3.1 Introduction

3.1.1 Thiotetrazoles

Sulphur containing organic compounds are found in many natural products and have emerged as a powerful means for the synthesis of many molecules that are of biological, pharmaceutical, and materials interest [1,2]. In particular, sulphur containing heterocyclic derivatives find application in many pharmacological activities like antiviral, anti-inflammatory, activator in RNA synthesis and cholinergic receptors (Figure **3.1**) [3-6]. The introduction of sulphur group on the aryl or heteroaryl moiety enhances the synthetic utility and biological activity of the resulting organo-sulphur compounds [7]. Interestingly, thiotetrazoles which are sulphur-based heterocyclic compounds containing both *S*– and *N*–atoms possess a wide variety of biological activities [8]. Thiotetrazoles are characterized with relative stability to oxidation and high coordination ability. The ability of thiotetrazoles to form stable complexes with various metal ions is widely used in photo processes and for corrosion protection of metals [9,10].

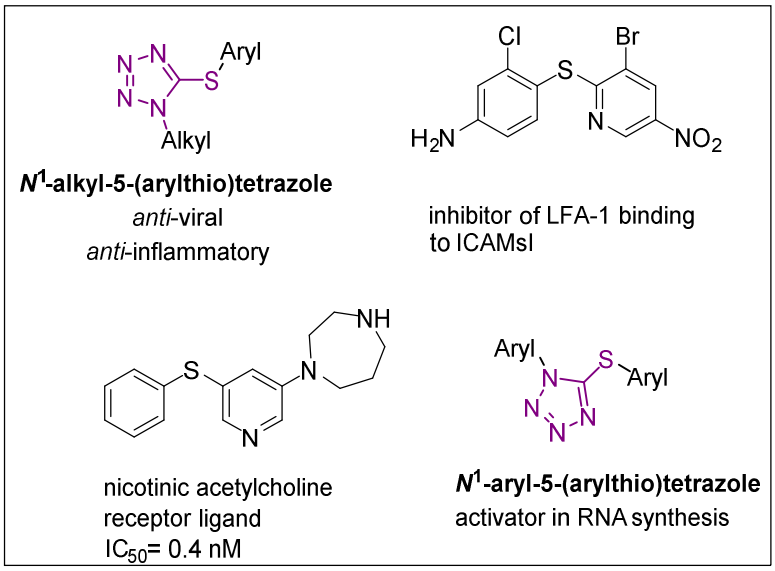
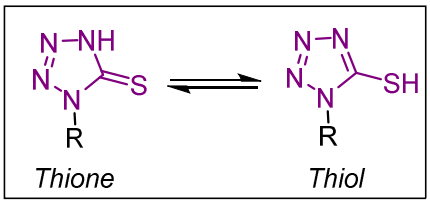


Figure **3.1** Examples of sulphur-based biologically active compounds

It is well known that thiotetrazoles function both as sulphur and nitrogen nucleophiles. They are useful precursors for C–S and C–N bond-formation; however utility to form C–N bond is rare. Due to the presence of two nucleophilic sites in thiotetrazoles, the formation of two products arising from *N*–and *S*– addition are favourable. Therefore, controlling the chemoselectivity of the reaction to obtain

either *N*– or *S*– substituted product constitutes a difficult task. Thiotetrazoles exist in two tautomeric forms i.e. thione and thiol as depicted below (Scheme **3.1**) [11,12].



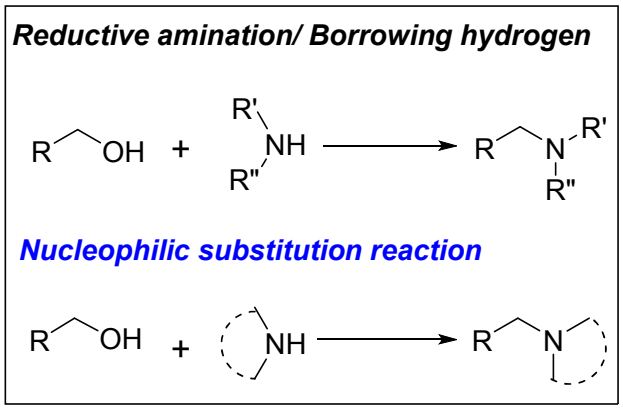
Scheme **3.1** Tautomeric forms of thiotetrazoles

3.1.2 Amination of alcohol

Amination of alcohols represent an important and active field in synthetic organic chemistry because these reactions can generate functional amines that are ubiquitous structural units in a wide range of natural products and other organic compounds [13]. Since, nitrogen heterocycles are common synthetic targets due to their prevalence in natural products and pharmaceutically active structures, the development of versatile and efficient methods for the synthesis of amines have attracted the attention of modern chemists [14].

Alcohols are cheap, readily available organic compounds and can be extracted from natural resources such as biomass feed stocks [15]. Among the various known synthetic procedures to prepare amines; such as Chan-Lam coupling, Ullmann coupling, Buchwald-Hartwig, the reaction of organonitrogen compounds with alcohols is of special significance as it constitutes the most advantageous method for the preparation of C–N bonds [16,17]. Owing to the green features of the readily available alcohols and their advantages over organic halides or organometallic compounds and water being the only by-product released, alcohols holds a unique significance towards amination of alcohol. If the use of alcohols as starting materials for C–N bond formation proceeds with equimolar amounts of starting compounds, the process can be realized as atom economical and less hazardous. From green chemistry perspectives, it is highly desirable to develop an atom economical route for C-N bond formation using alcohols and amines. Consequently, different protocols have been devised for the amination of alcohols [17]. In reductive amination processes, the reaction proceeds in two tandem steps; condensation

between carbonyl compounds and amines to generate an imine intermediate followed by reduction of imine by a reducing agent (Scheme **3.2**) [18]. Another methodology involved in the amination of alcohol includes oxidation of an alcohol into a carbonyl compound in presence of transition metal catalyst, followed by an intermediate imine bond between an amine and a carbonyl compound and finally the reduction of an imine to an amine (Scheme **3.2**). The overall process is termed as the 'borrowing hydrogen' methodology or hydrogen auto-transfer [19]. In the aforesaid methodologies; use of toxic metals, reducing agents, high temperature and most importantly generation of side products make these reactions cumbersome and hazardous. In recent years another methodology has been developed for amination of alcohols using heterocyclic thiones involving Lewis acid catalysed dehydration of alcohol, followed by nucleophilic substitution reaction (Scheme **3.2**) [4]. Here, Lewis acids help to generate carbocation from alcohols which is then attacked by nucleophiles to obtain the aminated product releasing water as by-product.



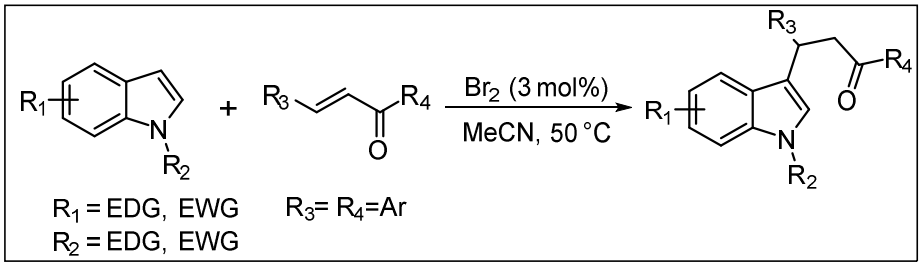
Scheme **3.2** Schematic representation of different protocols used in the amination of alcohol

3.1.3 Lewis acids catalysed nucleophilic substitution reaction

Lewis acids have played a pivotal role in organic synthesis. The inherent Lewis acidity of metal or semimetal ions, which stems from possession of empty orbital or electron-accepting ability, has allowed the ability to catalyse numerous organic transformations and methods for carbon-carbon (C–C) bond and carbon-heteroatom C–X bond formation reactions [20]. Over the years, the development of Lewis acids from conventional catalysts (BF_3 and $AlCl_3$) to modern green ones

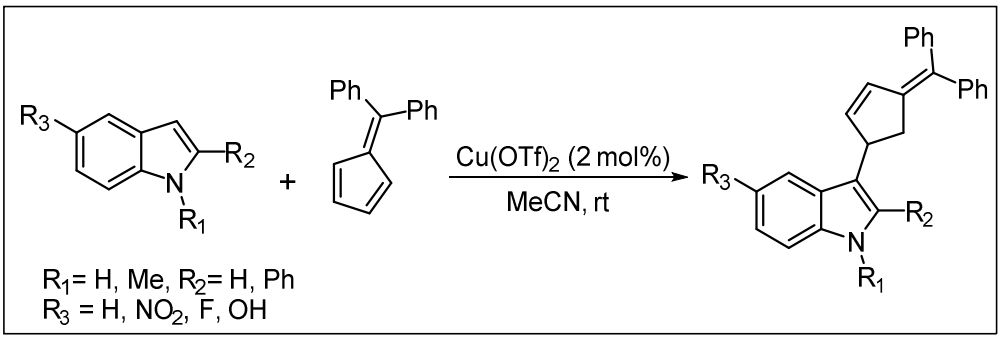
(lanthanide triflates) have enabled a wide range of chemical transformations in various fields, such as pharmaceutical and industrial applications. Recent advances have shown that mild Lewis acidic conditions [I_2, $Cu(OTf)_2$, $FeCl_3$, $Ga(OTf)_3$] can lead to arylation of various heterocycles. Here, we intend to highlight some of the important Lewis acid catalysed organic transformations [21].

In 2016, Cheng and group has carried out alkylation of indoles with α,β-unsaturated ketones under the catalysis of only 3 mol% of Br_2 that lead to efficient synthesis of *β*-indolylketone derivatives (Scheme **3.3**) [22].



Scheme **3.3** Br_2 catalysed alkylation of indoles with α,β-unsaturated ketones

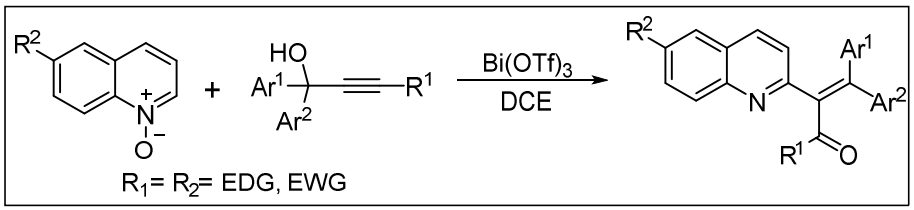
In 2016, Radhakrishnan and co-workers developed a diverse approach toward the catalytic regioselective nucleophilic addition of nitrogen heterocycles to Lewis acid activated pentafulvenes. The established protocol introduces pentafulvenes as nonsymmetrical alkenes for the hydroheteroarylation reaction, providing alkylidenecyclopentenylation at the C-3 position of indoles (Scheme **3.4**) [23].



Scheme **3.4** $Cu(OTf)_2$ catalysed regioselective nucleophilic addition of nitrogen heterocycles to pentafulvenes

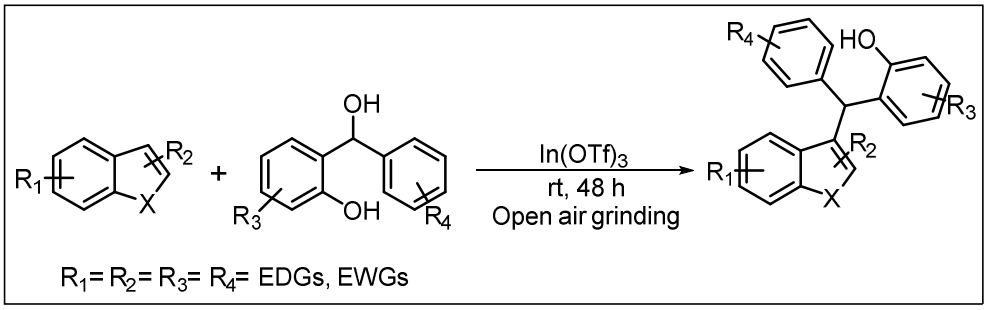
In 2017, Liang and his group disclosed Lewis acid catalysed dehydrogenative coupling of tertiary propargylic alcohols with quinoline *N*-oxides that leads to

efficient synthesis of 2-(quinolin-2-yl)prop-2-en-1-ones with satisfactory yields (Scheme **3.5**) [24].



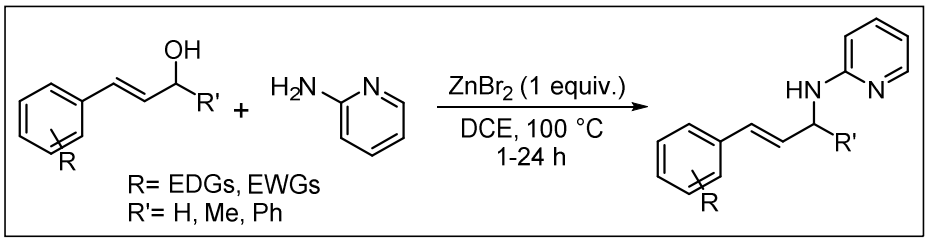
Scheme **3.5** $Bi(OTf)_3$ catalysed dehydrogenative coupling of tertiary propargylic alcohols with quinoline *N*-oxides

In 2017, Panda and his group used indium(III) triflate as a mild Lewis acid catalyst for the Friedel-Crafts alkylation of *o*-hydroxybisbenzylic alcohols with aromatic or heteroaromatic arenes under solvent free conditions to give unsymmetrical triarylmethanes in high yields. The protocol was found to be operationally simple and could be carried out in an "open-flask" leaving behind water as the sole by product (Scheme **3.6**) [25].



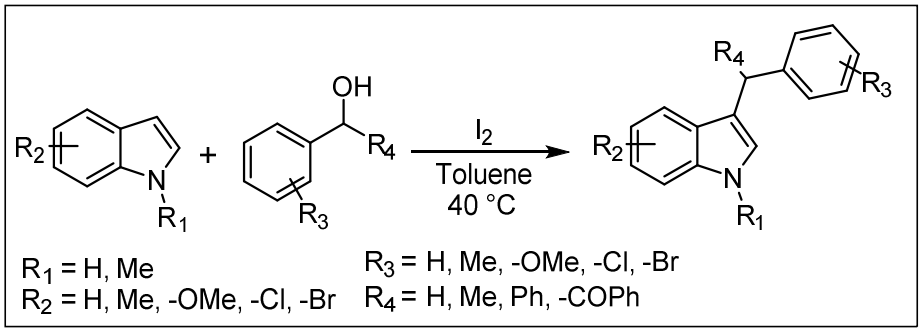
Scheme **3.6** $In(OTf)_3$ catalysed alkylation of *o*-hydroxybisbenzylic alcohols with aromatic or heteroaromatic arenes

In 2021, Prabhu and his group carried out C–N bond forming reaction using cinnamyl alcohols and 2-amino pyridine derivatives using stoichiometric amount of zinc bromide ($ZnBr_2$). A wide range of substrates including primary, secondary, and homoallylic alcohols were found to be compatible with this protocol (Scheme **3.7**) [26].



Scheme **3.7** $ZnBr_2$ mediated C–N bond formation using cinnamyl alcohol and 2-amino pyridines

Bora et al., developed iodine catalysed selective C–3 benzylation of indoles with benzylic alcohols. The protocol was simple and environmentally benign, proceeded under ligand, metal, and base-free conditions and tolerated a wide range of functional groups (Scheme **3.8**) [27].

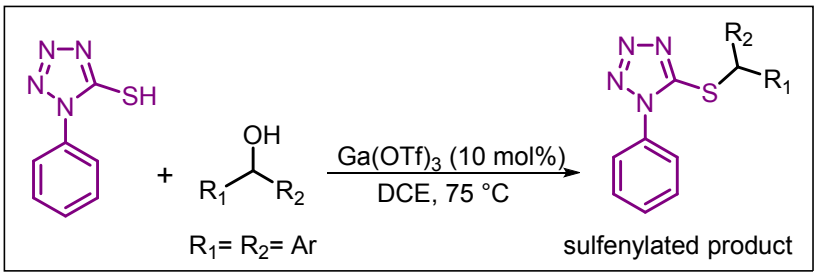


Scheme **3.8** I_2 catalysed selective C–3 benzylation of indoles with benzylic alcohols

3.2 Background of the present work

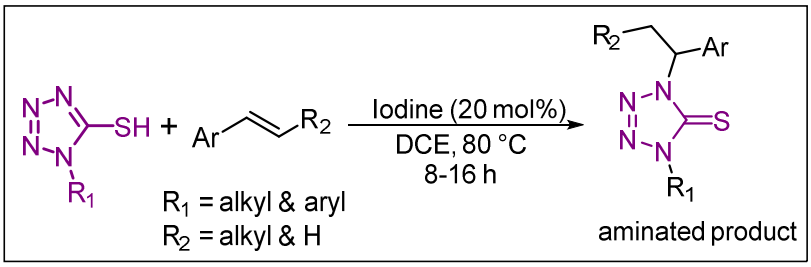
As discussed earlier (section **3.1.3**), thiotetrazoles function both as sulphur and nitrogen nucleophiles and therefore, the chemoselectivity of the reaction constitutes a relevant issue to be considered. This implies that conditions favouring the chemoselective formation of the *N*- addition product need to be explored. Some important *N*– and *S*– arylation reactions of thiotetrazoles are discussed below.

Wu's group has reported sulfenylation protocol of alcohols catalysed by $Ga(OTf)_3$. However, the scope of this reaction was limited to *S*-arylated dehydrative substitution of alcohols only (Scheme **3.9**) [2].



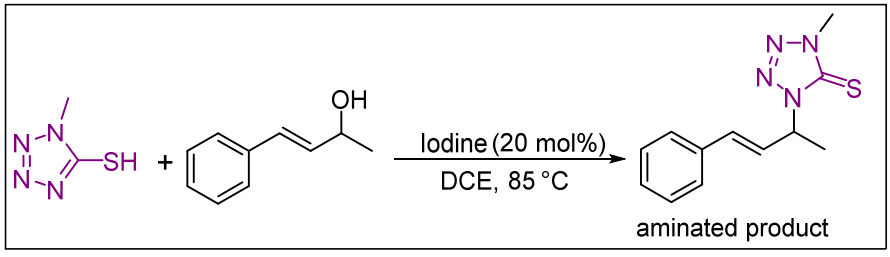
Scheme **3.9** *S*-arylated dehydrative substitution of alcohols using $Ga(OTf)_3$

In 2018, Prabhu and co-workers carried out chemoselective hydroamination of styrene derivatives using a catalytic amount of iodine with high chemoselectivity over sulfenylation of 1*H*-tetrazole-5-thiol (Scheme **3.10**). This reaction involves a single-step C–N bond formation preserving atom economy [11].



Scheme **3.10** I_2 catalysed chemoselective hydroamination reaction using 5-mercaptotetrazoles derivatives

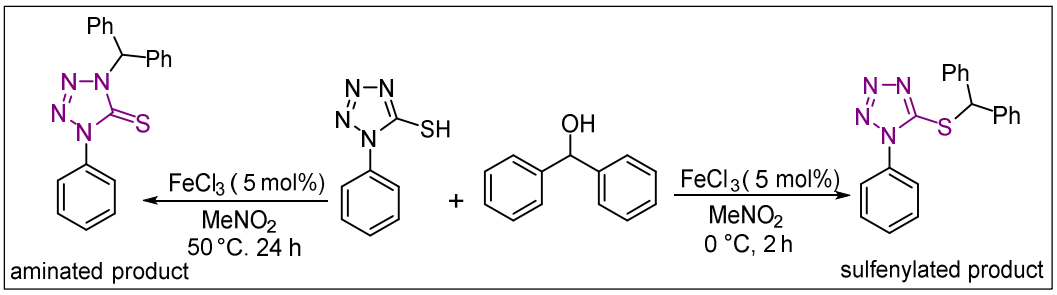
In 2018, the same group disclosed a novel method for the chemoselective amination of alcohols using the same procedure (Scheme **3.11**). In this protocol, they have taken 1-methyl-1*H*-tetrazole-5-thiol and cinnamyl alcohol and the product yield obtained was excellent [4].



Scheme **3.11** Chemoselective amination of alcohols using I_2 as a catalyst

Restricting to only secondary alcohols, Nakata's group recently reported dehydrative nucleophilic substitutions of diarylmethanols with 1-phenyl-1*H*-tetrazole-5-thiol in the presence of $FeCl_3$ catalyst (Scheme **3.12**). Both *N*- and *S*-

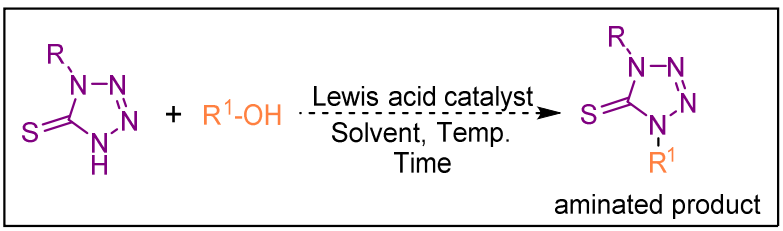
arylation products were achieved using $FeCl_3$ as a catalyst at different temperatures in $MeNO_2$ [8].



Scheme **3.12** *N*- and *S*- nucleophilic substitutions of various diarylmethanols with 1-phenyl-1H-tetrazole-5-thiol

3.3 Objectives of the present work

Based on the above findings, we sought to develop a method for construction of C–N bond. Specifically, we envisioned the formation of selective C–N bond rather than C–S bond using thiotetrazole and alcohol derivatives. The use of environmentally benign, readily accessible substrates i.e. thiotetrazoles and alcohols would provide a greener approach to our developed protocol. Due to the presence of two nucleophilic sites in thiotetrazoles *N*- and *S*-, both pathways are feasible, because of which finding the chemoselective product exclusively is a challenging task. Such envisioned synthetic routes would expand the arsenal of methodologies for the synthesis of new class of biologically active *N*-alkylated thiotetrazole derivatives. With an intention to design a robust methodology, we attempted to work with both aromatic as well as aliphatic alcohols. Herein, we describe a protocol that shows exceptional selectivity of thiotetrazole towards *N*- rather than *S*-nucleophilic substitution by primary, secondary, tertiary and homoallylic alcohols (Scheme **3.13**).



Scheme **3.13** Proposed schematic representation of amination of alcohols

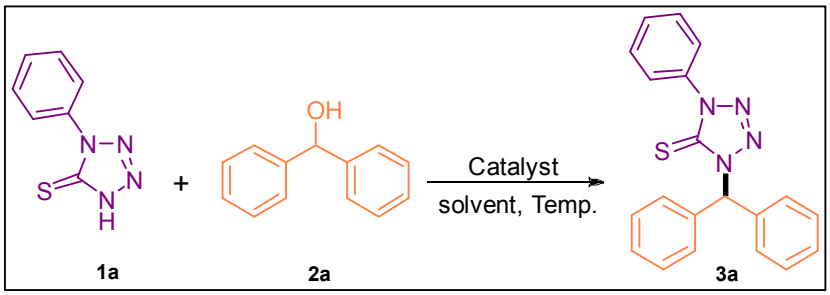
3.4 Results and Discussion

3.4.1 Optimization of reaction conditions

To optimize the reaction conditions, we first attempted to find the chemoselective aminated product by reacting alcohols and thiotetrazole derivatives. We commenced our studies by taking **1a** (0.5 mmol) and **2a** (0.5 mmol) in presence of Brønsted acids such as Hexafluoroisopropanol (HFIP), triflic acid and *p*-toluenesulfonic acid (*p*-TsOH) which unfortunately furnished no desired results (Table **3.1**, entries 1-3). Several other acid catalysts such as L-proline, Fe_3O_4, $AuCl_3$, $BF_3{\cdot}OEt_2$, were also tested but product obtained was either in low yield or reaction did not proceed at all (Table **3.1**, entries 4-7). Remarkably, when $Cu(OTf)_2$ was used as catalyst, a significant increase in product yield was observed. Further optimization studies were continued using $Cu(OTf)_2$ as a catalyst. Treatment of **1a** with **2a** afforded **3a** exclusively in 85% yield upon employing 20 mol% $Cu(OTf)_2$ in dichloroethane (DCE) at 85 °C (Table **3.1,** entry 8). Interestingly, upon lowering the reaction time from 12 h to 4 h, no significant decrease in product yield was observed; which implied that 4 h was the optimum time required to accomplish the arylation of thiotetrazole derivatives reaction (Table **3.1**, entry 9). It was noted that the reaction proceeded faster and was completed in 4 h. Notably, 90% of the chemoselective aminated product was obtained at 60 °C (Table **3.1,** entry 9). No competing sulfenylation product was observed in presence of the catalyst. Further exploration of the reaction conditions revealed that, when the catalyst loading was decreased to 10 mol% from 20 mol%, the product yield increased to 90% (Table **3.1,** entry 10). Further decrease of the amount of $Cu(OTf)_2$ to 5 mol% resulted in decreased product yield (Table **3.1,** entry 11). Thus, 10 mol% was the optimum amount that delivered the product in excellent yield. Thereafter, the reaction was studied by taking the catalyst amount at 10 mol%. It was noted that amongst various acid catalysts tested so far, none was found to be better than $Cu(OTf)_2$. To find out the solvent effect, the same set of reactions were allowed to run in different solvents such as DMSO, ACN, 1,4-dioxane and toluene. A trace amount of **3a** was observed with 1,4-dioxane (Table **3.1,** entry 12) whereas no product was observed with DMSO, ACN and toluene (Table **3.1,** entries 13-15). Higher yield of the product was seen when the reaction was performed with DCE as the solvent. Other copper

salts such as $Cu(OAc)_2{\cdot}2H_2O$ and $CuSO_4{\cdot}5H_2O$, failed to deliver results but CuI delivered 77% yield of the desired product (Table **3.1,** entries 16-18). No aminated product was observed in absence of $Cu(OTf)_2$ (Table **3.1,** entry 19). In view of the above extensive optimizations, the best reaction conditions were fixed at 10 mol% $Cu(OTf)_2$ in DCE for 4 h (Table **3.1**, entry 10).

Table **3.1** Optimization of reaction conditions[a]



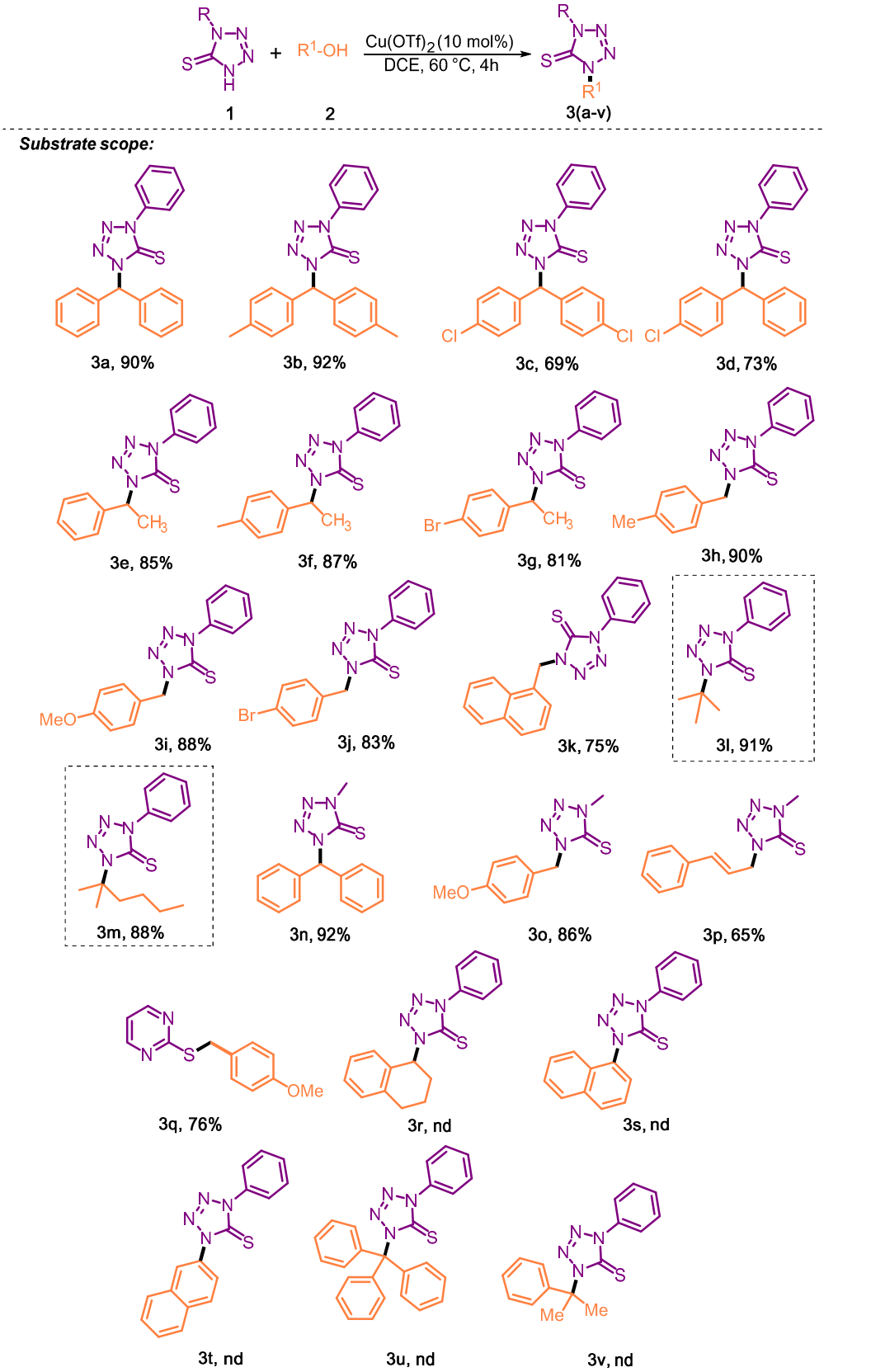
Entry	Catalyst (mol%)	Solvent (mL)	Time (h)	Temp. (°C)	Yield[b] (%) 3a
1	HFIP (20)	-	12	60	nr
2	CF_3SO_3H (20)	HFIP	12	60	nr
3	*P*-TsOH (20)	DCE	12	85	nr
4	L-Proline (20)	ACN	12	85	nr
5	Fe_3O_4(20)	ACN	12	85	nr
6	$AuCl_3$ (20)	DCE	12	85	trace
7	$BF_3.OEt_2$ (20)	-	12	rt	trace
8	$Cu(OTf)_2$(20)	DCE	12	85	85
9	$Cu(OTf)_2$(20)	DCE	4	85	88
10	**$Cu(OTf)_2$(10)**	**DCE**	**4**	**60**	**90**
11	$Cu(OTf)_2$(5)	DCE	4	60	87
12	$Cu(OTf)_2$(10)	1,4-dioxane	4	60	trace
13	$Cu(OTf)_2$(10)	DMSO	4	60	nr
14	$Cu(OTf)_2$(10)	MeCN	4	60	nr
15	$Cu(OTf)_2$(10)	Toluene	4	60	nr
16	$Cu(OAc)_2{\cdot}2H_2O$(10)	DCE	4	60	nr
17	$CuSO_4.5H_2O$(10)	DCE	4	60	nr
18	CuI (10)	DCE	4	60	77
19	-	DCE	4	60	nr

*[a]Reaction Conditions: **1a** (0.5 mmol), **2a** (0.5 mmol) and solvent (3 mL). [b]Yields are obtained from the ^1H NMR spectra; nr = no reaction.*

3.4.2 Substrate scope study

With optimal conditions achieved, we next sought to study the scope and limitation of the reaction. Initially, we explored thiotetrazole with diphenylmethanol under the optimized reaction conditions and the product yield obtained was 90% (Table **3.2**, entry 3a). Next, we tested varied derivatives of diphenylmethanol to evaluate the effect of substituents on the aromatic ring. Diphenylmethanol carrying –Me substituent at the *para* position furnished excellent result i.e. 92% yield (Table **3.2** entry 3b). Conversely, diphenylmethanol bearing –Cl substituent at the *para* position, showed a declining trend in reactivity that could be attributed to the carbocation intermediate being destabilized due to the electron-withdrawing nature of the −Cl substituent (Table **3.2**, entries 3b-c) [8]. Another *para*- substituted –Cl atom on one of the aromatic rings of diphenylmethanol yielded moderate results (Table **3.2**, entry 3d). We tested various secondary alcohols with aryl substitution at α-position to the hydroxyl group to examine the effect of steric hindrance on the outcome of the reaction. Interestingly, the product yield obtained was excellent. Thus, diphenylmethanol and its derivatives reacted smoothly to give the corresponding products in good to excellent yields. Next, we investigated our reaction with 1-phenylethanol and its derivatives bearing electron-donating and withdrawing groups on the aromatic ring (Table **3.2**, entries 3e-g). To our delight, high yields of the aminated products were obtained with unsubstituted, -Me and -Br substituted 1-phenylethanol except a slight decrease in conversion rate with electron-withdrawing -Br substituent (Table **3.2**, entry 3g). Subsequently, under the same optimized reaction conditions, we shifted to benzyl alcohols and its derivatives bearing -Me, -OMe, and -Br substituents (Table **3.2,** entries 3h-j). Similarly, both EDGs (Table **3.2**, entries 3h and 3i) and EWGs (Table **3.2**, entry 3j) were studied and fortunately they were all well tolerated under our developed methodology. 1-(Naphthalen-1-yl)ethan-1-ol afforded the aminated product in good yield (Table **3.2**, entry 3k). Notably, *tert*-butyl alcohol which was unexplored in earlier established protocols also reacted smoothly (Table **3.2**, entries 3l and 3m). Thus, alcohols with diverse substitutions on the aryl ring produced good to excellent yields of the product with 1-phenyl-1*H*-tetrazole-5-thiol. Next, we diversified our reaction protocol towards 1-methyl-1*H*-tetrazole-5-thiol with a variety of alcohols such as diphenylmethanol, (4-Methoxyphenyl)methanol and

Table **3.2 Substrate scope study**[a]



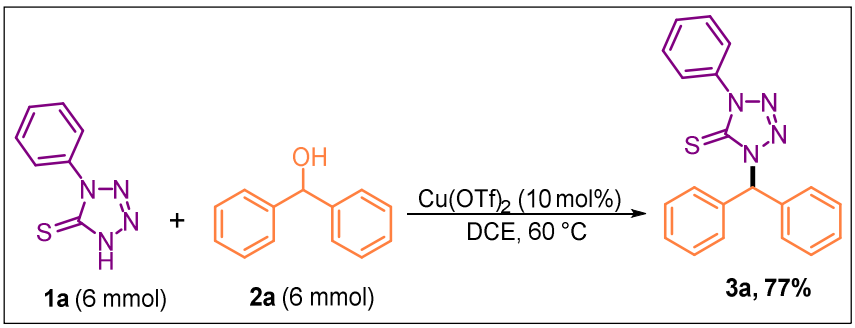
[a]*Reaction conditions:* ***1*** *(0.5 mmol),* ***2*** *(0.5 mmol), and Cu(OTf)₂ (10 mol%) in 1,2-dichloroethane (DCE) (3 mL) at 60 °C for 4 h, nd = not detected*

cinnamyl alcohol and interestingly, product yield obtained was excellent (Table **3.2**, entries 3m-o). Gratifyingly, the reaction proceeded smoothly with different types of alcohols whether primary, secondary or tertiary to give the corresponding product in good yields. A similar outcome in product yield was observed when cinnamyl alcohol was allowed to react with 1-methyl-1*H*-tetrazole-5-thiol (Table **3.2**, entry 3p).

Substrates bearing methoxy, methyl, bromo, and chloro substituents were well tolerated under the optimized conditions and gave good yields of the corresponding products. However, under the standard optimized reaction conditions, pyrimidine-2-thiol was not successful in furnishing the corresponding aminated product and resulted in formation of the corresponding sulfenylated product (Table **3.2**, entry 3q). Thus, the developed protocol was applicable to a wide variety of alcohols and thiotetrazoles. Tetralone, α-naphthol, β-naphthol, triphenylmethanol, and 2-phenyl-2-propanol failed to furnish the desired results (Table **3.2**, entries 3r-v).

3.4.3 Gram-scale experiment

It was interesting to note that our developed reaction system could be scaled up efficiently under the optimized reaction conditions. The reaction of **1a** (1.07 g, 6 mmol) with **2a** (1.10 g, 6 mmol) delivered the aminated product, **3a** in 77% yield (Scheme **3.14**). This reaction demonstrated the efficacy of the developed method as a potential application in synthetic chemistry.

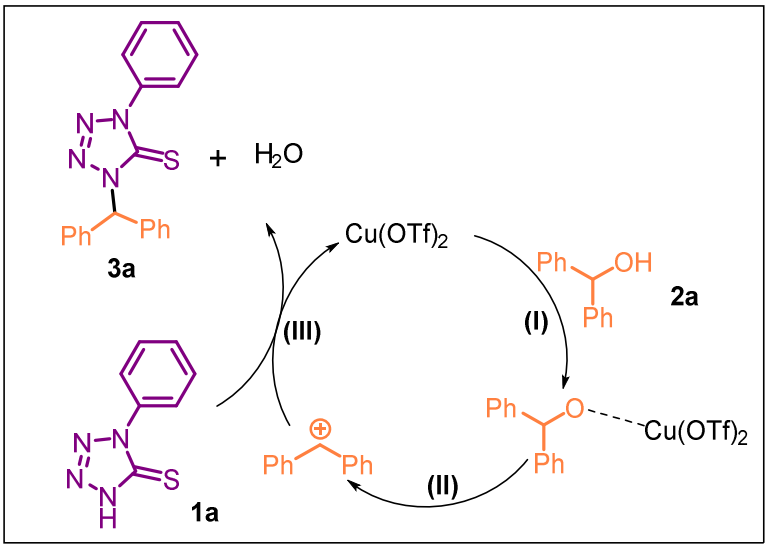


Scheme **3.14** Gram-scale experiment of a thiotetrazole derivative

3.4.4 Mechanism

On the basis of literature reports and results of our experiment, a plausible mechanism has been proposed for our reaction as shown in Scheme **3.15** [4,8].

Initially, in the presence of $Cu(OTf)_2$, dehydration of diphenylmethanol generates carbocation (step **II**). In the next step, *N*– atom of tetrazole-5-thiol acts as a nucleophile and attacks the carbocation generated from the alcohol (step **II**) to form the product, **3a** (step **III**) and the cycle continues.



Scheme **3.15** Proposed mechanism for C–N bond formation

3.5 Conclusion

In summary, we have developed a Lewis acid catalysed selective amination of alcohols using heterocyclic thiols. This protocol provides a straightforward and atom-economical route for the construction of thiotetrazole derivatives, which acts as an important structural motif in a wide variety of pharmaceuticals and bioactive molecules. The use of cost-effective and readily-available copper salt, with alcohols as starting materials render this methodology advantageous for obtaining chemoselective aminated product. The salient features of this methodology are its cost effectiveness, high atom economy, high chemoselectivity, convenient use, short reaction time and broad substrate scope.

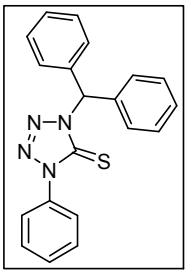
3.6 Experimental Section

3.6.1 General procedure

Thiotetrazole (**1**, 0.5 mmol) alcohol derivatives (**2**, 0.5 mmol), and $Cu(OTf)_2$ (10 mol%) were stirred in dichloroethane, DCE (3 mL) at 60 °C for 4 h and monitored by TLC. The crude mixture was extracted with EtOAc and washed with distilled

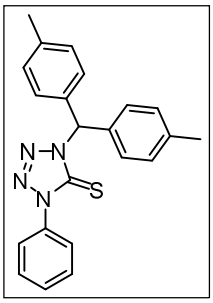
water. The aqueous layer was separated and organic layer was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting reaction mixture was purified by column chromatography on silica (hexane/EtOAc = 95:5) to afford the desired product, **3a**.

3.6.2 Characterisation data of the products



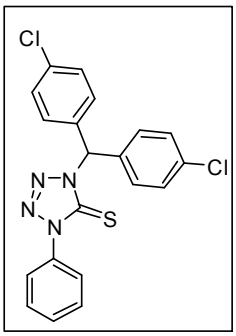
1-benzhydryl-4-phenyl-1,4-dihydro-5H-tetrazole-5-thione (**3a**)

White solid (154 9 mg, 90%); IR (neat, cm^{-1}) 3041, 2954, 1953, 1595, 1499, 1448, 1416, 1332, 1296, 1015, 957; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 8.03 (dd, J = 8.1, 1.7 Hz, 2H), 7.58 (dd, J = 8.6, 7.1 Hz, 2H), 7.54–7.47 (m, 2H), 7.46–7.34 (m, 10H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 163.8, 137.1, 135.0, 129.7, 129.3, 129.0, 128.8, 128.7, 123.9, 64.8.



1-(di-p-tolylmethyl)-4-phenyl-1,4-dihydro-5H-tetrazole-5-thione (**3b**)

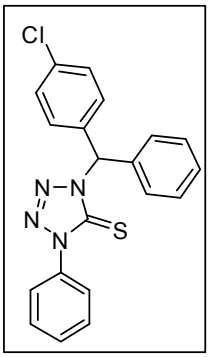
White solid (171.34 mg, 92%); IR (neat, cm^{-1})) 3054, 2977, 1961, 1600, 1545, 1487, 1436, 1379, 1256, 1189, 872; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.00–7.94 (m, 2H), 7.52–7.46 (m, 2H), 7.45–7.37 (m, 2H), 7.26 (dd, J = 8.3, 2.0 Hz, 4H), 7.20–7.14 (m, 4H), 2.33 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.6, 138.5, 135.0, 134.2, 129.6, 129.3, 128.6, 123.8, 64.5, 21.3.



1-(bis(4-chlorophenyl)methyl)-4-phenyl-1,4-dihydro-5H-tetrazole-5-thione (**3c**)

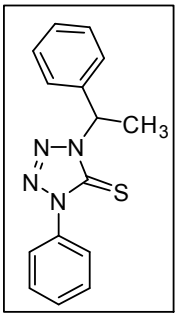
White solid (150.86 mg, 69%); IR (neat, cm^{-1}) 3063, 2985, 1959, 1689, 1597, 1496, 1416, 1332, 1296, 1494, 1093, 809, 761; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.90–7.84 (m, 2H), 7.44–7.35 (m, 3H), 7.29–7.15 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.6, 135.0, 135.0, 134.8, 130.0, 129.7, 129.3, 129.3, 123.7, 63.4.

1-((4-chlorophenyl)(phenyl)methyl)-4-phenyl-1,4-dihydro-5H-tetrazole-5-thione (**3d**)



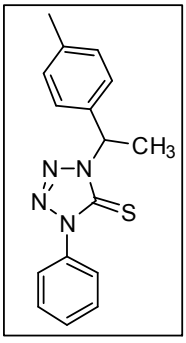
White solid (130.43 mg, 73%); IR (neat, cm^{-1}) 3058, 2893, 1950, 1899, 1583, 1489, 1410, 1360, 1165, 1000, 813, 727; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.03 (dd, J = 7.7, 1.9 Hz, 2H), 7.68–7.30 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.6, 136.5, 135.5, 134.8, 134.7, 130.0, 129.6, 129.2, 129.1, 129.1, 128.8, 128.6, 123.7, 64.0; HRMS (ESI-TOF) m/z $(M+H)^+$ calculated for $C_{20}H_{16}N_4ClS^+$, 379.0779 found, 379.0830.

1-phenyl-4-(1-phenylethyl)-1,4-dihydro-5H-tetrazole-5-thione (**3e**)



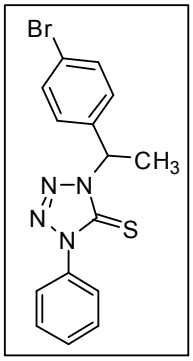
Pale yellow oil (119.8 mg, 85%); IR (neat, cm^{-1}) 2933, 1996, 1897, 1496, 1339, 1283, 1055, 742; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.97 (d, J = 8.3 Hz, 2H), 7.60–7.48 (m, 5H), 7.40 (dt, J = 13.4, 7.0 Hz, 3H), 6.25 (q, J = 7.2 Hz, 1H), 2.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.9, 138.4, 134.9, 129.5, 129.2, 128.9, 128.7, 127.4, 123.9, 57.5, 20.2.

1-phenyl-4-(1-(p-tolyl)ethyl)-1,4-dihydro-5H-tetrazole-5-thione (**3f**)



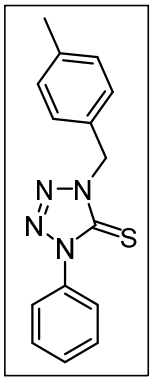
Dirty white solid (128.92 mg, 87%); IR (neat, cm^{-1}) 3029, 2977, 2916, 1948, 1897, 1611, 1498, 1202, 1080, 897, 744; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.87–7.82 (m, 2H), 7.42 (dd, J = 8.6, 6.8 Hz, 3H), 7.39–7.33 (m, 3H), 7.10 (d, J = 8.0 Hz, 2H), 6.10 (d, J = 7.1 Hz, 1H), 2.25 (s, 3H), 1.88 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 161.7, 137.5, 134.4, 133.8, 128.5, 128.5, 128.1, 126.2, 122.8, 56.2, 20.1, 19.1; HRMS (ESI-TOF) m/z $(M+H)^+$ calculated for $C_{16}H_{17}N_4S^+$, 297.1168; found 297.1163.

1-(1-(4-bromophenyl)ethyl)-4-phenyl-1,4-dihydro-5H-tetrazole-5-thione (**3g**)



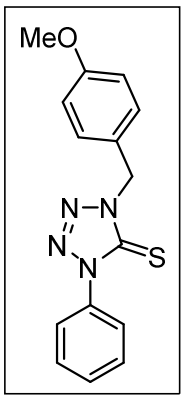
White solid (146.31 mg, 81%); IR (neat, cm^{-1}) 3051, 2994, 2928, 1886, 1590, 1497, 1360, 1295, 1050, 813, 763; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.86 (dd, J = 7.4, 1.9 Hz, 2H), 7.50–7.36 (m, 5H), 7.34 (d, J = 8.5 Hz, 2H), 6.08 (d, J = 7.2 Hz, 1H), 1.89 (d, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 161.8, 136.3, 133.7, 131.0, 128.6, 128.2, 128.0, 122.8, 121.8, 55.8, 19.0; HRMS (ESI-TOF) m/z $(M+H)^+$ calculated for $C_{15}H_{14}BrN_4S^+$, 361.0117; found, 361.0081.

1-(4-methylbenzyl)-4-phenyl-1,4-dihydro-5H-tetrazole-5-thione (**3h**)



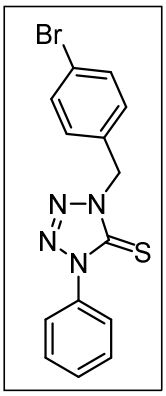
Pale white solid (126.94 mg, 90%); IR (neat, cm^{-1}) 3071, 3001, 2954, 2875, 1917, 1595, 1435, 1123, 1056, 1015; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01–7.95 (m, 2H), 7.62–7.44 (m, 5H), 7.23 (d, J = 7.8 Hz, 2H), 5.54 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.3, 138.9, 134.9, 130.5, 129.6, 129.6, 129.2, 129.0, 123.8, 51.2, 21.3; HRMS (ESI-TOF) m/z $(M+H)^+$ calculated for $C_{15}H_{15}N_4S^+$, 283.0994; found, 283.0993.

1-(4-methoxybenzyl)-4-phenyl-1,4-dihydro-5H-tetrazole-5-thione (**3i**)



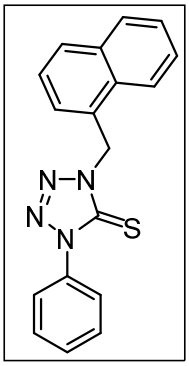
White crystalline solid (131.27 mg, 88%); IR (neat, cm^{-1}) 3065, 2987, 2835, 1889, 1617, 1473, 1177, 1139, 1026, 913; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.97 (d, J = 8.4 Hz, 2H), 7.60–7.48 (m, 5H), 6.94 (d, J = 8.8 Hz, 2H), 5.52 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.2, 160.0, 134.9, 130.6, 129.6, 129.2, 125.6, 123.8, 114.3, 55.3, 51.0; HRMS (ESI-TOF) m/z $(M+H)^+$ calculated for $C_{15}H_{15}N_4OS$, 299.0938; found, 299.0938.

1-(4-bromobenzyl)-4-phenyl-1,4-dihydro-5H-tetrazole-5-thione (**3j**)



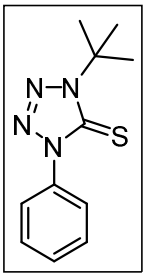
Pale white solid (144.10 mg, 83%); IR (neat, cm^{-1}) 3037, 2922, 2849, 2346, 1634, 1230, 1497, 1381, 1245, 1058, 863; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.60–7.51 (m, 5H), 7.50–7.43 (m, 2H), 7.36–7.31 (m, 2H), 4.58 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.5, 134.5, 133.5, 132.0, 131.0, 130.2, 129.8, 123.8, 122.3, 36.8; HRMS (ESI-TOF) m/z $(M+H)^+$ calculated for $C_{14}H_{12}BrN_4S^+$, 348.9919; found, 348.9918.

1-(naphthalen-1-ylmethyl)-4-phenyl-1,4-dihydro-5H-tetrazole-5-thione (**3k**)



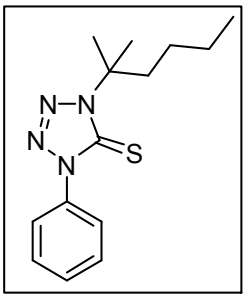
White solid (119.4 mg, 75%); IR (neat, cm^{-1}) 2972, 2922, 2842, 1626, 1353, 1259, 1086, 1022; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.36 (d, J = 8.5 Hz, 1H), 8.02–7.91 (m, 4H), 7.77 (dd, J = 7.1, 1.1 Hz, 1H), 7.64 (ddd, J = 8.4, 6.8, 1.4 Hz, 1H), 7.60–7.46 (m, 5H), 6.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.4, 134.8, 133.9, 131.3, 130.0, 129.6, 129.3, 129.2, 129.0, 127.2, 126.3, 125.3, 123.8, 123.6, 49.4; HRMS (ESI-TOF) m/z $(M+H)^+$ calculated for $C_{18}H_{15}N_4S^+$, 319.0989; found 319.0989.

1-(tert-butyl)-4-phenyl-1,4-dihydro-5H-tetrazole-5-thione (**3l**)

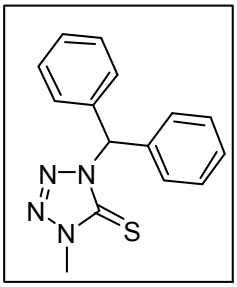


Pale white solid (106.61 mg, 91%); IR (neat, cm^{-1}) 3065, 2972, 2922, 1950, 1886, 1597, 1497, 1331, 1281, 1079, 1007, 813; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.76 (dd, J = 7.5, 2.0 Hz, 2H), 7.52– 7.36 (m, 3H), 1.84 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 161.8, 133.6, 128.6, 128.0, 123.9, 62.9, 26.4; HRMS (ESI-TOF) m/z $(M+H)^+$ calculated for $C_{11}H_{15}N_4S^+$, 235.1012; found, 235.1002.

1-(2-methylhexan-2-yl)-4-phenyl-1,4-dihydro-5H-tetrazole-5-thione (**3m**)



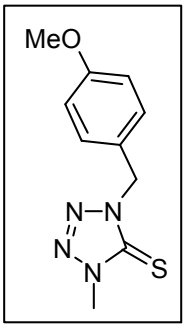
White solid (121.6 mg, 88%); IR (neat, cm^{-1}) 3071, 2980, 2965, 2943, 2870, 1961, 1890, 1600, 1545, 1451, 1346, 1297, 1129, 993; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.85 (d, J = 9.8 Hz, 2H), 7.59–7.43 (m, 3H), 1.87 (s, 6H), 1.34 (q, J = 7.4 Hz, 3H), 1.23–1.09 (m, 2H), 0.90 (t, J = 7.3 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.8, 134.7, 129.6, 129.1, 124.6, 66.8, 26.12, 26.0, 22.7, 14.0; HRMS (ESI-TOF) m/z $(M+H)^+$ calculated for $C_{11}H_{15}N_4S^+$, 277.1481; found, 277.1481.



1-benzhydryl-4-methyl-1,4-dihydro-5H-tetrazole-5-thione (**3n**)

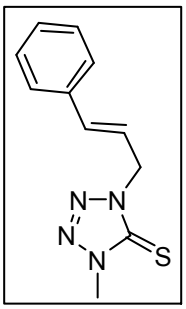
White solid (129.8 mg, 92%); IR (neat, cm^{-1}) 3062, 3030, 1963, 1689, 1599, 1497, 1441, 1343, 1121, 1095, 871; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.29–7.19 (m, 11H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 163.6, 135.9, 127.8, 127.5, 64.0, 33.8.

1-(4-methoxybenzyl)-4-methyl-1,4-dihydro-5H-tetrazole-5-thione (**3o**)



White solid (101.60 mg, 86%); IR (neat, cm^{-1}) 3056, 3038, 2961, 2836, 2569, 2309, 1635, 1513, 1231, 873; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.48–7.40 (m, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.39 (s, 2H), 3.87 (s, 3H), 3.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 164.2, 160.0, 130.5, 125.7, 114.3, 55.3, 51.2, 34.8.

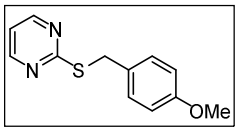
1-cinnamyl-4-methyl-1,4-dihydro-5H-tetrazole-5-thione (**3p**)



White solid (47.62 mg, 65%); IR (neat, cm^{-1}) 3065, 2945, 2857, 2361, 2336, 1724, 1676, 987, 834; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.39 (d, J = 7.1 Hz, 2H), 7.35–7.29 (m, 2H), 7.29–7.25 (m, 1H), 6.77 (d, J = 15.8 Hz, 1H), 6.34 (dt, J = 15.8, 6.8 Hz, 1H), 5.05 (dd, J = 6.8, 1.4 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 164.2, 136.4, 135.6, 128.7, 128.5, 126.8, 119.9, 50.1,

34.8.

2-((4-methoxybenzyl)thio)pyrimidine (**3q**)



White solid (88.27 mg, 76%); IR (neat, cm^{-1}) 3029, 2922, 2828, 2065, 1612, 1547, 1367, 1238, 1180, 1029, 806; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.50 (d, J = 4.9 Hz, 2H), 7.40–7.30 (m, 2H), 6.94 (t, J = 4.8 Hz, 1H), 6.86–6.79 (m, 2H), 4.37 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 172.3, 158.8, 157.2, 130.2, 129.3, 116.5, 113.9, 55.3, 34.8; HRMS (ESI-TOF) m/z $(M+H)^+$ calculated for $C_{12}H_{13}N_2OS^+$, 233.0743; found, 233.0740.

3.6.3 Representative NMR spectra of a selected compound

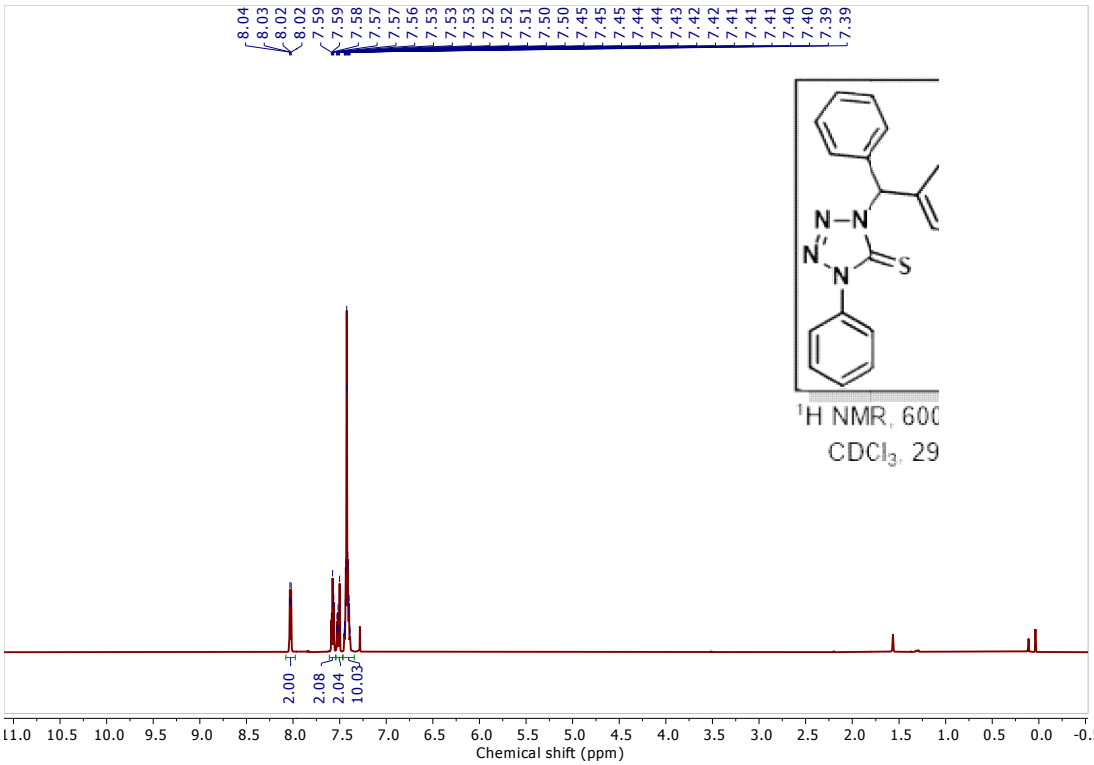


Figure **3.2** ^{1}H NMR Spectrum of **3a** in $CDCl_3$

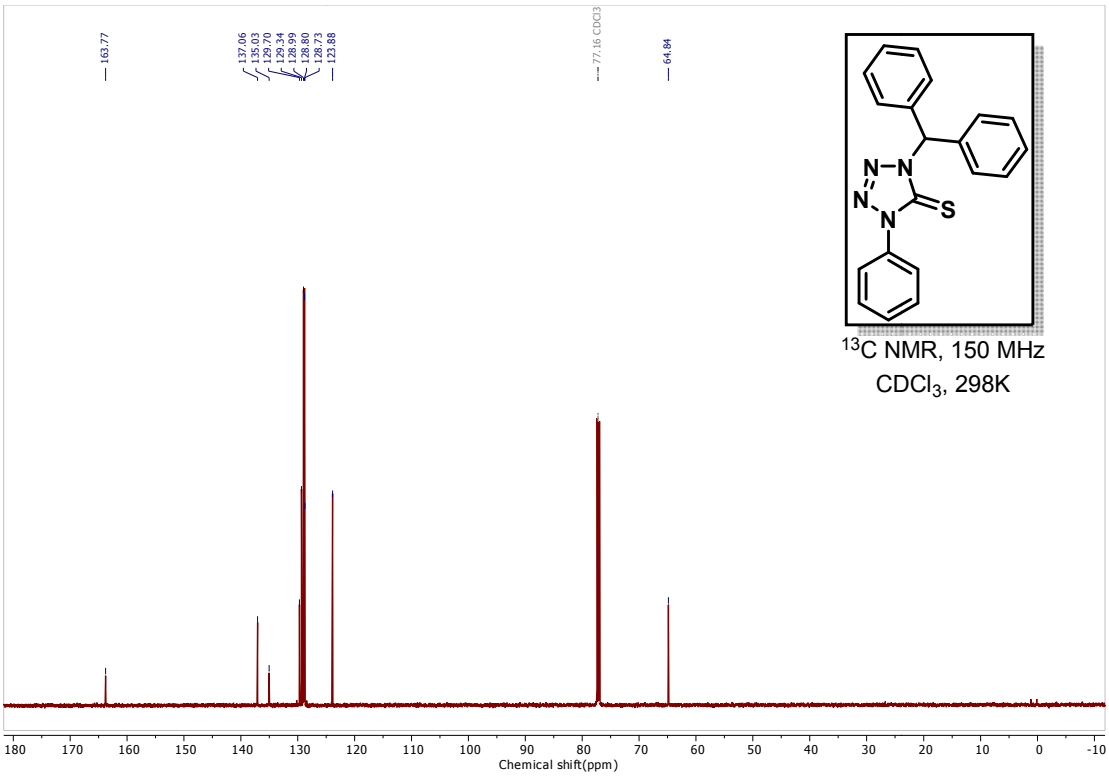


Figure **3.3** ^{13}C NMR Spectrum of **3a** in $CDCl_3$

3.7 Bibliography

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