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Desulfurization Strategy in the Construction of Azoles Possessing Additional Nitrogen, Oxygen or Sulfur using a Copper(I) Catalyst

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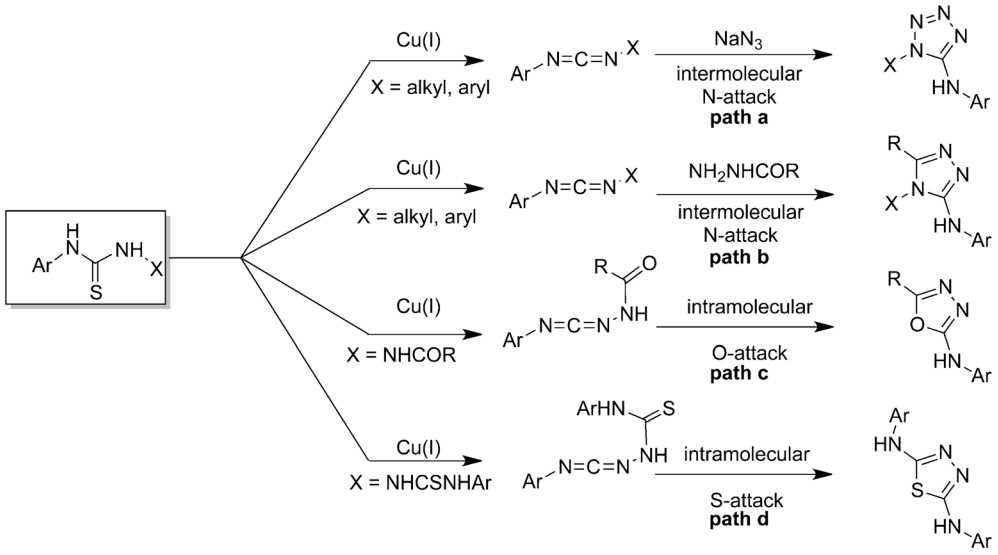
Abstract: A tandem and convergent approach to various N-, O-, or S-containing azoles has been developed by exploiting the thiophilic property of copper(I) iodide used in a catalytic quantity. The present protocol gives access to amino-substituted tetrazoles, triazoles, oxadiazoles and thiadiazoles *via* oxidative desulfurization of their respective precursors followed by inter- or intramolecular attack of suitable nucleophiles. For aminotetrazoles and triazoles an excellent regioselectivity has been achieved through proper tuning of the pK_a values of the parent amines attached to unsymmetrical thioureas. The method represents an autocatalytic process in which copper(I) iodide gets converted to copper(II) sulfide which in turn transforms to active copper(II) oxide that effectively carries forward the catalytic cycle. The fate of the copper catalyst has also been studied using scanning electron microscopic (SEM) and energy-dispersive X-ray spectroscopic (EDS) analyses which give an insight into the mechanism for this catalytic process.

Keywords: azoles; copper catalysis; oxidative desulfurization; tandem reactions

Introduction

The interest in transition metal-catalyzed processes for the synthesis of various N-, O-, or S-containing heterocyclic frameworks employing different strategies has experienced an explosive development in recent years.[1] Among these protocols, the copper salts serving as catalysts exhibited a promising potential in the synthesis of heterocyclic cores, which is due to its multifaceted properties.[2] With the advent of such copper-catalyzed strategies the formation of C–C and C–X (X = heteroatom) bonds could now be realized to give access to structurally important molecules easily.[3] However, most of these methodologies stand on the two pillars of the modern organic synthesis: (a) cross-coupling[2,3a] and (b) oxidative C–H functionalization[4] reactions. Despite the successful exploitation of such advantageous properties of copper toward a plethora of synthetic protocols, the basic feature that remained unexplored is its thiophilic character which could be utilized to the same effect as that of other thiophiles in bringing about oxidative desulfurization. To date the metals that are being explored mostly as thiophiles are confined to toxic heavy metals such as mercury and lead salts in a stoichiometric quantity. In one of our recent studies we have shown that a copper salt in a catalytic quantity with the assistance of a base could indeed bring about a desulfurization in the synthesis of various aryl/alkyl cyanamides from monosubstituted thioureas.[5a] Prior to our report, other groups had also reported similar copper-catalyzed oxidative desulfurization of thioamides and subsequent transformations.[5b,c] With the acquired knowledge from this transformation, we envisaged that the mono- or disubstituted thioureas under our earlier reported condition[5a] would give the heterocumulenes (cyanamides or carbodiimides). Since these heterocumulenes are potent reactive intermediates to various nitrogen-containing heterocycles, thus in a one-pot strategy we could generate the heterocumulenes *in situ via* a Cu(I) mediated strategy[5a] which, upon trapping with suitable nucleophiles (inter- or intramolecularly), would lead to the formation of our desired heterocycles (azoles). With this rationale behind our strategy we probed the synthesis of various azoles *via* a tandem convergent approach (Scheme 1). Herein, we report our one-pot tandem strategies for the synthesis of 5-aminotetrazoles (path



Scheme 1. Envisaged routes to various N-, O-, or S-containing azoles.

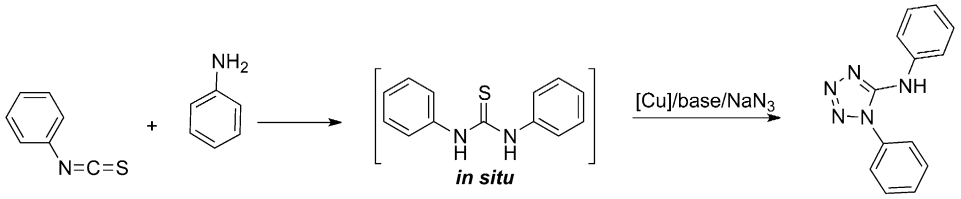
a), 3-amino[1,2,4]triazoles (path b), 2-amino-[1,3,4]oxadiazoles (path c), and 2,5-diamino-[1,3,4]thiadiazoles (path d).

Results and Discussion

Azoles occupy a central position in modern heterocyclic chemistry pertaining to their importance in medicinal and pharmaceutical industries. They also find diverse applications in agricultural and material research.[6] As a privileged fragment, the aminotetrazoles hold paramount significance from the stanpoint of their widespread applications in high energy density materials,[7] as ligands in coordination chemistry,[8] and as non-classical isosteres for the carboxylic acid moiety in biologically active molecules.[9] Furthermore, tetrazoles are reported to exhibit a wide scope of biological activities which include antiallergic/anti-asthmatic,[10] antiviral,[11] anti-inflammatory,[11] anti-neoplastic,[12] and cognition disorder[13] activities. The classical routes for the synthesis of 5-aminotetrazoles are grouped into four categories:[14] (a) amino group or ring functionalization of 5-aminotetrazole; (b) the substitution of a leaving group in the 5-position of tetrazole with amines; (c) reactions of aminoguanidine derivatives with sodium nitrite; and (d) various azide-mediated tetrazole ring constructions from carbodiimides. Among these approaches, the attack of inorganic azide to carbodiimide intermediate constitutes one of the most useful methods for the synthesis of aminotetrazoles. Relying on the aforesaid strategy recently we have developed a protocol for the regioselective synthesis of 5-aminotetrazoles using molecular iodine as the thiophile.[15] Also the hypervalent iodine reagent, *o*-iodoxybenzoic acid, has been successfully employed in bringing about the same transformation.[16] However, strictly adhering to the use of metal catalysts, only Hg and Pb salts (stoichiometric quantity) have been exploited to generate the carbodiimide intermediate *via* desulfurization of the corresponding thiourea followed by attack of an azide ion to construct the tetrazole core.[17] Thus, in an attempt to avoid the use of such toxic and hazardous metal salts (Pb and Hg) and taking cues from our earlier method, we wanted to invoke a copper salt in a catalytic quantity to effect the transformation of thiourea to the intermediate carbodiimide or cyanamide.[5a] These carbodiimide or cyanamide intermediates would subsequently lead to the formation of 5-aminotetrazole upon attack by an azide ion.

To initiate the investigation, phenyl isothiocyanate (1 equiv.) in DMSO was treated with aniline (1 equiv.) and stirred at 80 °C for 10 min to give 1,3-diphenylthiourea (**1a**). After complete formation of 1,3-diphenylthiourea (**1a**) (judged by TLC), to this reaction mixture were added sequentially CuI (10 mol%), NaOH pellets (2 equiv.) and NaN_3 (1 equiv.) and the heating was continued for 5 h. These reaction conditions were chosen keeping our earlier catalytic synthesis of the cyanamides in mind.[5a] However, this reaction was associated with the formation of a major amount of the corresponding urea as by-product along with a minor amount of aniline, probably by the decomposition of thiourea or intermediate carbodiimide and only traces (<5%) of the expected 5-aminotetrazole (**2a**) (Table 1, entry 1). It was obvious from this observation that the Cu(I) salt does cause the desulfurization to form the intermediate carbodiimide which is being attacked either by hydroxide ion or the water present in ordinary DMSO to form the corresponding urea rather than

Table 1. Screening of reaction conditions.



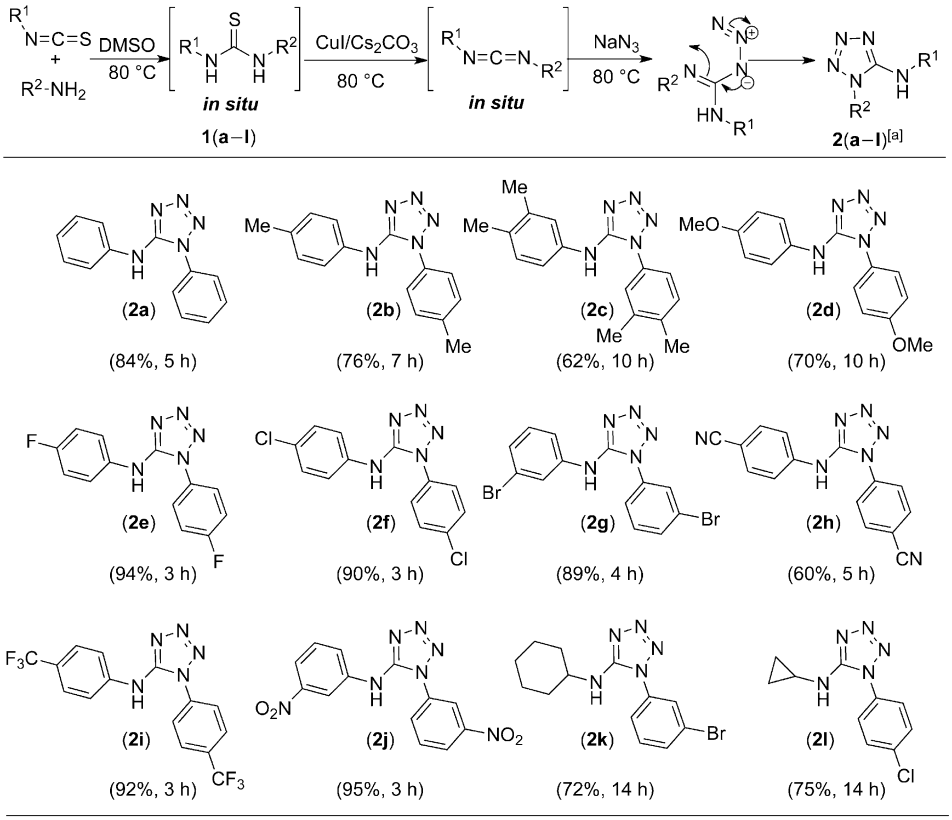
1a 2a

Entry	Catalyst (mol%)	NaN_3 (equiv.)	Base (equiv.)	Solvent	Temperature	Time [h]	Yield [%][a]
1	CuI (10)	1	NaOH (2)	DMSO	80 °C	5	< 5
2	CuI (10)	1	K_2CO_3 (2)	DMSO	80 °C	5	25
3	CuI (10)	1	Cs_2CO_3 (2)	DMSO	80 °C	5	32
4	CuI (10)	1	Cs_2CO_3 (3)	DMSO	80 °C	5	35
5	CuI (10)	1	Cs_2CO_3 (2)	DMSO (dry)	80 °C	5	67
6	CuI (10)	1	Cs_2CO_3 (2)	DMSO (dry)	100 °C	5	55
7	CuI (10)	2	Cs_2CO_3 (2)	DMSO (dry)	80 °C	5	75
8	**CuI(10)**	**3**	**Cs_2CO_3 (2)**	**DMSO (dry)**	**80 °C**	**5**	**84**
9	CuI (10)	4	Cs_2CO_3 (2)	DMSO (dry)	80 °C	5	86
10	CuI (7.5)	3	Cs_2CO_3 (2)	DMSO (dry)	80 °C	5	70
11	CuI (5)	3	Cs_2CO_3 (2)	DMSO (dry)	80 °C	5	55
12	CuBr (10)	3	Cs_2CO_3 (2)	DMSO (dry)	80 °C	7	72
13	CuCl (10)	3	Cs_2CO_3 (2)	DMSO (dry)	80 °C	10	65
14	$CuBr_2$ (10)	3	Cs_2CO_3 (2)	DMSO (dry)	80 °C	7	75
15	$CuCl_2 \cdot 2H_2O$ (10)	3	Cs_2CO_3 (2)	DMSO (dry)	80 °C	7	70
16	$CuSO_4 \cdot 5H_2O$ (10)	3	Cs_2CO_3 (2)	DMSO (dry)	80 °C	12	50
17	CuI (10)	3	Cs_2CO_3 (2)	DMF (dry)	80 °C	10	30
18	CuI (10)	3	Cs_2CO_3 (2)	toluene (dry)	80 °C	15	< 5
19	CuI (10)	3	Cs_2CO_3 (2)	dioxane (dry)	80 °C	12	20
20	CuI (10)	3	Cs_2CO_3 (2)	CH_3CN (dry)	80 °C	15	< 5
21	none	3	Cs_2CO_3 (2)	DMSO (dry)	80 °C	24	nd

[a] Isolated yields.

being attacked by a weak azide nucleophile. Replacement of NaOH with K_2CO_3 (2 equiv.) (Table 1, entry 2) or Cs_2CO_3 (2 equiv.) (Table 1, entry 3) made an improvement in the yield, it being slightly more with Cs_2CO_3 (32%) in comparison to K_2CO_3 (25%). Furthermore, an increase in the base quantity (3 equiv.) did not improve the yield (Table 1, entry 4). The methodology was thus disadvantageous with respect to the formation of urea as the major by-product. Hence the reaction was carried out in dry DMSO under a nitrogen atmosphere to keep out any moisture that could affect the yield. It was gratifying to observe that there was a substantial improvement in the yield (67%) without the formation of urea by-product (Table 1, entry 5). The reaction carried out at 100 °C had an adverse effect on the product yield due to possible decomposition of the substrate or intermediate carbodiimide to aniline (Table 1, entry 6). Next the amount of sodium azide was increased to 2 equiv. and 3 equiv. from 1 equiv. and the best result was obtained with the latter (84%) (Table 1, entries 7 and 8). With further increase in sodium azide quantity (4 equiv.) a marginal improvement (2%) in the yield was observed (Table 1, entry 9). A decrease in the catalyst loading to 7.5 and 5 mol% had negative effects on the product yield (Table 1, entries 10 and 11). With this initial result in hand other reaction parameters such as catalysts and solvents were varied to arrive at the optimum conditions required for this methodology. The results are summarized in Table 1.

As can be seen from Table 1, CuI (10 mol%) invariably proved to be superior to the other copper salts such as CuBr, CuCl, $CuBr_2$, $CuCl_2 \cdot 2H_2O$, and $CuSO_4 \cdot 5H_2O$ both in terms of product yield and reaction time (Table 1, entries 12–16). Other anhydrous solvents examined such as DMF, toluene, dioxane and CH_3CN were unable to provide satisfactory yields as compared to DMSO (Table 1, entries 17–20). Reactions in these solvents either gave a multitudes of side products or the starting material remained unreacted under the reaction conditions. Notably, the reaction did not proceed at all in the absence of the metal catalyst, thus implying the requirement of metal catalyst to effect the transformation (Table 1, entry 21). Therefore, for subsequent reactions we continued to use our optimized reaction conditions [disubstituted



[a] Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

Scheme 2. Substrate scope for 5-aminotetrazoles.

thiourea (1 equiv.), Cs_2CO_3 (2 equiv.), NaN_3 (3 equiv.), CuI (10 mol%) in anhydrous DMSO (2 mL) under a nitrogen atmosphere].

The optimized conditions were applied to various *in situ* generated 1,3-diarylthioureas to explore the scope and generality of this methodology. The results shown in Scheme 2 attest that the methodology is compatible to a wide range of functionalities giving moderate to excellent yields of the respective 5-aminotetrazoles. Symmetrical thioureas bearing electron-donating groups such as *p*-Me (**1b**), 3,4-di-Me (**1c**), *p*-OMe (**1d**) all underwent the reaction smoothly to give their respective 5-aminotetrazoles (**2b**–**2d**) in good yields. Also for thioureas bearing moderately electron-withdrawing substituents *viz*. *p*-F (**1e**), *p*-Cl (**1f**), *p*-Br (**1g**), and strong electron-withdrawing substituents such as *p*-CF_3 (**1i**) and *m*-NO_2 (**1j**) under the present conditions the reactions were very fast to give excellent yields of the corresponding tetrazoles (**2e**–**2i**). The only exception in the trend in yield was observed with *p*-CN (**1h**) where the corresponding tetrazole (**2h**) was obtained in a moderate yield of 60%. The moderate yield observed for cyano substrate (**1h**) could be due to the interference of the cyano group in the elecrocyclization with the azide ion leading to the formation of other by-products. Furthermore, structure of the product (**2f**) has been confirmed by X-ray crystallographic analysis as shown in Figure 1.

Notably, the reactions were superior in terms of yield and shorter reaction time for thioureas bearing electron-withdrawing groups (**1e–1j**) in comparison to those bearing electron-donating ones (**1a–1d**) (Scheme 2). Moreover, for unsymmetrical thioureas possessing aryl and alkyl moieties (**1k**) and (**1l**) exclusive formation of single regioisomers (**2k**) and (**2l**) was observed but the reactions were sluggish in con-

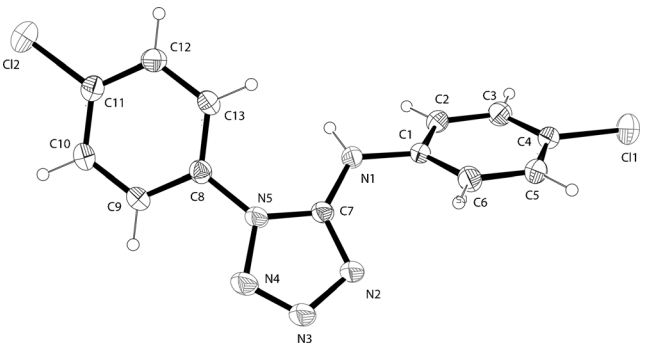
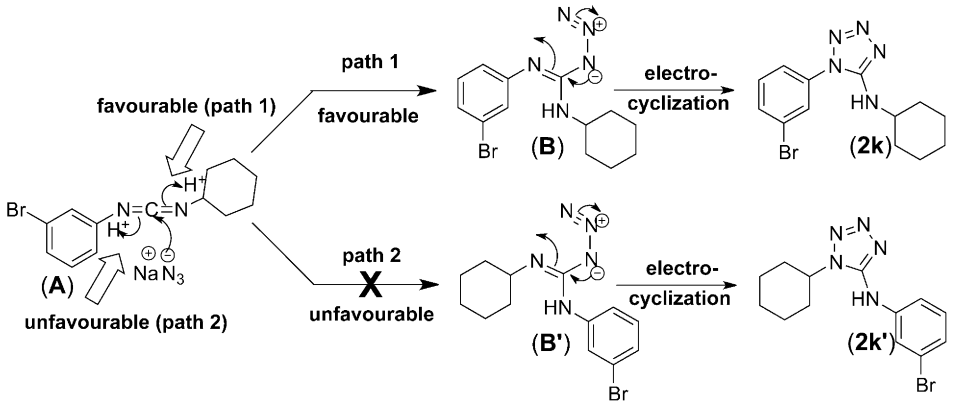


Figure 1. ORTEP view of (**2f**).[44]

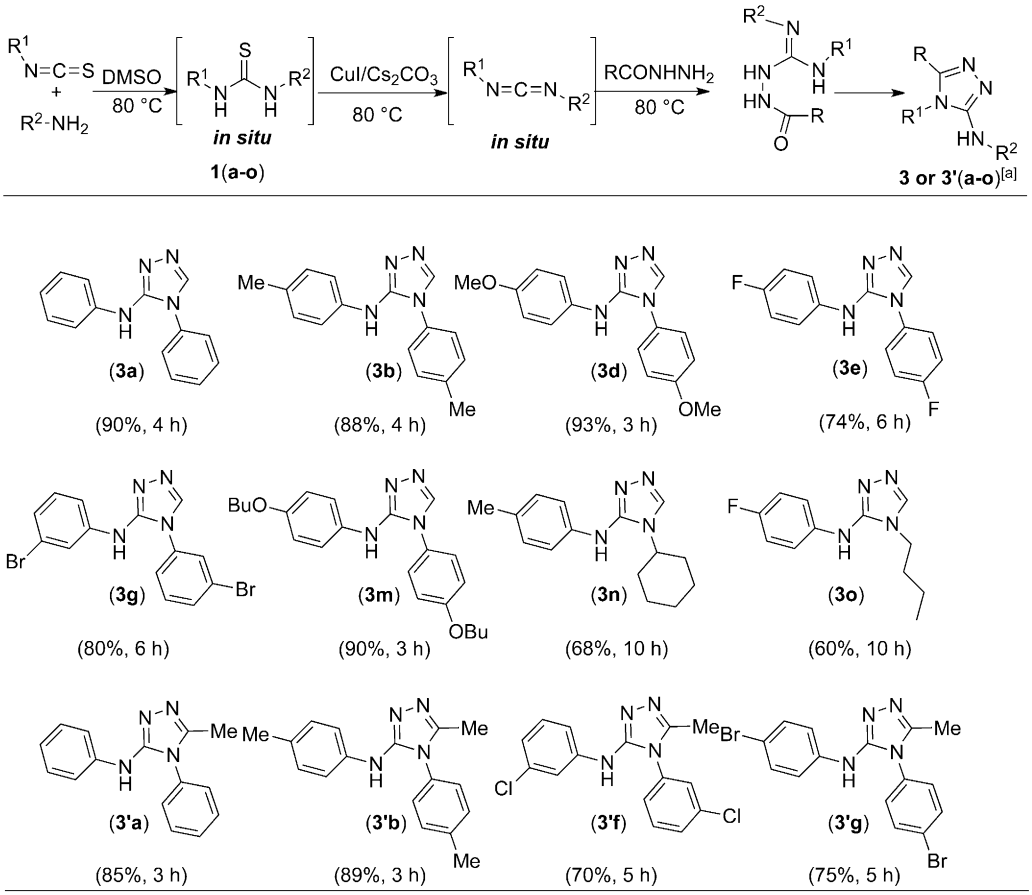


Scheme 3. Regioselective formation of product (**2k**).

trast to those of the diarylthioureas. These observations are consistent with our earlier report where the aminotetrazoles have been synthesized using molecular iodine.[15] Formation of a single regioisomer could be judged from the pK_a difference of the amines attached to the unsymmetrical thioureas.[15] As a typical illustration, substrate (**1k**) has been chosen as the model substrate. Thiourea (**1k**) underwent desulfurization upon treatment with CuI to give the unsymmetrical carbodiimide (**A**) (Scheme 3). This carbodiimide intermediate (**A**) upon attack by the azide nucleophile could lead to the formation of either guanidyl intermediate (**B**) or (**B′**). However, the formation of that guanidyl intermediate would be favoured (path-1) where the protonation occurs at the more basic nitrogen (i.e., nitrogen attached to cyclohexyl moiety) while the other nitrogen remains in the imine form. The favoured intermediate (**B**) then undergoes an electrocyclization to give tetrazole (**2k**) exclusively.

As an extension of this study, we proceeded toward the synthesis of another important heterocyclic scaffold *viz.* 3-amino[1,2,4]triazole which could be achieved through a sequential addition–dehydration path upon reaction between carbodiimide and hydrazides (Scheme 1, path b). Triazoles display a wide array of biological activities in the field of medicinal and agrochemicals. To exemplify their biological relevance, they serve as bioisosteres in lieu of amides and thioamides,[18] are also present in potent pharmacophores which exhibit antifungal,[19] antimicrobial,[20] anti-inflammatory,[21] antiviral,[22] antiasthmatic,[23] and antiproliferative[24] activities. Several efficient protocols have been developed for the synthesis of [1,2,4]triazoles that include both solid phase[25] and solution phase[26] synthesis. However, in all these methodologies the [1,2,4]triazoles have different substitution patterns in the ring as well as in the exocyclic region. Thus focusing solely on the synthesis of 3-amino-[1,2,4]triazole where thiourea and hydrazides have been used as the precursors, not much has been demonstrated in the literature. Very recently we have developed a protocol for the regioselective synthesis of 3-amino[1,2,4]triazoles mediated by molecular iodine.[27] A similar transformation has also been carried out by other groups using the hypervalent iodine reagent *o*-iodoxybenzoic acid.[16] The usage of metal catalysts has been explored to accomplish the synthesis of 3-amino[1,2,4]triazoles employing mercury[26b] and silver[26d] salts as the thiophiles. Pertaining to the metal-catalyzed synthesis, it would be of considerable importance if the toxic and expensive metal salts used in stoichiometric amounts could be substituted by a copper salt in a catalytic quantity. Hence we pursued the reaction with our pre-optimized conditions by replacing sodium azide with formic acid hydrazide (1 equiv.) with the *in situ* generated 1,3-diphenylthiourea (**1a**) as the model substrate. A fairly good yield (65%) of the product (**3a**) was obtained under the present conditions within a span of 4 h. An attempt to enhance the yield was carried out by increasing the quantity of formic acid hydrazide to 2 equiv. and 2.5 equiv. A substantial improvement in yield of the product was observed with the latter (2.5 equiv.) providing 90%. Further increase in the formic acid hydrazide quantity provided no variation in yield. Since it has been established earlier that CuI (10 mol%) with the assistance of base Cs_2CO_3 (2 equiv.) in dry DMSO serves the purpose to generate the carbodiimide intermediate, so further optimization was not carried out for the synthesis of 3-amino[1,2,4]triazoles. For subsequent reactions the following conditions were applied [disubstituted thiourea (1 equiv.), Cs_2CO_3 (2 equiv.), $RCONHNH_2$ (R = H, CH_3) (2.5 equiv.), CuI (10 mol%) in anhydrous DMSO (2 mL) under a nitrogen atmosphere].

Symmetrical thioureas bearing electron-donating groups such as *p*-Me (**1b**), *p*-OMe (**1d**), and *p*-OBu (**1m**) afforded excellent yields of their respective aminotriazoles (**3b**), (**3d**) and (**3m**) in shorter reaction times (Scheme 4). While those bearing electron-withdrawing groups *viz.* *p*-F (**1e**) and *m*-Br (**1g**) underwent reaction to give the corresponding products (**3e**)



[a] Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

Scheme 4. Substrate scope for 3-amino[1,2,4]triazoles.

and (**3g**) in good yields, however in slightly lesser yield and requiring longer reaction time as compared to substrates possessing electron-donating ones. These observations are in contrast to reactivity trends observed during the formation of 5-aminotetrazoles discussed above but, however, are in good agreement with our recently reported protocol on 3-amino-[1,2,4]triazole synthesis mediated by iodine.[27] The structure of the product (**3e**) has been further confirmed by X-ray crystallographic analysis as shown in Figure 2.

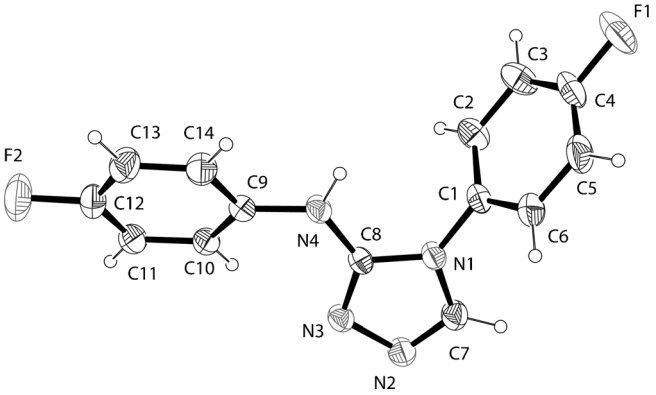
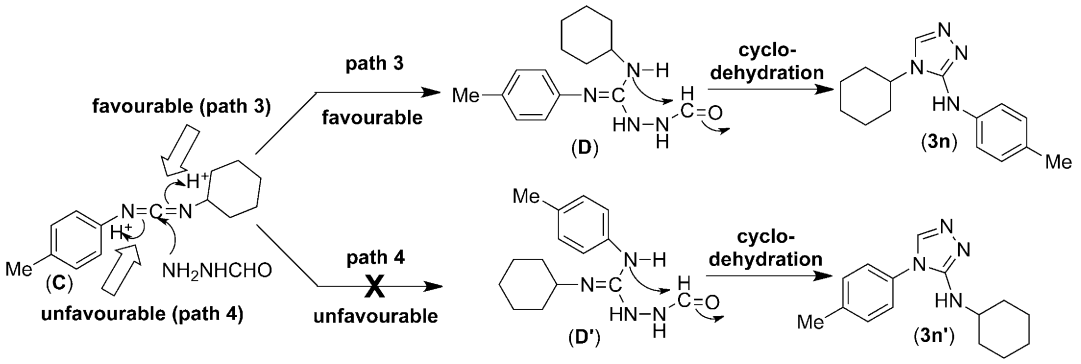


Figure 2. ORTEP view of (**3e**).[44]

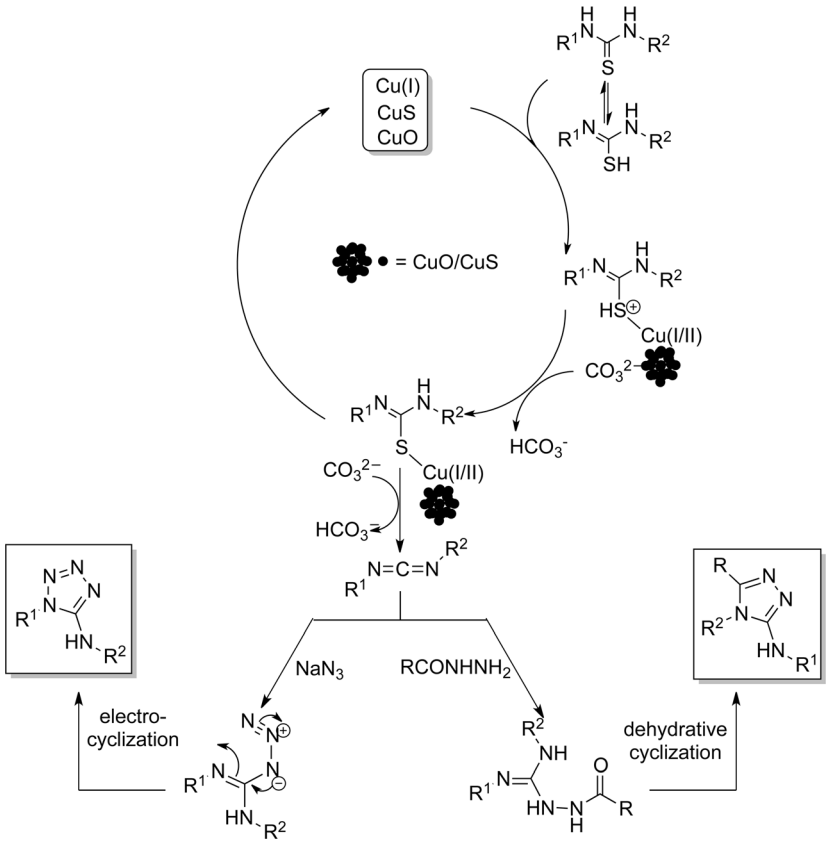
Unsymmetrical aryl-alkylthioureas (**1n**) and (**1o**) under the present reaction conditions gave single regioisomers (**3n**) and (**3o**), respectively, though requiring longer reaction times (Scheme 4). In these regioisomers the nitrogen atom having the higher pK_a forms part of the ring while the other nitrogen (lower pK_a) remains flanked as the exocyclic nitrogen of the triazole core. The disposition of the nitrogen atoms in aminotriazoles is in keeping with our recent report on the regioselectivity,[27] that could be explained on the basis of the pK_a difference of the amines attached to unsymmetrical thioureas. Noteworthy, again a reverse trend is followed in the case of aminotriazoles (Scheme 4) to that of aminotetrazoles (Scheme 2) in terms of the regioselective disposition of the nitrogen atoms attached to the unsymmetrical thioureas. As an illustration of the regioselective formation of the aminotriazoles, substrate (**1n**) has been chosen as the model substrate. As has been stated earlier the intermediate carbodiimide (**C**) formed *in situ* from thiourea (**1n**) upon the copper-catalyzed desulfurization un-



Scheme 5. Regioselective formation of product (**3n**).

dergoes a nucleophilic attack from formic acid hydrazide. This could lead to the possibility of intermediates (**D**) and (**D′**), which are tautomeric forms of each other (Scheme 5). However, the equilibrium would be shifted toward (**D**) (path 3), due to favourable protonation at the more basic nitrogen than at the less basic nitrogen (path 4). The intermediate (**D**) then undergoes a dehydrative cyclization to render the aminotriazole regioisomer (**3n**) solely and no traces of the other regioisomer (**3n′**) was observed. Having successfully synthesized the aminotriazoles, we focused on the synthesis of 5-methyl-substituted aminotriazoles by replacing formic acid hydrazide with acetohydrazide. In these cases also all the *in situ* generated thioureas (**1a**), (**1b**), (**1f**) and (**1g**) underwent reactions smoothly to give fair yields of the products (**3′a**), (**3′b**), (**3′f**) and (**3g**), respectively. Worth mentioning is that the same trend in yield was observed with acetohydrazide as was with formic acid hydrazide (Scheme 4).

A plausible mechanism for the formation of aminotetrazoles and aminotriazoles has been depicted in Scheme 6. As demonstrated in our earlier report,[5a] herein as well CuI after the first catalytic cycle is sup-



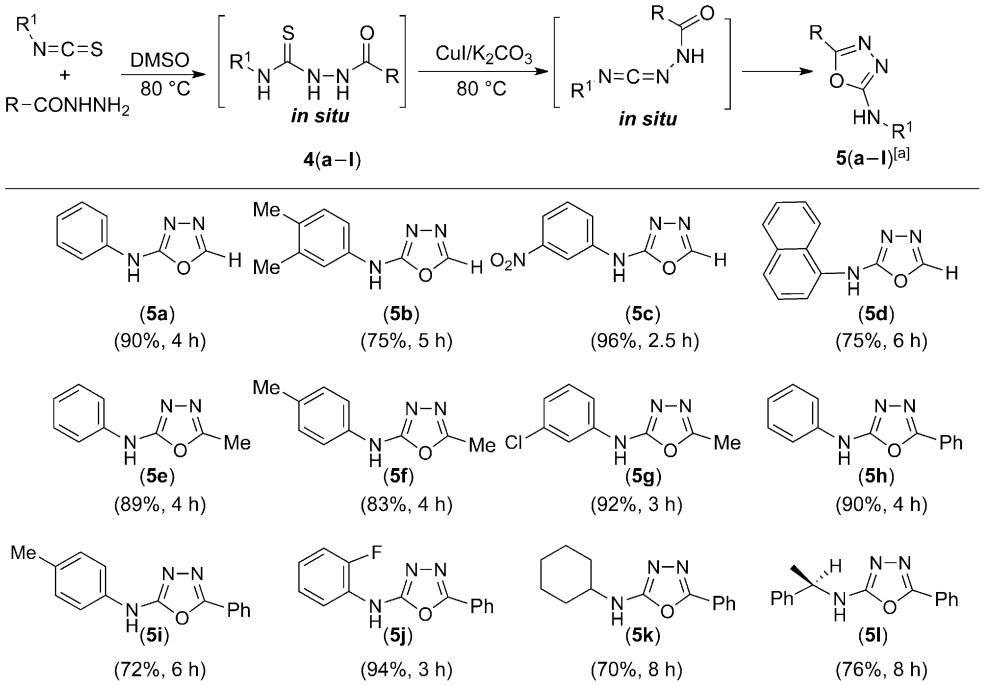
Scheme 6. Plausible mechanism for the formation of 5-aminotetrazole and 3-amino[1,2,4]triazole catalyzed by CuI.

posed to get converted to CuS or forms an array of polynuclear anions containing sulfur rings or a chain.[28] Under these conditions and temperature, some of the *in situ* generated CuS gets converted/decomposed to CuO. Thus the active CuO generated in the reaction suffices for the purpose of oxidative desulfurization in the next catalytic cycles to give the intermediate carbodiimide. In the case of 5-aminotetrazole (Scheme 2, Scheme 3 and Scheme 6) the intermediate carbodiimide undergoes nucleophilic attack by the azide ion to give a guanidyl kind of intermediate which on subsequent electrocyclization affords the 5-aminotetrazole. During the formation of 3-amino-[1,2,4]triazoles (Scheme 4), hydrazides are the active nucleophiles which attack the carbodiimide to give the acylureidrazone intermediate. Subsequent dehydrative cyclization and aromatization leads to the formation of 3-amino[1,2,4]triazoles (Scheme 4, Scheme 5 and Scheme 6).

The success of this copper-mediated heterocyclization prompted us to apply the strategy to thiosemicarbazides (*in situ* generated), where a similar desulfurization would generate intermediate carbodiimide. This on intramolecular nucleophillic attack by the amidic oxygen could form 2-amino[1,3,4]oxadiazoles (Scheme 1, path c). The aminooxadiazoles are recognized as biologically important pharmacophores due to their wide range of biological activities that include analgesic,[29] anti-inflammatory,[29] anticonvulsant,[30] diuretic,[29] antineoplastic,[31] and muscle relaxant[32] properties. Additionally, some exhibit insecticidal[33] and herbicidal[34] properties as well. However, their relevance is not restricted to the bioactivities alone. Their potentialities have further extensions to well-defined applications in materials research particularly in the field of organic electronics owing to their good electron-transporting and hole-blocking abilities.[35] Such a wide spectrum of applications has led to the emergence of various protocols for the synthesis of 2-amino[1,3,4]oxadiazoles. The classical strategies that have been documented till date fall under two major heads: (a) cyclodehydration of semicarbazides[36] and (b) cyclodesulfurization of thiosemicarbazides.[37] Straightforward to the latter strategy, recently a mild approach involving the mediation of molecular iodine has been reported by us,[38] while a similar transformation has been carried out using the hypervalent iodine reagent *o*-iodoxybenzoic acid by another group.[16] But a scrutiny of the metal-based transformations suggest the use of toxic thiophilic Hg[39] and Pb[32] salts in stoichiometric quantity for the purpose of desulfurization of the thiosemicarbazides. To do away with the handling of such hazardous metal salts, a copper-catalyzed method would be more appreciable. As a primary study, thiosemicarbazide (**4a**) obtained *in situ* [phenylisothiocyanate (1 equiv.) and formic acid hydrazide (1 equiv.) in anhydrous DMSO at 80 °C] when subjected to treatment of CuI (10 mol%) and Cs_2CO_3 (2 equiv.) in the same pot under the pre-optimized conditions afforded an excellent yield (90%) of the product (**5a**). A sub-optimization carried out with thiosemicarbazide (**4a**) revealed that K_2CO_3 (2 equiv.) worked as effectively as Cs_2CO_3 (2 equiv.). Additionally, the reaction could be carried out in ordinary DMSO under normal atmospheric conditions rather than under a nitrogen atmosphere in anhydrous DMSO solvent. It was reasoned that since this reaction goes *via* an intramolecular attack of the amidic oxygen, it is expected to be faster than the intermolecular attack of the water present in ordinary DMSO. However, other trials such as lowering of catalyst loading or the temperature proved to be unsatisfactory for the current methodology.

Thus having a standardized protocol in hand the method was subsequently applied to various *in situ* generated thiosemicarbazides to examine the generality and scope of the reaction (Scheme 7). Herein as well diverse functionalities have been tolerated giving good to excellent yields of the desired 3-amino-[1,3,4]oxadiazoles. Thiosemicarbazides obtained from formic acid hydrazide, acetohydrazide or benzohydrazide all underwent reactions smoothly to render the respective 3-amino[1,3,4]oxadiazoles. For thiosemicarbazides bearing electron-donating substituents *viz*.3,4-di-Me (**4b**), *p*-Me (**4f** and **4i**), the reactions provided the desired products (**5b**), (**5f**) and (**5i**) in good yields (Scheme 7). However, for the electron-withdrawing ones *viz*. *m*-NO_2 (**4c**), *m*-Cl (**4g**) and *o*-F (**4j**), excellent yields of the corresponding oxadiazoles (**5c**), (**5g**) and (**5j**) were obtained in shorter reaction times as compared to their electron-donating analogues. Naphthyl thiosemicarbazide (**4d**) yielded oxadiazole (**5d**) in decent yield under the present conditions. Also aliphatic thiosemicarbazide (**4k**) and chiral benzylthiosemicarbazide (**4l**) gave their corresponding oxadiazoles (**5k**) and (**5l**) in modest yields. The structure of (**5i**) has further been confirmed by X-ray crystallographic analysis as shown in Figure 3.

The reactivity order followed in the formation of the oxadiazoles can be explained on the basis of the dual role of electronic effects of the electron-withdrawing functionalities present in the aryl moiety. Noteworthy is that the electron-withdrawing groups cause a faster deprotonation of aryl N–H proton followed by a copper-mediated desulfurization to give the intermediate carbodiimide (Scheme 7 and Scheme 9). Additionally, the electron-withdrawing effect increases the electrophilicity at the carbodiimidic carbon and thus facilitates the intramolecular attack of the amidic O-atom to give the oxadiazoles. These dual positive role exhibited by electron-withdrawing groups present in the aryl ring have a significant effect on the yield and the reaction time of the aforesaid reactions (Scheme 7).



[a] Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

Scheme 7. Substrate scope for 2-amino[1,3,4]oxadiazoles.

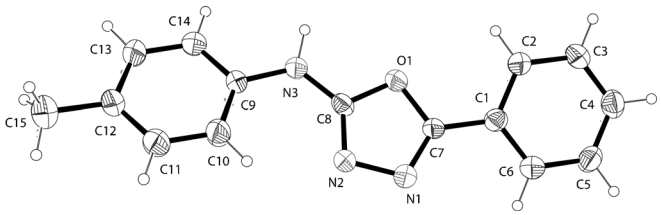
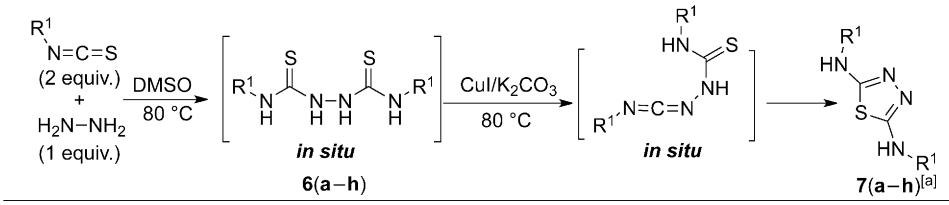
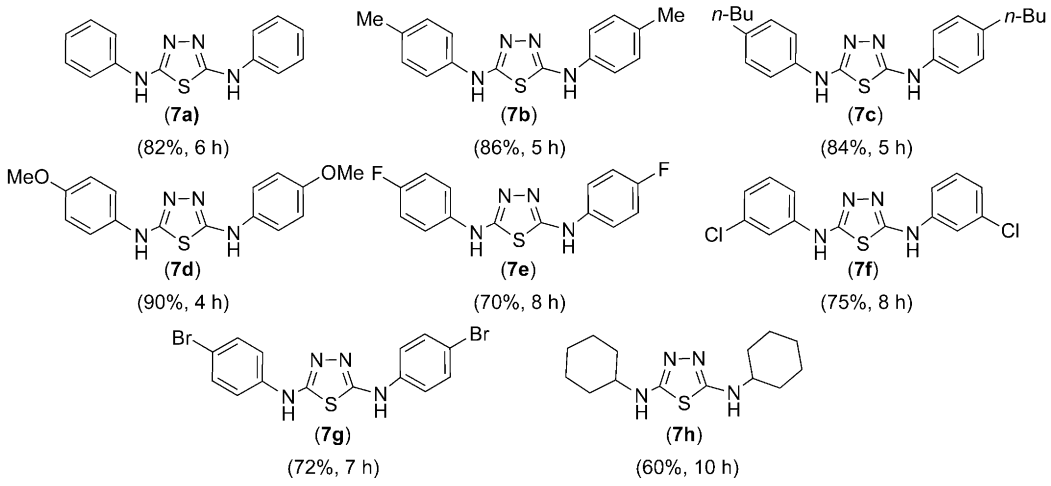


Figure 3. ORTEP view of (**5i**).[44]

Having a successful strategy in hand, we extended the present protocol toward the synthesis of 2,5-diamino[1,3,4]thiadiazole from *in situ* generated bis-thiourea (Scheme 1, path d). The [1,3,4]thiadiazoles are important entities that are widely employed in drug discovery. There has been intense investigation on the biological activities of different classes of thiadiazole compounds, many of which are reported to be pharmacologically active. Of significance are their anticonvulsant, anti-inflammatory, antioxidant, antimicrobial, antituberculosis and antifungal properties.[40] Recently, [1,3,4]thiadiazole cores have received much attention in material science due to their interesting electronic and optical properties.[41] Various methodologies that exist in literature[42] for their synthesis are associated with number of drawbacks that impedes their applicability in the long run. Moreover, the methods for the synthesis of 2,5-diamino-[1,3,4]thiadiazoles *via* oxidative desulfurization of bis-thioureas have been rarely explored. The desulfurization strategies to date use reagents such as chloranil,[43] bromonil,[43] iodine[15] and most recently the hypervalent iodine reagent *o*-iodoxybenzoic acid[16] but no metal-based catalytic transformation is reported so far. In the present methodology, we have synthesized various 2,5-diamino[1,3,4]thiadiazoles employing Cu(I) catalyst. The optimized conditions for their synthesis are the same as those applied for the 2-amino[1,3,4]oxadiazoles. The results are summarized in Scheme 8.

All the bis-thioureas provided excellent to decent yields of the respective diaminothiadiazoles. For the bis-arylthioureas having electron-donating substituents (**6b–6d**) the yields of the products (**7b–7d**) were superior to the bis-arylthioureas having electron-withdrawing substituents (**6e–6g**) for which the product (**7e–7g**) yields were fairly decent (Scheme 8). However for the bis-dialkyl thiourea (**6h**) the reaction was sluggish and the product (**7h**) yield was moderate. A probable reason for such reactivity trend could be due to the attack of the sulfur nucleophile onto the carbodiimide facilitated by the electron-donating effects compared to the electron-withdrawing effects that cause the differences in yields and reaction time. The structure of the product (**7f**) has further been confirmed by X-ray crystallographic analysis as shown in Figure 4.





[a] Reactions were monitored by TLC. Confirmed by spectroscopic analysis. Yield of isolated pure product reported.

Scheme 8. Substrate scope for 2,5-diamino[1,3,4]thiadiazoles.

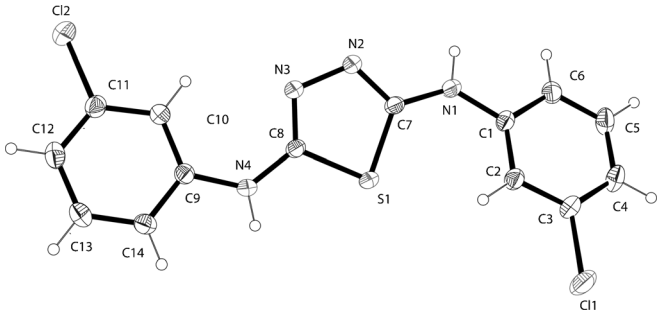
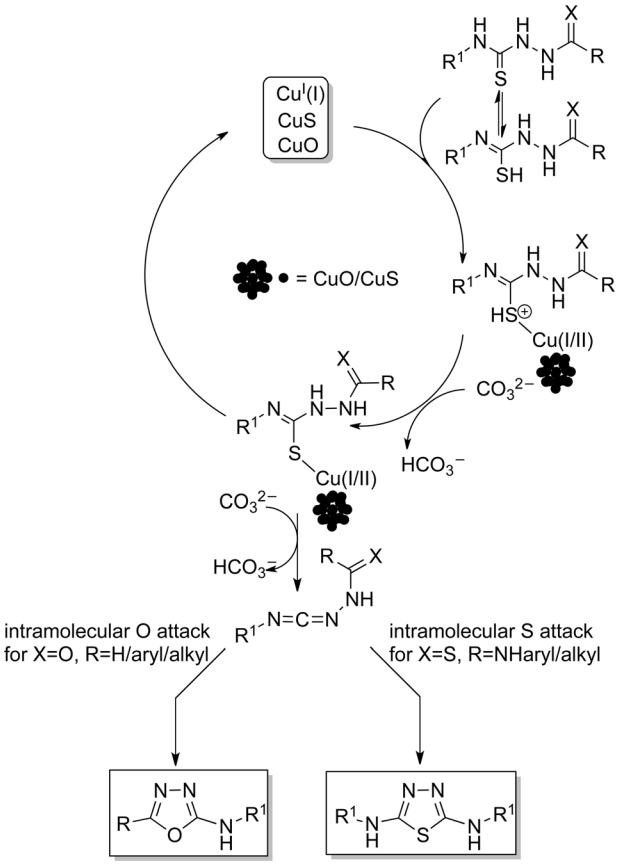


Figure 4. ORTEP view of (**7f**).[44]

An analogous mechanism is expected to operate in the formation of 2-amino[1,3,4]oxadiazoles and 2,5-diamino[1,3,4]-thiadiazoles where CuS and CuO generated during the reaction carry forward the catalytic cycle by an oxidative desulfurization as has been mentioned earlier. The carbodiimidic intermediate thus formed undergoes an intramolecular nucleophilic attack of amidic oxygen or thioamidic sulfur, followed by aromatization to give 2-amino[1,3,4]oxadiazoles or 2,5-diamino[1,3,4]thiadiazoles as the case may be (Scheme 9).

The assumption that CuO and CuS are formed *in situ*, which probably catalyzes the reaction further, has been supported by the SEM and EDS analyses of the sample obtained from one of the reactions. As can been seen from Figure 5, there are clear indica-



Scheme 9. Plausible mechanism for the Cu catalyzed formation of 2-amino[1,3,4]oxadiazole and 2,5-diamino-[1,3,4]thiadiazole.

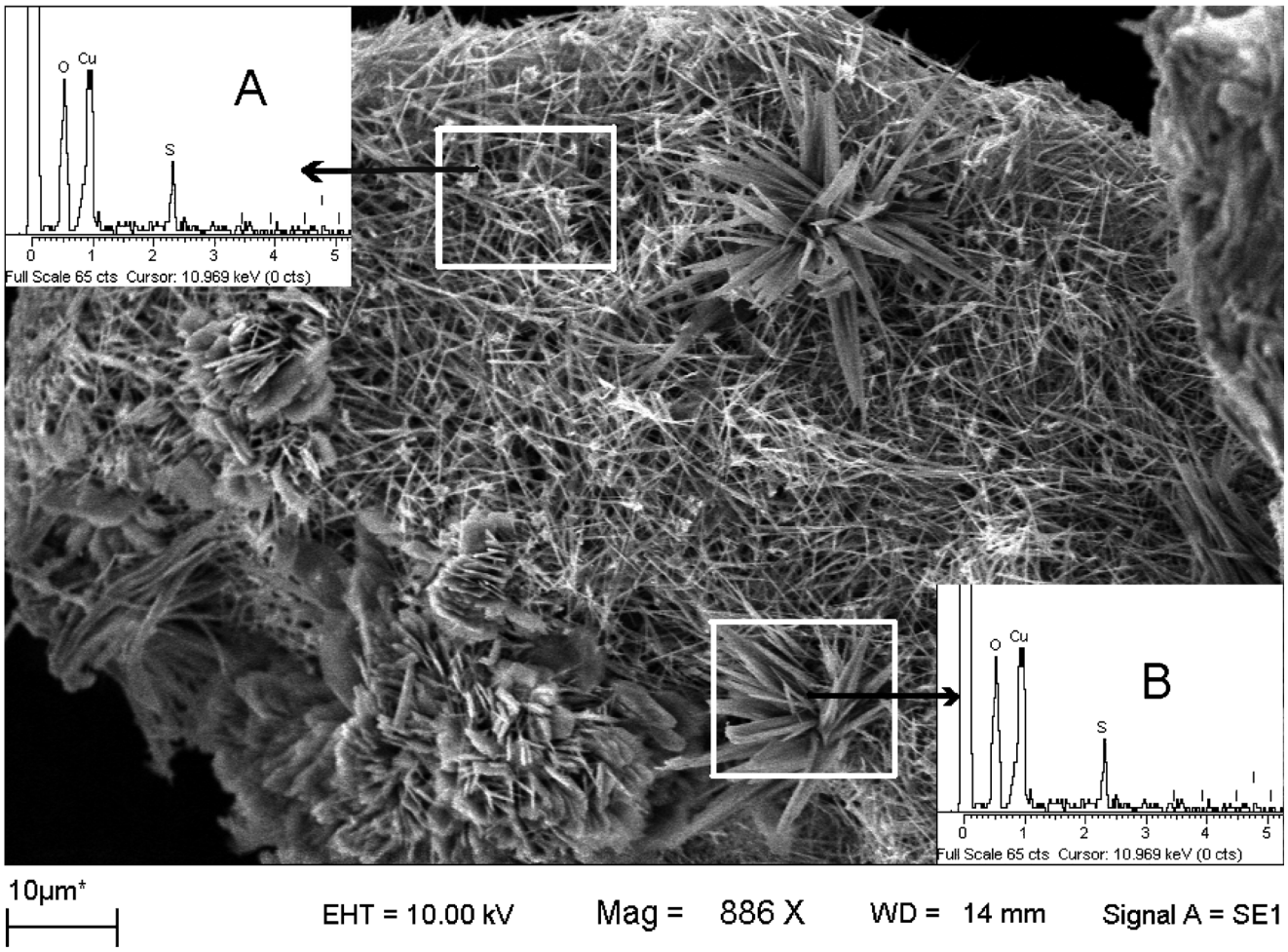


Figure 5. SEM and EDS analyses of the Cu salt.

tions for the existence of CuO and CuS in the SEM picture. Some of the regions are rich in CuO (region B) while other parts contain fine fibrous CuS (region A). Also treating the filtered Cu catalyst to the *in situ* generated thiosemicarbazide **4a** (Scheme 7) under the identical experimental conditions gave 2-amino-[1,3,4]oxadiazoles (**5a**) in 88% isolated yield thus supporting our proposed catalytic cycle. We believe the filtered catalyst should also be equally effective in bringing about all the above transformations.

Conclusions

In conclusion, we have developed a tandem convergent synthesis of various N-, O-, and S-containing azoles employing CuI in a catalytic quantity. This methodology involves two different approaches. In the first approach an oxidative desulfurization of thioureas by Cu catalyst gives intermediate carbodiimide which is followed by intermolecular attack by an azide or hydrazide nucelophile to give 5-aminotetrazoles or 3-amino[1,2,4]triazoles, respectively. Regioselective formation of tetrazoles and triazoles was observed in the case of unsymmetrical thioureas. This phenomenon is dependent on the pK_a values of the nitrogen atoms attached to the precursor thioureas. In the second approach oxidative desulfurization of thiosemicarbazides or bis-thioureas afforded the respective carbodiimidic intermediates, which upon intramolecular attack by an amidic O or a thioamidic S atoms gave 2-amino[1,3,4]oxadiazoles or 2,5-diamino-[1,3,4]thiadiazoles. The fate of the copper catalyst at the end of reaction has also been studied using SEM and EDS analysis. On a practical note, the use of a cheap copper salt in a catalytic amount replacing the toxic and expensive metal salts of Hg, Pb and Ag used in a stoichiometric quantity to give easy access of such important heterocycles make this methodology a suitable alternative for industrial applications and perhaps the best metal-based catalytic approach reported so far.

Experimental Section

General Procedure for the Synthesis of *N*,1-Diphenyl-1*H*-tetrazol-5-amine (2a)

A mixture of aniline (93 mg, 1 mmol) and phenyl isothiocyanate (135 mg, 1 mmol) in anhydrous DMSO solvent (2 mL) was stirred at preheated oil bath at 80 °C under a nitrogen balloon for 10 min. After complete formation of diphenylthiourea (**1a**) to the reaction mixture were sequentially added CuI (19 mg, 0.1 mmol), Cs_2CO_3 (650 mg, 2 mmol) and NaN_3 (195 mg, 3 mmol). The heating was continued and the progress of the reaction was monitored by TLC. After 5 h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). Then the reaction mixture was filtered through a bed of celite and washed with an additional amount of ethyl acetate (20 mL). The filtrate was washed with water (3×5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified over a column of silica gel and eluted with (7:3, hexane/ethyl acetate) to give *N*,1-diphenyl-1*H*-tetrazol-5-amine (**2a**); yield: 199 mg (84%).

General Procedure for the Synthesis of *N*,4-Diphenyl-4*H*-1,2,4-triazol-3-amine (3a)

A mixture of aniline (93 mg, 1 mmol) and phenyl isothiocyanate (135 mg, 1 mmol) in anhydrous DMSO solvent (2 mL) was stirred at preheated oil bath at 80 °C under a nitrogen balloon for 10 min. After complete formation of diphenylthiourea (**1a**) to the reaction mixture were sequentially added CuI (19 mg, 0.1 mmol), Cs_2CO_3 (650 mg, 2 mmol) and NH_2NHCHO (150 mg, 2.5 mmol). The heating was continued and the progress of the reaction was monitored by TLC. After 4 h, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). Then the reaction mixture was filtered through a bed of celite and washed with an additional amount of ethyl acetate (20 mL). The filtrate was washed with water (3×5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified over a column of silica gel and eluted with (3:7, hexane/ethyl acetate) to give *N*,4-diphenyl-4*H*-1,2,4-triazol-3-amine (**3a**); yield: 212 mg (90%).

General Procedure for the Synthesis of *N*-Phenyl-1,3,4-oxadiazol-2-amine (5a)

To phenyl isothiocyanate (135 mg, 1 mmol) was added formichydrazide (NH_2NHCHO) (60 mg, 1 mmol) in DMSO solvent (2 mL) and stirred at preheated oil bath at 80 °C for 10 min to afford the thiosemicarbazide (**4a**). Subsequently, CuI (19 mg, 0.1 mmol) and K_2CO_3 (276 mg, 2 mmol) were added to the reaction mixture and heating was continued for 4 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). Then the reaction mixture was filtered through a bed of celite and washed with an additional amount of ethyl acetate (20 mL). The filtrate was washed with water (3×5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified over a column of silica gel and eluted with (8:2, hexane/ethyl acetate) to give *N*-phenyl-1,3,4-oxadiazol-2-amine (**5a**); yield: 145 mg (90%).

General Procedure for the Synthesis of N^2,N^5-Diphenyl-1,3,4-thiadiazole-2,5-diamine (7a)

Phenyl isothiocyanate (270 mg, 2 mmol) upon treatment with hydrazine hydrate (50 mg, 1 mmol) under neat conditions gave bis-thiourea (**6a**). Subsequently CuI (19 mg, 0.1 mmol), K_2CO_3 (276 mg, 2 mmol) and DMSO solvent (2 mL) were added to the bis-thiourea (**6a**) and the reaction mixture was subjected to heating in a preheated oil bath at 80 °C for 6 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (10 mL). Then the reaction mixture was filtered through a bed of celite and washed with an additional amount of ethyl acetate (20 mL). The filtrate was washed with water (3×5 mL). The ethyl acetate layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was purified over a column of silica gel and eluted with (1:1, hexane/ethyl acetate) to give N^2,N^5-diphenyl-1,3,4-thiadiazole-2,5-diamine (**7a**); yield: 220 mg (82%).

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[44] CCDC 876571 (**2f**), CCDC 876572 (**3e**), CCDC 876573 (**5i**) and CCDC 787035 (**7f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. See also the Supporting Information.

