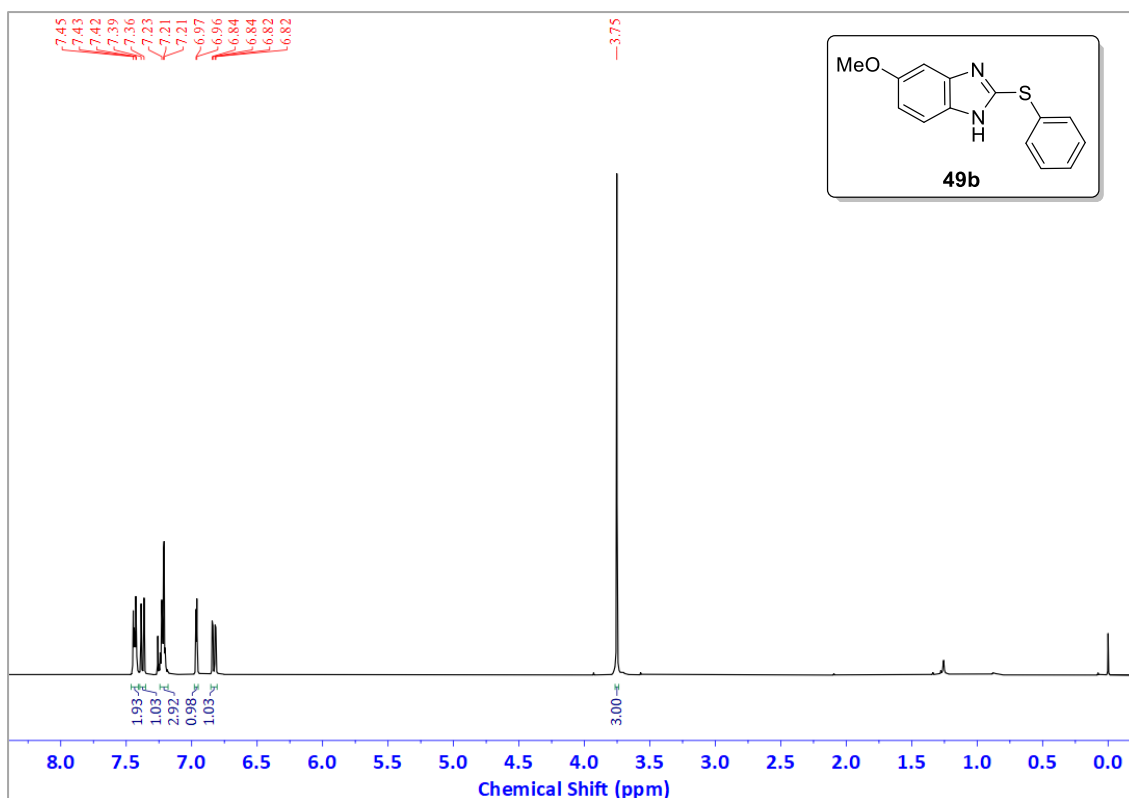


Figure 3.6 ^1H NMR spectrum of **49b** (CDCl_3 , 400 MHz, 298 K)

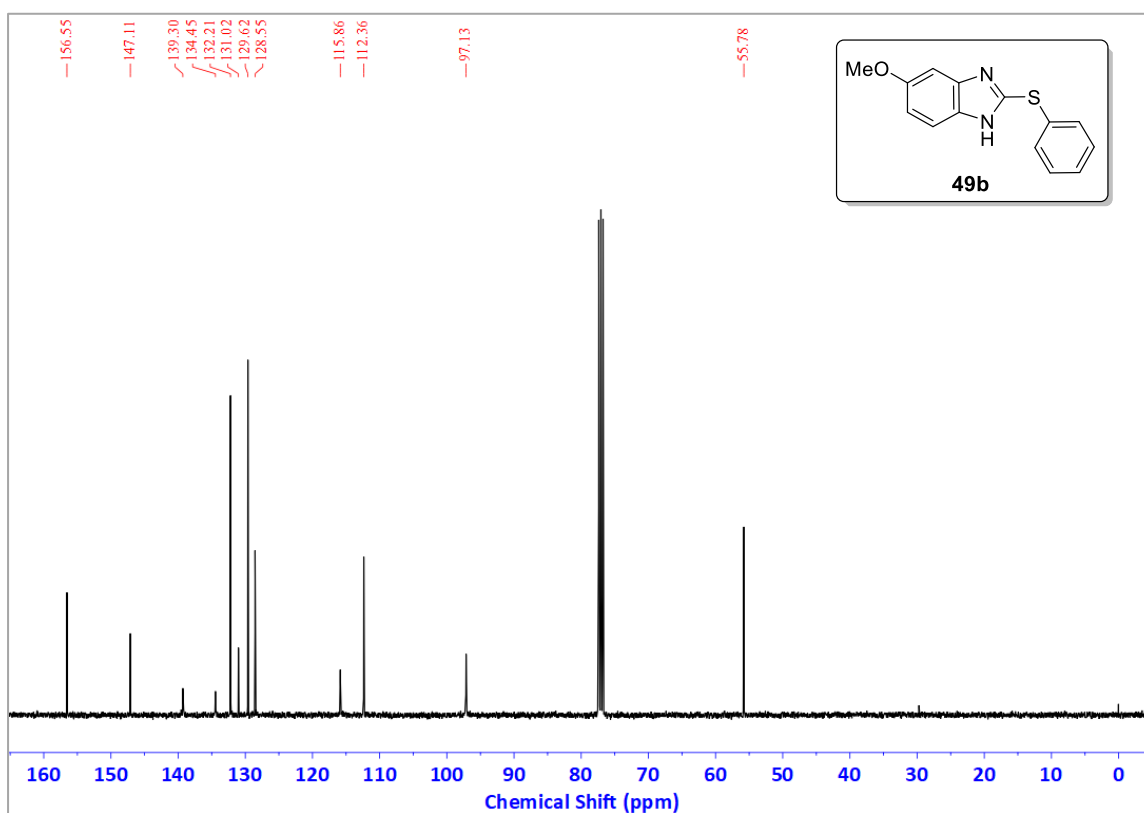


Figure 3.7 ^{13}C NMR spectrum of **49b** (CDCl_3 , 100 MHz, 298 K)

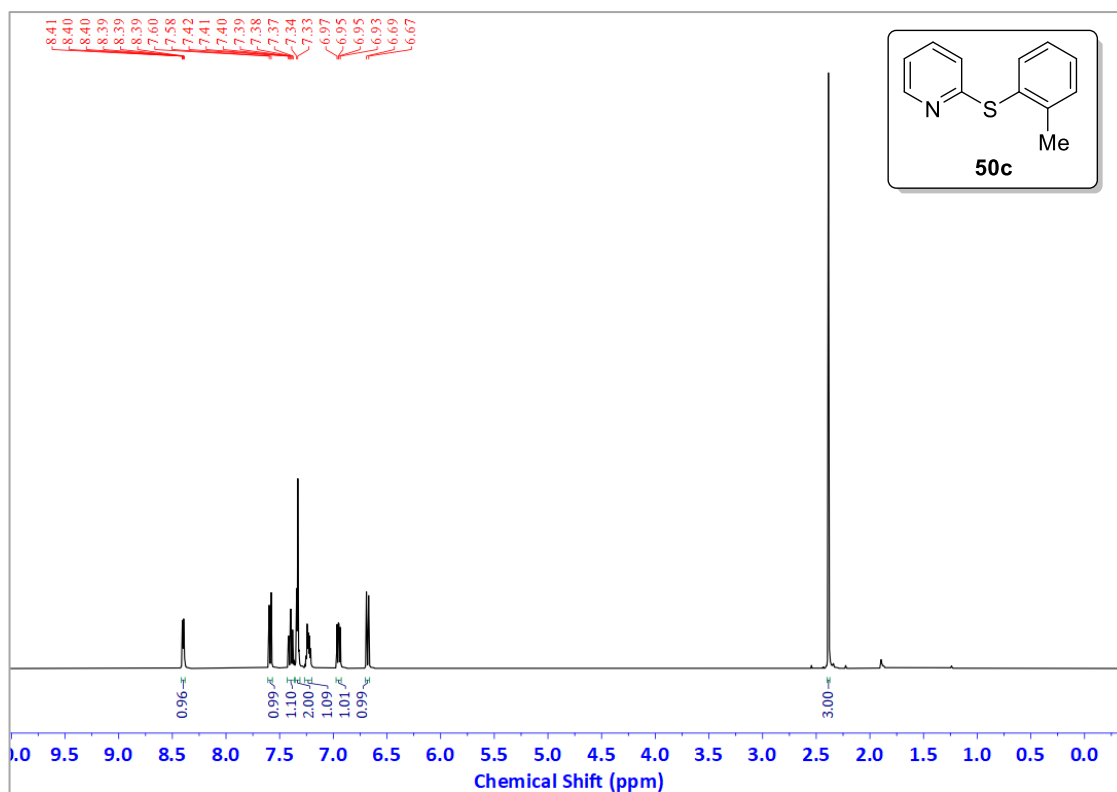


Figure 3.8 ^1H NMR spectrum of **50c** (CDCl_3 , 400 MHz, 298 K)

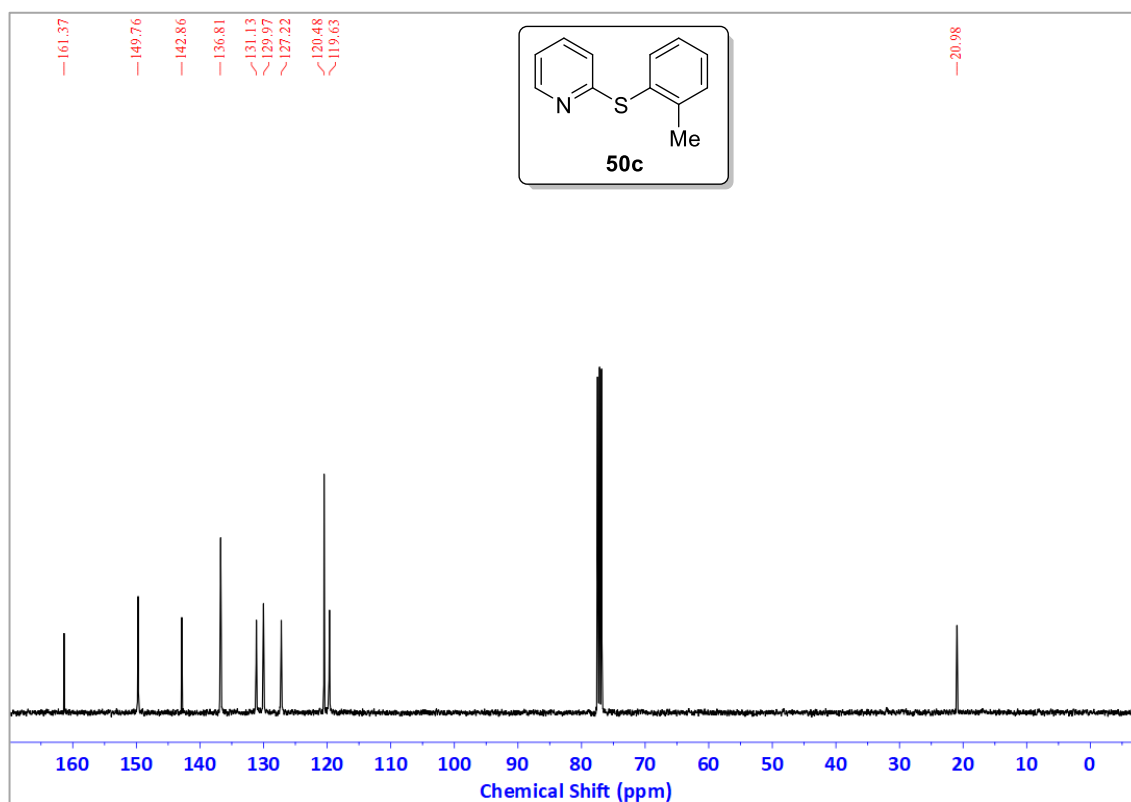


Figure 3.9 ^{13}C NMR spectrum of **50c** (CDCl_3 , 100 MHz, 298 K)

3.11 DFT Calculations

3.11.1 Absolute and Relative Gibbs free energies for reaction pathway at B3LYP/LANL2DZ level

Table 3.8 Absolute and Relative Gibbs free energies

Species	G (in a.u)	Relative G (in kcal/mol)
47a-An+2-MP (deprotonated)	-1419.761809	0.00
IM1+OTf	-1419.795936	-21.41499964
TS1+OTf	-1419.772011	-6.401846818
50a+An-I+OTf	-1419.895501	-83.89293323
47a-An+2-MP (deprotonated)	-1419.761809	0.00
IM2+OTf	-1419.796404	-21.70867386
TS2+OTf	-1419.769484	-4.816131575
50i+Ph-I+OTf	-1419.896029	-84.22425798

3.11.2 Intrinsic reaction co-ordinate (IRC) plots of all transition states

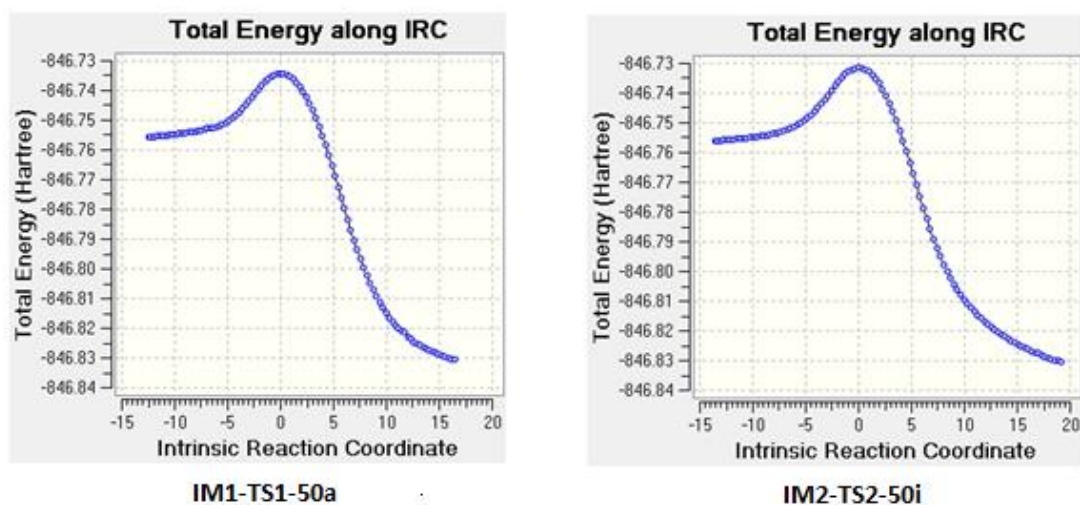


Figure 3.10 IRC plots of TS1 and TS2

3.12 Bibliography

- [1] Scott, K. A. and Njardarson, J. T. Analysis of US FDA-Approved Drugs Containing Sulfur Atoms. In Jiang, X., editor, *Sulfur Chemistry*, pages 1–34, Springer International Publishing, Cham, 2019.
- [2] Wang, N., Saidhareddy, P., and Jiang, X. Construction of sulfur-containing moieties in the total synthesis of natural products. *Natural Product Reports*, 37(2):246–275, 2020.
- [3] Okamoto, T., Mitsui, C., Yamagishi, M., Nakahara, K., Soeda, J., Hirose, Y., Miwa, K., Sato, H., Yamano, A., and Matsushita, T. V-shaped organic semiconductors with solution processability, high mobility, and high thermal durability. *Advanced Materials*, 25(44):6392–6397, 2013.
- [4] Mori, T., Nishimura, T., Yamamoto, T., Doi, I., Miyazaki, E., Osaka, I., and Takimiya, K. Consecutive thiophene-annulation approach to π -extended thienoacene-based organic semiconductors with [1]benzothieno[3,2-*b*][1]benzothiophene (BTBT) substructure. *Journal of the American Chemical Society*, 135(37):13900–13913, 2013.
- [5] Gao, F., Xiao, J., and Huang, G. Current scenario of tetrazole hybrids for antibacterial activity. *European Journal of Medicinal Chemistry*, 184:111744, 2019.
- [6] Ding, M., Wan, S., Wu, N., Yan, Y., Li, J., and Bao, X. Synthesis, Structural Characterization, and Antibacterial and Antifungal Activities of Novel 1,2,4-Triazole Thioether and Thiazolo [3,2-*b*]-1,2,4-triazole Derivatives Bearing the 6-Fluoroquinazolinylyl Moiety. *Journal of Agricultural and Food Chemistry*, 69(50):15084–15096, 2021.
- [7] Fan, Z., Shi, J., Luo, N., Ding, M., and Bao, X. Synthesis, crystal structure, and agricultural antimicrobial evaluation of novel quinazoline thioether derivatives incorporating the 1,2,4-triazolo [4,3-*a*] pyridine moiety. *Journal of Agricultural and Food Chemistry*, 67(42):11598–11606, 2019.
- [8] Li, P., Yang, Y., Wang, X., and Wu, X. Recent achievements on the agricultural applications of thioether derivatives: A 2010–2020 decade in review. *Journal of Heterocyclic Chemistry*, 58(6):1225–1251, 2021.

- [9] Wang, C., Zieger, M. M., Schenzel, A., Wegener, M., Willenbacher, J., Barner-Kowollik, C., and Bowman, C. N. Photoinduced Tetrazole-Based Functionalization of Off-Stoichiometric Clickable Microparticles. *Advanced Functional Materials*, 27(7):1605317, 2017.
- [10] Wang, X., Hu, H., Tian, A., Lin, H., and Li, J. Application of tetrazole-functionalized thioethers with different spacer lengths in the self-assembly of polyoxometalate-based hybrid compounds. *Inorganic Chemistry*, 49(22):10299–10306, 2010.
- [11] Yang, L., Shen, Y., Chen, Y., Pan, X., Wang, X., and Wang, X. A novel octamolybdate-based metal-organic complex constructed from a bis(tetrazole)-functionalized thioether ligand and an Anderson-type polyoxometalate. *Inorganic Chemistry Communications*, 108:107493, 2019.
- [12] Hrabalek, A., Myznikov, L., Kunes, J., Vavrova, K., and Koldobskii, G. A simple method for the preparation of 5-alkylsulfinyl-1-aryltetrazoles. *Tetrahedron Letters*, 45(42):7955–7957, 2004.
- [13] Welz, R. and Müller, S. 5-(Benzylmercapto)-1H-tetrazole as activator for 2'-O-TBDMS-phosphoramidite building blocks in RNA synthesis. *Tetrahedron Letters*, 43(5):795–797, 2002.
- [14] Nielsen, S. F., Nielsen, E. Ø., Olsen, G. M., Liljefors, T., and Peters, D. Novel potent ligands for the central nicotinic acetylcholine receptor: synthesis, receptor binding, and 3D-QSAR analysis. *Journal of Medicinal Chemistry*, 43(11):2217–2226, 2000.
- [15] Lian, Z., Bhawal, B. N., Yu, P., and Morandi, B. Palladium-catalyzed carbon-sulfur or carbon-phosphorus bond metathesis by reversible arylation. *Science*, 356(6342):1059–1063, 2017.
- [16] Yang, P., Wang, X., Li, B., Yang, Y., Yue, J., Suo, Y., Tong, H., He, G., Lu, X., and Chen, G. Streamlined construction of peptide macrocycles *via* palladium-catalyzed intramolecular S-arylation in solution and on DNA. *Chemical Science*, 12(16):5804–5810, 2021.
- [17] Fang, Y., Rogge, T., Ackermann, L., Wang, S. Y., and Ji, S. J. Nickel-catalyzed reductive thiolation and selenylation of unactivated alkyl bromides. *Nature Communications*, 9(1):1–10, 2018.

- [18] Wu, J. R., Lin, C. H., and Lee, C. F. Iron-catalyzed thioetherification of thiols with aryl iodides. *Chemical Communications*, (29):4450–4452, 2009.
- [19] Herrero, M. T., SanMartin, R., and Domínguez, E. Copper (I)-catalyzed S-arylation of thiols with activated aryl chlorides on water. *Tetrahedron*, 65(7):1500-1503, 2009.
- [20] Abadi, P. G.-S., Rafiee, E., and Joshaghani, M. Pd-PVP-Fe (palladium-poly(*N*-vinylpyrrolidone)-iron) catalyzed S-arylation of thiols with aryl halides in aqueous media. *Inorganica Chimica Acta*, 451:162–170, 2016.
- [21] Singh, R., Allam, B. K., Singh, N., Kumari, K., Singh, S. K., and Singh, K. N. Nickel-Catalyzed C–S Bond Formation: Synthesis of Aryl Sulfides from Arylsulfonyl Hydrazides and Boronic Acids. *Advanced Synthesis & Catalysis*, 357(6):1181–1186, 2015.
- [22] Hanaya, K., Ohata, J., Miller, M. K., Mangubat-Medina, A. E., Swierczynski, M. J., Yang, D. C., Rosenthal, R. M., Popp, B. V., and Ball, Z. T. Rapid nickel(II)-promoted cysteine S-arylation with arylboronic acids. *Chemical Communications*, 55(19):2841–2844, 2019.
- [23] Xu, H. J., Zhao, Y. Q., Feng, T., and Feng, Y. S. Chan–Lam-type S-Arylation of thiols with boronic acids at room temperature. *The Journal of Organic Chemistry*, 77(6):2878–2884, 2012.
- [24] Sandin, R. B., Christiansen, R. G., Brown, R. K., and Kirkwood, S. The reaction of iodonium salts with thiol compounds. *Journal of the American Chemical Society*, 69(6):1550–1550, 1947.
- [25] Huang, X., Zhu, Q., and Xu, Y. Synthesis of Polymeric Diaryliodonium Salts and Its Use in Preparation of Diaryl Sulfides and Diaryl Ethers. *Synthetic Communications*, 31(18):2823–2828, 2001.
- [26] Krief, A., Dumont, W., and Robert, M. Arylation of *N*-hexylthiol and *N*-hexyl phenyl sulfide using diphenyliodonium triflate: synthetic and mechanistic aspects-application to the transformation of *N*-hexylthiol to *N*-hexylselenide. *Synlett*, 2006(03):0484–0486, 2006.
- [27] Wagner, A. M. and Sanford, M. S. Transition-metal-free acid-mediated synthesis of aryl sulfides from thiols and thioethers. *The Journal of Organic Chemistry*, 79(5):2263–2267, 2014.

- [28] Wang, D., Yu, X., Zhao, K., Li, L., and Ding, Y. Rapid synthesis of aryl sulfides through metal-free C–S coupling of thioalcohols with diaryliodonium salts. *Tetrahedron Letters*, 55(42):5739–5741, 2014.
- [29] Wang, F. Y., Chen, Z. C., and Zheng, Q. G. Organic reactions in ionic liquids: a novel method for the synthesis of 2-arylthiobenzothiazoles by the *S*-arylation of benzothiazole-2-thiol with diaryliodonium salts. *Journal of Chemical Research*, 2004(2):127-128, 2004.
- [30] Zhang, B., Kang, Y., Yang, L., and Chen, X. A *S*-Arylation of 2-Mercaptoazoles with Diaryliodonium Triflates under Metal-Free and Base-Free Conditions. *ChemistrySelect*, 1(8):1529–1532, 2016.
- [31] Sarkar, S., Wojciechowska, N., Rajkiewicz, A. A., and Kalek, M. Synthesis of Aryl Sulfides by Metal-Free Arylation of Thiols with Diaryliodonium Salts under Basic Conditions. *European Journal of Organic Chemistry*, 2022(2):e202101408, 2022.
- [32] Zhu, K., Wang, Y., Fang, Q., Song, Z., and Zhang, F. Enantioselective synthesis of axially chiral biaryls *via* copper-catalyzed thiolation of cyclic diaryliodonium salts. *Organic Letters*, 22(5):1709–1713, 2020.
- [33] Hou, M., Deng, R., and Gu, Z. Cu-Catalyzed Enantioselective Atropisomer Synthesis *via* Thiolytic Ring Opening of Five-Membered Cyclic Diaryliodoniums. *Organic Letters*, 20(18):5779–5783, 2018.
- [34] Wang, M., Chen, S., and Jiang, X. Construction of functionalized annulated sulfone *via* SO₂/I exchange of cyclic diaryliodonium salts. *Organic Letters*, 19(18):4916–4919, 2017.
- [35] Parida, S. K., Jaiswal, S., Singh, P., and Murarka, S. Multicomponent Synthesis of Biologically Relevant *S*-Aryl Dithiocarbamates Using Diaryliodonium Salts. *Organic Letters*, 23(16):6401–6406, 2021.
- [36] Schlegel, H. B. Optimization of equilibrium geometries and transition structures. *Journal of Computational Chemistry*, 3(2):214–218, 1982.
- [37] Gonzalez, C. and Schlegel, H. B. Improved algorithms for reaction path following higher-order implicit algorithms. *The Journal of chemical Physics*, 95(8):5853–5860, 1991.

- [38] Ghosh, M. K., Rzymkowski, J., and Kalek, M. Transition-Metal-Free Aryl–Aryl Cross-Coupling: C–H Arylation of 2-Naphthols with Diaryliodonium Salts. *Chemistry–A European Journal*, 25(41):9619–9623, 2019.
- [39] Ma, X. P., Shi, W.-M., Mo, X. L., Li, X.-H., Li, L. G., Pan, C. X., Chen, B., Su, G. F., and Mo, D. L. Synthesis of α,β -Unsaturated *N*-Aryl Ketonitrone from Oximes and Diaryliodonium Salts: Observation of a Metal-Free *N*-Arylation Process. *The Journal of Organic Chemistry*, 80(20):10098–10107, 2015.
- [40] Sun, N., Li, B., Shao, J., Mo, W., Hu, B., Shen, Z., and Hu, X. A general and facile one-pot process of isothiocyanates from amines under aqueous conditions. *Beilstein Journal of Organic Chemistry*, 8(1):61–70, 2012.
- [41] Ando, K. and Takama, D. Stereoselective Synthesis of Trisubstituted (*Z*)-Alkenes from Ketones *via* the Julia–Kocienski Olefination Using 1-Methyl- and 1-*tert*-Butyl-1*H*-tetrazol-5-yl-Alkyl Sulfones. *Organic Letters*, 22(17):6907–6910, 2020.
- [42] Ma, X., Liu, Q., Jia, X., Su, C., and Xu, Q. Efficient synthesis of unsymmetrical heteroaryl thioethers and chalcogenides by alkali hydroxide mediated S_NAr reactions of heteroaryl halides and dichalcogenides. *RSC Advances*, 6(62):56930–56935, 2016.
- [43] García-Rubia, A., Fernández-Ibáñez, M. Á., Gomez Arrayas, R., and Carretero, J. C. 2-Pyridyl Sulfoxide: A Versatile and Removable Directing Group for the Pd(II)-Catalyzed Direct C–H Olefination of Arenes. *Chemistry–A European Journal*, 17(13):3567–3570, 2011.