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PAPER

Tandem regioselective synthesis of tetrazoles and related heterocycles using iodine†

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A one-pot, tandem process has been developed for the synthesis of a library of tetrazoles from aryl isothiocyanates. Condensation of aryl isothiocyanates with ammonia, and aryl amines (R-NH_2) provided mono, 1,3-disubstituted symmetrical and unsymmetrical thioureas, which on desulfurization with molecular iodine (I_2) led to formation of the corresponding heterocumulene (cyanamides or carbodiimides). The *in situ* generated heterocumulene on subsequent treatment with sodium azide at room temperature gave corresponding tetrazoles. The product regioselectivity for unsymmetrical 1,3-disubstituted thioureas was found to be correlated with the basicities (pK_a's) of the parent amines attached to the thiourea. Aryl-*sec*-alkyl unsymmetrical thioureas gave thioamido guanidino products rather than the 5-aminotetrazoles produced by $HgCl_2$ mediation of the reaction. *Bis*-thioureas derived from aryl isothiocyanates and hydrazine gave thiadiazoles exclusively.

Introduction

In combinatorial chemistry, tandem reactions have gained vital role in the construction of small molecule libraries. Usually, they involve multiple chemical transformations in one synthetic approach, and the advantage is that the intermediate need not be stable enough to be isolated. Tandem reactions also provide powerful methods to construct structurally complex molecules containing biologically and pharmacologically important C–N bonds from a relatively simple starting materials in a convergent approach.[1]

Aminotetrazoles are an interesting class of heterocyclic compounds that have not been found in the nature so far. They are resistant to metabolic degradation as well as towards chemical oxidants,[2] and have found application in propellents,[3a] explosives[3b] and as structural components of many biologically important molecules.[4] For a drug to be effective, it should be sufficiently lipophilic in nature so as to pass through the cell membrane effectively. Hansch has shown that anionic tetrazoles are at least ten times more lipophilic than the corresponding carboxylates.[5] Due to the tunable lipophilicity of various tetrazole derivatives; it is possible to use them as "isosteric substituents" of various functional groups. 5-Substituted (alkyl/aryl) tetrazoles (RCN_4H) in particular, may serve as "non-classical isosteres" for the carboxylic acid moiety (RCO_2H) in biologically active molecules.[6,7] Additionally, aminotetrazoles are found in compounds having anti-allergic/anti-asthmatic,[8] antiviral,[9] anti-inflammatory,[9] antineoplastic,[10] and cognition disorder activities.[11]

Few examples of aminotetrazoles having pharmacological,[12] antiviral,[13] and receptor modulator[14] activities are shown in Fig. 1. They are also used in high energy density materials (HEDM)[15] as ligands in coordination chemistry[16] and in the preparation of imidoylazides.[17]

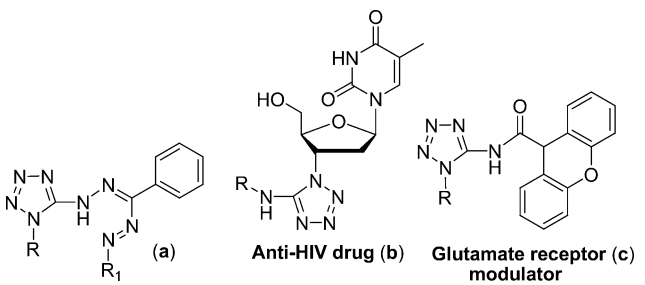

Fig. 1 Some of the biologically important aminotetrazoles.

As shown in Scheme 1, many of these reported methods require harsh reaction conditions, high temperature, and the use of toxic reagents or metal salts. We regard the development of new methods for aminotetrazole synthesis having qualities of reagent economy, metal free conditions, and tandem or one-pot operation as being highly desirable.

In recent years, molecular iodine (I_2) has emerged as a useful catalyst for various organic transformations because of its inexpensive, non-toxic, readily available and eco-friendly nature.[25] It has high tolerance to air and moisture that can be removed from the reaction systems easily, and so has also been explored as a useful reagent in organic synthesis.[26] Our interest in the thiophilic properties of hypervalent iodine reagents[27] made us

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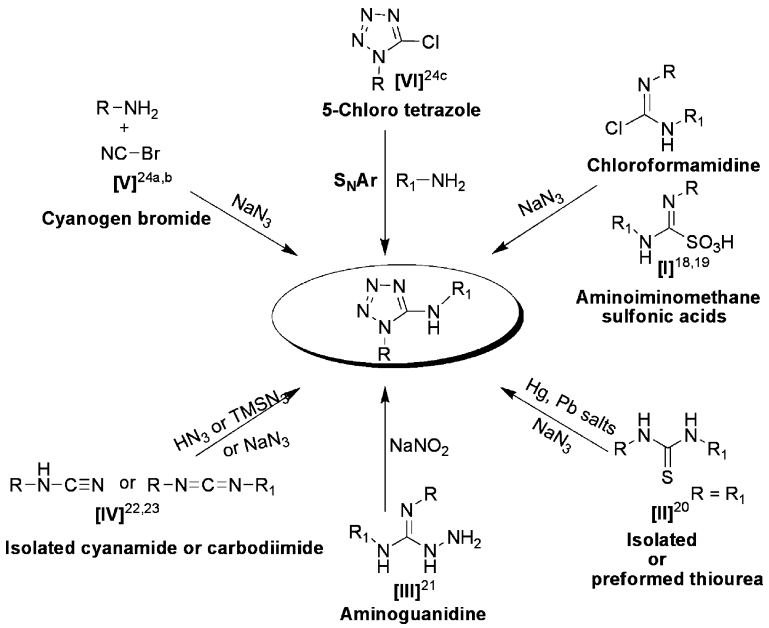


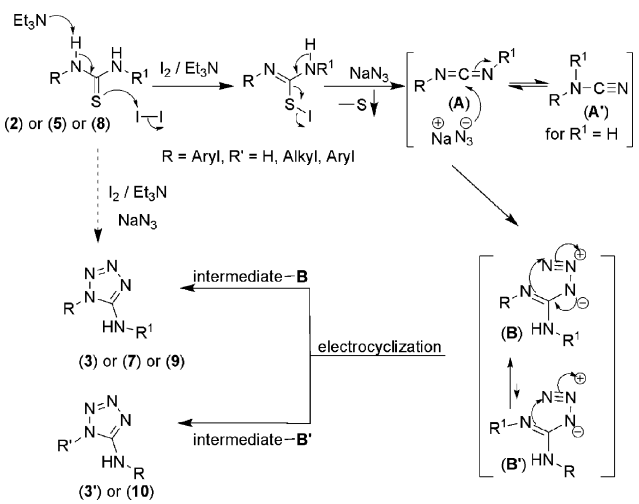
Scheme 1 Available literature methods (I–VI) for the preparation of aminotetrazoles.[18–24]

envisage the development of an efficient three step tandem process to construct the aminotetrazoles utilizing isothiocyanates. The synthetic sequence for the proposed one-pot tandem process can be accomplished by treating the organic isothiocyanates with amines (ammonia, aryl or alkyl amine) to form the corresponding thiourea. The *in situ* generated thiourea gives cyanamides/carbodiimides in the medium when reacted with molecular iodine in the presence of a base. Subsequent treatment of the cyanamides/carbodiimides with sodium azide generates the tetrazole.

Results and discussion

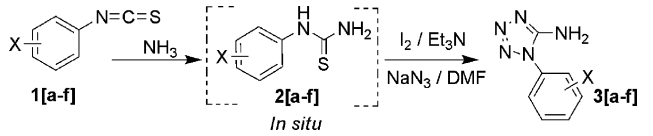
The development of the three step tandem process was carried out using freshly prepared phenyl isothiocyanate (**1a**)[26h,27b] (1 equiv) to which was added aqueous ammonia (25%, 1 mL) in an ice-cold condition and the mixture was stirred for 20 min to give 1-phenylthiourea (**2a**). The excess ammonia was removed in a rotary evaporator to prevent the formation of nitrogen triiodide NI_3.[29] Subsequently, DMSO (2 mL) was admixed to the 1-phenylthiourea (**2a**), and to which was added sequentially, NaN_3 (2 equiv), I_2 (1 equiv) followed by a drop wise addition of triethylamine (2 equiv) at room temperature. During this time the reaction was exothermic. After complete addition of triethylamine the reaction mixture was stirred for 14 h to convert the *in situ* generated 1-phenylthiourea (**2a**) to 1-phenyl-1*H*-tetrazole-5-amine (**3a**) in moderate yield (55%). Other organic solvents such as chloroform, tetrahydrofuran, toluene, acetonitrile, dioxane, ethanol *etc.* were not effective in converting the cyanamide into the corresponding tetrazole (**3a**) even at higher temperature as sodium azide remains insoluble in these solvents. Additionally, the optimization of the reaction conditions *e.g.* increase in the quantity of I_2 from 1 to 1.1 equiv, Et_3N from 2 to 3 equiv and switching the solvent from DMSO to DMF reduced the time to 4 h and improved the yield (75%) at room temperature. Therefore, we continued to use our optimized reaction condition [arylthiourea (1 equiv.), Et_3N (3 equiv.), iodine (1.1 equiv.), DMF (2 mL)] for the synthesis of various mono substituted tetrazoles.

A plausible reaction mechanism for this transformation has been proposed as shown in Scheme 2. The intermediate cyanamide (**A**) or (**A′**) obtained from thiourea (**2**) (where R^1 = H), has been confirmed by its isolation and characterization. The precipitation of elemental sulfur further supports our proposed mechanism. The intermediate cyanamide (**A**) is attacked by the azide ion giving the intermediate guanyl azide (**B**) which then undergoes electrocyclization giving 1-aryl-1*H*-tetrazole-5-amine (**3**). In the case of unsymmetrical thiourea an unsymmetrical guanyl azide **B** or **B′** intermediate shall be generated. However protonation or flow of the electron shall be on the nitrogen having more basicity (higher pK_a's). This observation is consistent with our earlier reports on regioselective reactions in unsymmetrical thioureas.[27a,28a–c]



Scheme 2 Plausible mechanism for formation of 5-aminotetrazole **3**.

Table 1 Formation of 1-aryl-1*H*-tetrazole-5-amines from aryl isothiocyanates[a,b]



Isothiocyanate	Thiourea	Time/h	Product[c]	Yields (%)[d]
X = H (**1a**)	(**2a**)	4.0	(**3a**)	75
X = *o*-Cl (**1b**)	(**2b**)	2.5	(**3b**)	88
X = *m*-Cl (**1c**)	(**2c**)	3	(**3c**)	79
X = *m*-NO_2 (**1d**)	(**2d**)	2.6	(**3d**)	86
X = *p*-Br (**1e**)	(**2e**)	3.5	(**3e**)	85
X = *p*-CH_3 (**1f**)	(**2f**)	5	(**3f**)	73

[a] Reactions were carried out at room temperature in DMF. [b] Reactions were monitored by TLC at an interval of 10 min. [c] Confirmed by IR, ^{1}H and ^{13}C NMR. [d] Isolated yield.

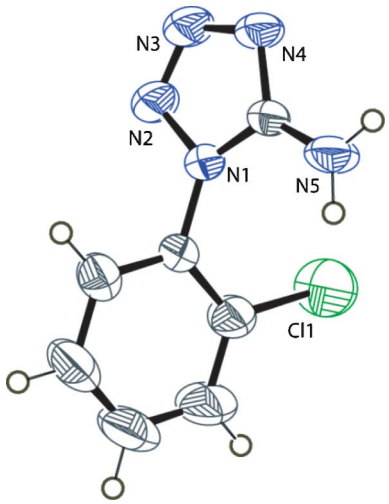


Fig. 2 ORTEP view with the atomic numbering scheme of **3b**.[30]

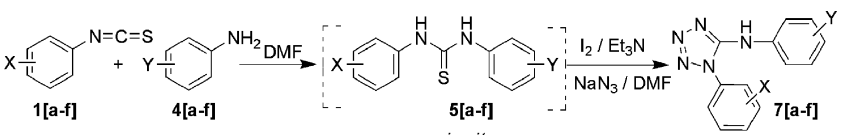
Employing this one-pot strategy, we have successfully prepared a series of 1-aryl-1*H*-tetrazole-5-amine (**3**) from their corresponding isothiocyanates (**1**) as shown in Table 1. Aryl isothiocyanates containing weakly deactivating groups (Cl and Br) (**1b**), (**1c**) and (**1e**) in their *ortho*, *meta* or *para* positions reacted efficiently to afford the corresponding tetrazoles (**3b**), (**3c**) and (**3e**) in good yields. Strongly deactivating group (-NO_2) (**1d**) when present in the *m*-position yielded the corresponding tetrazole (**3d**) in good yield. Further, the structure of (**3b**) has been confirmed by X-ray crystallographic analysis as shown in Fig. 2.[30]

Aryl isothiocyanate substituted with a weakly activating group (*p*-CH_3) (**1f**) also resulted in the corresponding tetrazole (**3f**) in good yield, though it required longer reaction time compared to the substrates possessing electron withdrawing groups (**1b–e**) (Table 1).

It may be mentioned here that formation of both the isomeric products *i.e.* 1-aryl-5-amino-1*H* tetrazole (**3**) and 5-arylamino-1*H*-tetrazole (**3′**) (where R = Aryl, R′ = H) from thiourea (**2**) have been observed using hydrazoic acid and aryl cyanamide under a thermal condition which is because of the thermal isomerization of the intermediates (**B**) and (**B′**) as shown in Scheme 2.[20c,d] Recently, exclusive formation of one of the isomer has been achieved using zeolite[22b] or $ZnCl_2$[22c] catalyst at an elevated temperature. This of course is dependent on the nature of the substituents attached to the aryl cyanamides. For substrates having electron donating substituents, the formation of 1-aryl-5-amino-1*H*-tetrazole (**3**) is favourable which goes *via* guanyl azide intermediate (**B**). As the electronegativity of the substituent increases, the product is shifted towards the 5-arylamino-1*H*-tetrazole (**3′**) which goes *via* guanyl azide intermediate (**B′**). Very recently, Katritzky *et al.* have investigated the tautomeric behavior of *N*-(α-aminoalkyl) tetrazoles using NMR spectroscopy.[31] Under the present experimental condition which is carried out at room temperature irrespective of the nature of the substituents present (**1a–1f**) in the aryl cyanamide, exclusive formation of the 1-aryl-5-amino-1*H* tetrazole (**3a–3f**) was observed (Table 1).

1,5-Disubstituted tetrazoles (**7a–7f**) were obtained by the reaction of aryl isothiocyanates (**1a–1f**) and aryl amines (**4a–4f**) by a similar mechanism as shown in Scheme 2. Symmetrical thioureas containing moderately electron-withdrawing substituents such as *o*-Cl, *m*-Cl, or *p*-Br and strongly electron-withdrawing substituent *m*-NO_2, all gave their corresponding tetrazoles (**7b–7e**) as shown in Table 2 in good to excellent yields. The structure of one of the products (**7b**) has been confirmed by X-ray crystallography as shown in Fig. 3.[32] This methodology was found to be equally

Table 2 Formation of aryl-(1-aryl-1*H*-tetrazol-5-yl)-amine from the *in situ* generated 1,3-diarylthiourea[a,b]



Isothiocyanate	Amine	Thiourea	Time/h	Product[c]	Yields (%)[d]
X = H (**1a**)	Y = H (**4a**)	(**5a**)	4.5	(**7a**)	75
X = *o*-Cl (**1b**)	Y = *o*-Cl (**4b**)	(**5b**)	2.6	(**7b**)	85
X = *m*-Cl (**1c**)	Y = *m*-Cl (**4c**)	(**5c**)	3	(**7c**)	80
X = *m*-NO_2 (**1d**)	Y = *m*-NO_2 (**4d**)	(**5d**)	2.8	(**7d**)	81
X = *p*-Br (**1e**)	Y = *p*-Br (**4e**)	(**5e**)	3.6	(**7e**)	78
X = *p*-CH_3 (**1f**)	Y = *p*-CH_3 (**4f**)	(**5f**)	8	(**7f**)	74

[a] Reactions carried out at room temperature in DMF solvent. [b] Reactions were monitored by TLC at an interval of 10 min. [c] Confirmed by IR and ^{1}H and ^{13}C NMR. [d] Isolated yield.

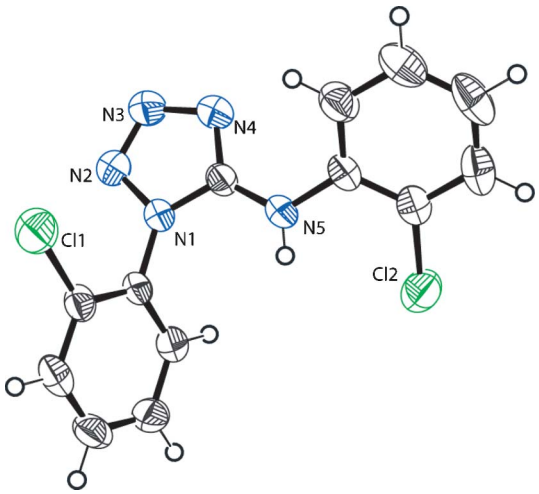


Fig. 3 ORTEP view with the atomic numbering scheme of **7b**.[32]

efficient with moderately electron-donating substituent *p*-Me attached to symmetrical thiourea (**7f**) obtained from isothiocyanate (**1f**) and amine (**4f**).

A noteworthy aspect is that the parent amines attached to the *in situ* generated thioureas Table 1 (**2a–e**) and Table 2 (**5a–e**) having lower pK_a's resulted in the formation of the intermediate cyanamide or carbodiimide faster because of the facile N–H deprotonation (Scheme 2) compared to the amine having higher pK_a's. Once the intermediate cyanamide/carbodiimide is built up, the attack by the azide ion is possibly the rate determining step. The effect of electron withdrawing groups facilitates this and hence faster formation of tetrazoles (**3a–3e**) and (**7a–7e**). The pK_a of *o*-Cl, *m*-NO_2, *m*-Cl, *p*-Br, *p*-Me anilines and aniline are 2.65, 2.46, 3.46, 3.86, 5.08 and 4.63 respectively, which is clearly reflected in their reactivity order as can be seen from Table 1 and Table 2 leading to the formation of heterocycles (**3a–3e**) and (**7a–7e**).

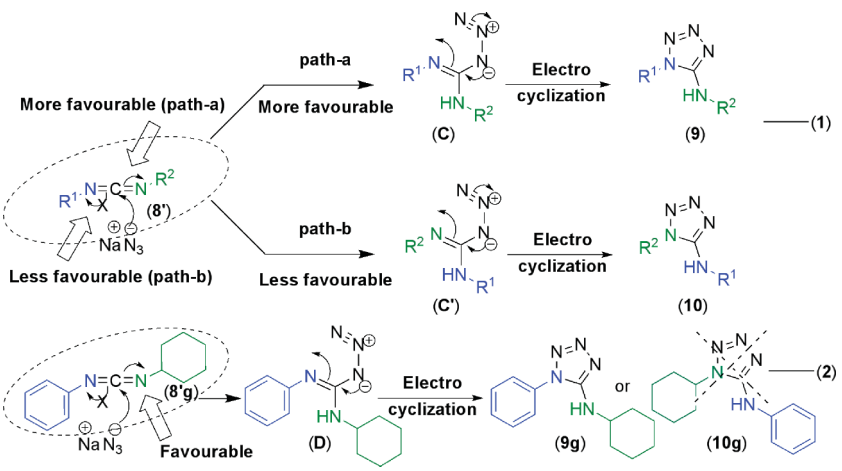
So far there are no literature reports on the regioselectivity in the formation of 1,5-disubstituted tetrazole from 1,3-disubstituted unsymmetrical thioureas (**8**). We were interested to investigate the regioselectivity of tetrazole formation from unsymmetrical thioureas (**8**) *i.e.* whether the amine having lower pK_a would be attached to the ring nitrogen or contribute to the exocyclic amino group giving product of the type (**9**) or a reverse orientation giving product (**10**) as shown in Scheme 3, eq 1.

Recently, we have found a good correlation between the regioselective *N*-acylation and the pK_a's of the precursor amines attached to the thioureas.[27a] A similar observation was also noticed during the synthesis of thiazole-2-imine [or 2-iminothiazoline],[28a] 2-imino-4-thiazolidinone,[28b] and in the synthesis of thioamido guanidines.[28c] The larger the difference in pK_a's between the precursor amines in 1,3-disubstituted thioureas, the higher is the regioselective *N*-acylation with preferential acylation taking place towards the amine having lower pK_a.[27a] Similarly, during the formation of 2-imino-4-thiazolidinone, the amine having lower pK_a is part of the heterocyclic nitrogen and amine having higher pK_a contributes the imino nitrogen.[28b] Again, during the formation of thioamido guanidino moiety resulted from aryl-*sec*-alkyl thiourea with bromine or its equivalent, amine having the lower pK_a as part of the imino nitrogen, and amino having the higher pK_a contributed to the thioamidic nitrogen.[28c] We wanted to see whether this is applicable for the synthesis of 1,5-disubstituted tetrazoles as well.

After the formation of an unsymmetrical carbodiimide (**8′**) (Scheme 3, eq 1), the attack of an azide group to an unsymmetrical carbodiimide would led to the flow of electron (protonation) towards the amine having more basic nature (higher pK_a) hence path-a is more favourable (Scheme 3, eq 1), without affecting the imine group on the other side. The resultant guanidyl intermediate (**C**), Scheme 3, eq 1 undergoes electrocyclization giving product of the type (**9**) where the amine having lower pK_a goes to the ring nitrogen and the other amine having higher pK_a is part of the exocyclic nitrogen.

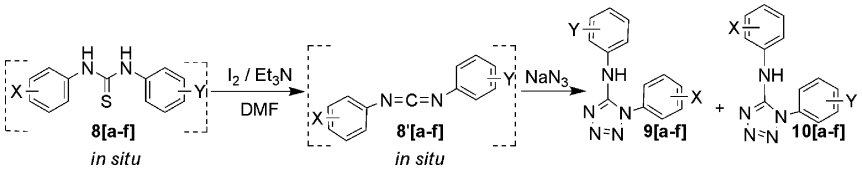
The flow of electron (protonation) towards the amine having less basic nature (lower pK_a) (path-b) is less favourable (Scheme 3, eq 1) and hence unlikely to generate the intermediate (**C′**) leading to the product type (**10**). This is illustrated using phenylcyclohexyl carbodiimide (**8′g**) as a typical example as shown in Scheme 3, eq 2. The measured pK_a of cyclohexyl amine and aniline are 10.66 and 4.63 respectively and hence product (**9g**) is expected to form exclusively as shown in Scheme 3, eq 2 and it is indeed the case.

As can be seen from Table 3, an unsymmetrical thiourea (**8a**) containing an aniline and a *p*-methylaniline group attached to



Scheme 3 Regioselective product of unsymmetrical thiourea (**8**).

Table 3 Regioselective formation of aryl-(1-aryl-*1H*-tetrazol-5-yl)-amine from unsymmetrical 1,3-diarylthiourea[a,b]



Thiourea	Carbodiimide	Time/h	Product(s)[c]	Yields (%)[d,e]
X = H, Y = *p*-CH_3 (**8a**)	(**8′a**)	6	(**9a**):(**10a**)	75 (77 : 23)
X = H, Y = *o*-OCH_3 (**8b**)	(**8′b**)	3	(**9b**):(**10b**)	84 (84 : 16)
X = *p*-Br, Y = *p*-OCH_3 (**8c**)	(**8′c**)	3	(**9c**):(**10c**)	77 (57 : 43)
X = *p*-Br, Y = H (**8d**)	(**8′d**)	6	(**9d**):(**10d**)	80 (59 : 41)
X = *m*-NO_2, Y = *p*CH_3 (**8e**)	(**8′e**)	6	(**9e**):(**10e**)	72 (61 : 39)
X = *o*-Cl, Y = H (**8f**)	(**8′f**)	3	(**9f**):(**10f**)	88 (100 : 00)
X = H, Ar–Y = cyclohexyl (**8g**)	(**8′g**)	12	(**9g**):(**10g**)	35 (100 : 00)

[a] Reactions carried out at room temperature in DMF solvent. [b] Reactions were monitored by TLC. [c] Confirmed by IR and ^{1}H and ^{13}C NMR. [d] Isolated yield. [e] Ratio of regioisomers determined by ^{1}H NMR.

the thiourea gave the corresponding unsymmetrical carbodiimide (**8′a**) *in situ*, which when reacted with sodium azide furnish a mixture of tetrazoles (**9a**) and (**10a**) in the ratio of 77 : 23. The measured pK_a of aniline and *p*-methylaniline are 4.63 and 5.08 respectively. Thus, as per the mechanism proposed, Scheme 3, eq 1, in the major product, the amine having lower pK_a (aniline) is a part of the heterocyclic nitrogen and the other amine (*p*-methylaniline) attached to the thiourea having a higher pK_a is part of the other exocyclic nitrogen in tetrazoles skeleton (**9**) and (**10**). This assumption is again demonstrated for another unsymmetrical thiourea (**8b**) having aniline and *o*-methoxyaniline. Earlier we have demonstrated that larger the difference between the pK_a's of the amines attached to the thiourea, greater is the regioselectivity.[27a,28a,b] In this case, the pK_a difference between the two amines, *o*-methoxyaniline (5.45) and aniline (4.63) is 0.82, hence, expected to give better selectivity. The ratio of the product (**9b**) and (**10b**) formed was (84 : 16) which can be explained based on the measured pK_a's of the parent amines. The X-ray crystallographic analysis of the major product (**9b**) as shown in Fig. 4 [33] clearly revealed the disposition of the phenyl group as part of the ring nitrogen and the *o*-methoxy phenyl group attached to the exocyclic nitrogen. It may be mentioned here that the regioisomeric mixture (**9a**) and (**10a**) could not be resolved in thin layer chromatography (TLC) whereas the regioisomer (**9b**) and (**10b**) are well separated by TLC. One of the regioisomer (**9b**) forms intramolecular hydrogen bonding between exocyclic NH and the *o*-methoxy group thereby reducing its polar character. Similar intramolecular hydrogen bonding possibility does not exist in the other isomer (**10b**) as shown in Scheme 4. The single crystal XRD structure of the product (**9b**) shows the intramolecular hydrogen

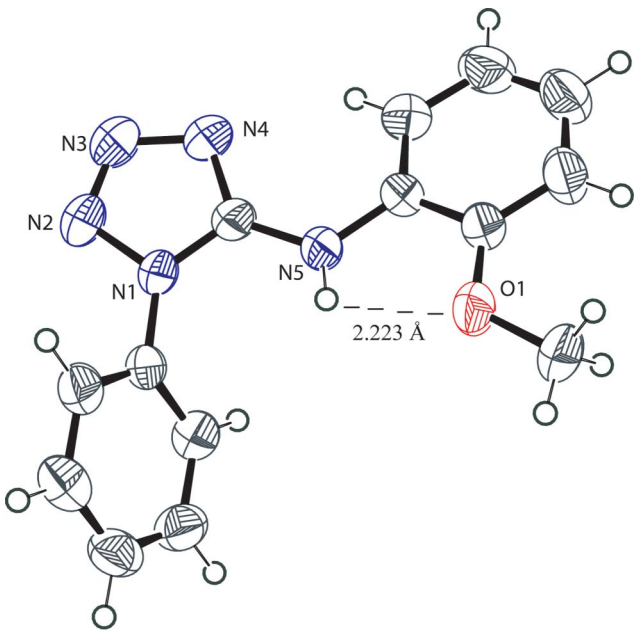
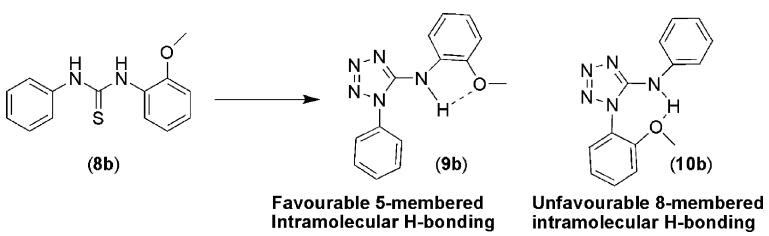


Fig. 4 ORTEP view with the atomic numbering scheme of **9b**.[33]

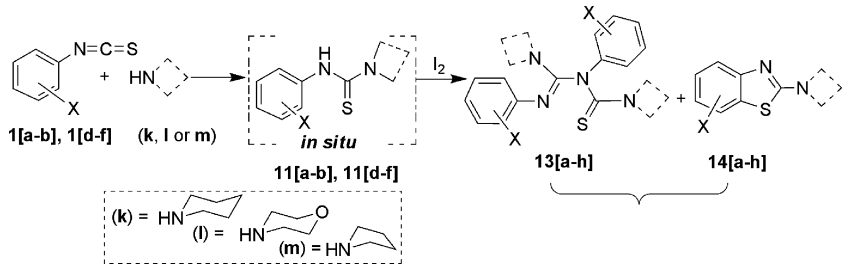
bonding N5H···O with a bond length of 2.223 Å as shown in Fig. 4.

An anomaly to the proposed regioselective mechanism was observed in the case of thiourea (**8c**) where the measured pK_a of *p*-methoxyaniline and *p*-bromoaniline are 5.37 and 3.84 respectively, a difference of 1.53 units, thus expected to give a better regioselectivity compared to the thioureas (**8a**) and (**8b**). However,



Scheme 4 Intramolecular H bonding in regioisomers **9b** and **10b**.

Table 4 Reaction of *in situ* generated aryl-*sec*-alkyl thiourea with iodine[a,b]



Isothiocyanate	*Sec*-amine(s)	Thiourea	Product(s)[c]	Yields (%)[d]
X = H (**1a**)	(k)	(**11a**)	(**13a**) 87	(**14a**) 10
X = H (**1a**)	(I)	(**11b**)	(**13b**) 93	(**14b**) nd[e]
X = *o*-Cl (**1b**)	(I)	(**11c**)	(**13c**) 94	(**14c**) nd[e]
X = *o*-Cl (**1b**)	(m)	(**11d**)	(**13d**) 91	(**14d**) nd[e]
X = *m*-NO_2 (**1d**)	(k)	(**11e**)	(**13e**) 88	(**14e**) nd[e]
X = *p*-Br (**1e**)	(k)	(**11f**)	(**13f**) 86	(**14f**) nd[e]
X = *p*-Br (**1e**)	(I)	(**11g**)	(**13g**) 89	(**14g**) nd[e]
X = *p*-CH_3 (**1f**)	(I)	(**11h**)	(**13h**) 60	(**14h**) 14

[a] Reactions carried out at room temperature in EtOH solvent. [b] Reactions were monitored by TLC. [c] Confirmed by IR and ^{1}H and ^{13}C NMR. [d] Isolated yield. [e] nd = not detected.

the ratio of product (**9c** : **10c**) was found to be 57 : 43, less than expected. This could be due to the possible interconversion of the two intermediates there by loss in the regioselectivity.

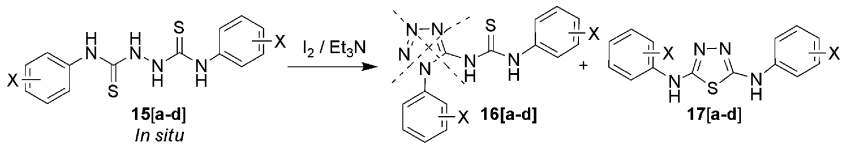
In the case of thiourea (**8d**), the pK_a difference between the two amines, aniline (4.63) and *p*-bromoaniline (3.84) is 0.79. The ratio of the product (**9d**) and (**10d**) formed was 59 : 41 which can be again explained based on the measured pK_a's of the amines. Unlike other regioisomers, the isomers (**9e**) and (**10e**) derived from thiourea (**8e**) could be separated by column chromatography and the regioisomeric product ratios is in agreement with measured pK_a's of the amine. However, when the pK_a difference between the amines attached to the thiourea is sufficiently large (<2 unit), only one of the regioisomer is obtained exclusively. This has been demonstrated with two other unsymmetrical thioureas (**8f**) and (**8g**). In the case of thiourea (**8f**), the pK_a's of the parent amines, aniline and *o*-chloroaniline are respectively 4.63 and 2.65, a difference of 1.98, which gave exclusively one of the regioisomer (**9f**). As discussed above, in the thiourea (**8g**), the pK_a's of the parent amines, aniline and cyclohexylamine are 4.63 and 10.66 respectively, a difference of 6.03, which gave exclusively one regioisomer (**9g**). The yield obtained in the case of thiourea (**8g**) was much less (35%) which is because of the inability of unsymmetrical thiourea (**8g**) to efficiently form corresponding carbodiimide (**8′g**) because of the presence of an aliphatic amine in one side, an observation consistent with our recent report on carbodiimide formation.[26j]

After the successful synthesis of various tetrazoles from mono substituted, symmetrical and unsymmetrical disubstituted thioureas, we were interested to apply this strategy on thioureas generated from isothiocyanates and alkyl *sec*-amines. Previously, Batey *et al.* have successfully synthesized several tetrazoles using mercuric chloride ($HgCl_2$) as the desulfurizing agent.[20a] To scrutinize this, phenyl isothiocyanate (**1a**) (1 equiv) was treated with piperidine (**k**) (1 equiv) to form the corresponding unsymmetrical thiourea under our optimized reaction condition. To this was added NaN_3 (3 equiv), iodine (1.1 equiv) followed by a drop wise addition of triethylamine (3 equiv) over a period of 10 min. After the complete addition of triethylamine, the reaction mixture was allowed to stir for an additional 3 h. TLC showed complete disappearance of the intermediate thiourea and the formation of a new product. Further, ^{1}H NMR, ^{13}C NMR analysis of the product reveals the formation of a thioamido guanidine (**13a**) as the major product (87%) along with 2-aminobenzothiazole (**14a**) (10%) (Table 4). This observation is consistent with our recent report on the formation of thioamido guanidino moiety rather than the expected 2-aminobenzothiazole (Hugerschoff product)[34] when the *in situ* generated thiourea, aryl-*sec*-alkyl thiourea was treated with bromine or its equivalents.[28c]

The difference in the desulfurizing ability of $HgCl_2$ and I_2 is quite evident. In the former, the intermediate imino S-HgCl **11′** (Scheme 5, eq 1) is attacked by an azide ion directly giving guanidyl azide intermediate **E** (Scheme 5, eq 1)[20a] whereas in the later case the imino S–I intermediate is attacked by a second molecule of the thiourea giving a disulfide intermediate **F** (Scheme 5, eq 2) which rearrange to give the thioamido guinidino moiety (**13**) (Scheme 5, eq 2).[28c] However when the aryl ring is sufficiently activated, it would prefer (**G**) an intramolecular electrophilic substitution reaction to give Hugerschoff product *i.e.* aminobenzothiazole (**14**) (Scheme 5, eq 2). It is pertinent to mention here that tetrazole formation is not possible from *N*,*N*-disubstituted thiourea using $HgCl_2$ possibly because of the formation of *bis*-thiomercury(II) complex.[20a,35]

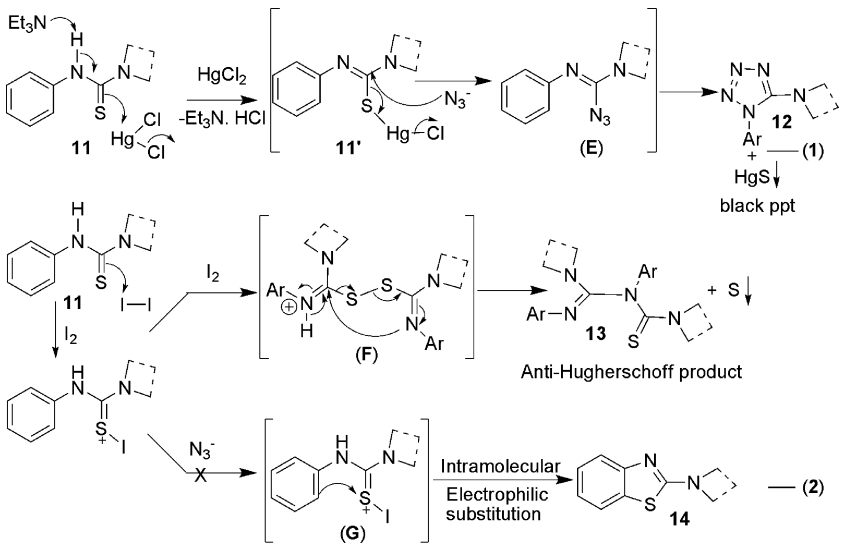
As can be seen from Table 4, a range of aryl isothiocyanates reacted with aliphatic secondary amines such as piperidine (**k**), morpholine (**l**), pyrrolidine (**m**) to give the major product having a thioamido guanidine skeleton in each case. Thiourea (**11b**) obtained by the reaction of phenyl isothiocyanate (**1a**) and morpholine (**l**) gave product (**13b**) in excellent yield. Similarly, weakly deactivating substituents (Cl, Br) when present in the *ortho*-position or *para*-position (**1b**) and (**1e**) reacts with secondary

Table 5 Formation of thiadiazoles from *in situ* generated *bis*-diaryl thiourea[a,b]



Thiourea	Product[c]	Yields (%)[d]
X = H (**15a**)	(**16a**) nd[e]	(**17a**) 81
X = *m*-Cl (**15b**)	(**16b**) nd[e]	(**17b**) 79
X = *p*-Br (**15c**)	(**16c**) nd[e]	(**17c**) 84
X = *p*-CH_3 (**15d**)	(**16d**) nd[e]	(**17d**) 87

[a] Reactions were carried out at room temperature in EtOH. [b] Reactions were monitored by TLC. [c] Confirmed by IR, ^{1}H and ^{13}C NMR. [d] Isolated yield. [e] nd = not detected.



Scheme 5 Differential reactivity of aryl-*sec*-alkyl thiourea.

amines morpholine (**l**), pyrrolidine (**m**) and piperidine (**k**) to give products (**13c**), (**13d**), (**13f**) and (**13g**) in good yields as shown in Table 4. This method also worked equally effective for aryl isothiocyanate bearing a strong electron withdrawing group (-NO_2) (**1d**) in its *meta*-position which on reaction with piperidine **k** followed by the treatment with iodine gave (**13e**) as the only isolated product.

Substrates (**1b**), (**1d**) and (**1e**) are moderately deactivating in nature hence are less susceptible to intramolecular nucleophilic substitution to give Hugerschoff reaction product 2-aminobenzothiazole.[36] Aryl isothiocyanate (**1f**) bearing moderately activating groups (Me) in its *para* position gave no significant amount (14%) of benzothiazole and the dominant product (60%) was still the thioamido guanidine product (**13h**).

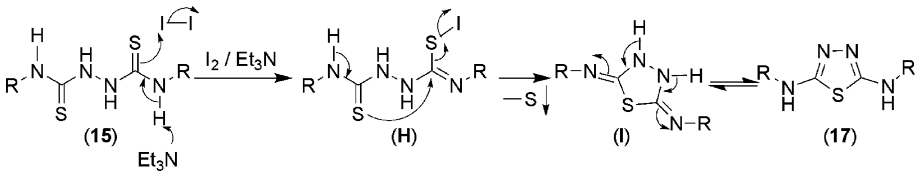
The success of this iodine mediated heterocyclization prompted us to apply this strategy to *bis*-diarylthiourea (**15**), obtained by reacting hydrazine hydrate (1 equiv) with phenyl isothiocyanate (**1a**) (2 equiv), to yield a aryl/alkyl tetrazoylthiourea of the type (**16**) as shown in Table 5. When the resultant *in situ* generated *bis*-diarylthiourea (**15**) was treated with iodine, the desired tetrazole derivative (**16**) was not observed at all; rather thiadiazole (**17**) was the sole isolated product as shown in Table 5.

The proposed mechanism for the formation of thiadiazole (**17**) can be explained as shown in Scheme 6. The initial imino S–I intermediate (**H**) (Scheme 6) obtained by the reaction of *bis*-diarylthiourea (**15**) with iodine undergoes an intermolecular attack by the adjacent soft sulfur atom on the imino carbon rather than the attack by a hard nitrogen nucleophile and not by the weak azido nucleophile thus forming a five membered ring with the expulsion of sulfur. This is consistent with our recent proposed mechanisms[27a,28b,c] and as proposed by others.[37]

Having a successful strategy in hand, we extended the present protocol toward the synthesis of various thiadiazoles as shown in Table 5. Aryl ring having mild electron withdrawing group (**15b**) and (**15c**) as well as weakly activating group (**15d**) all gave the desired products (**17b–17d**) in good yields. The structure of (**17b**) has been further confirmed by X-ray crystallographic analysis as shown in Fig. 5.[38]

Conclusions

In conclusion, we have developed an efficient tandem strategy for the preparation of tetrazoles from the *in situ* generated diverse mono and disubstituted symmetrical and unsymmetrical thiourea starting from the corresponding aryl isothiocyanates. For



Scheme 6 Mechanism for the formation of N^2-N^5 disubstituted thiadiazole.

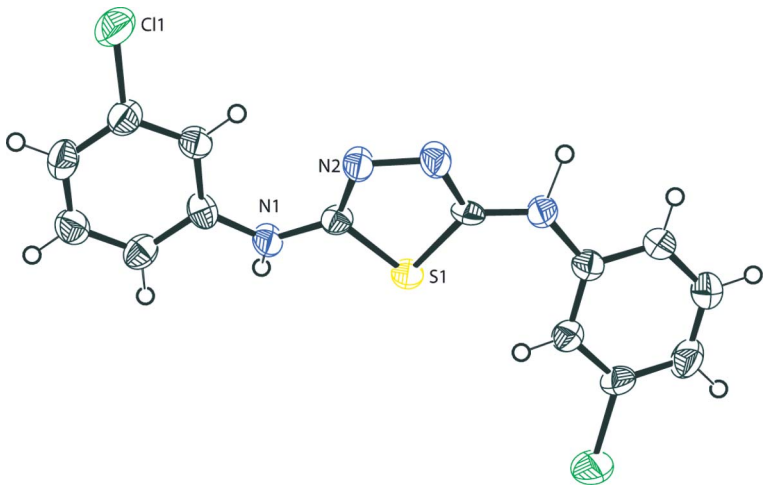


Fig. 5 ORTEP view with the atomic numbering scheme of **17b**.[38]

the first time, regioselective formation of tetrazoles have been studied for unsymmetrical thioureas in which amine attached to the thiourea having lower pK_a is a part of the heterocyclic nitrogen and the amine having higher pK_a is the contributor to the other exocyclic nitrogen. Further, aryl-*sec*-alkyl thiourea under the present experimental condition gave thioamido guanidine and not the expected tetrazole. *Bis*-thiourea resulted from hydrazine and aryl isothiocyanate gave exclusively thiadiazole. Although the overall isolated yields look moderate, considering that the reactions are multiprocesses, the yields are in fact good to excellent. Literature report enumerates a number of procedures for the preparation of aminotetrazoles, however, the simplicity, environmental acceptability and cost effectiveness of this iodine makes this method more practical.

Experimental

General remarks

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Reaction progress was monitored by TLC using Merck silica gel 60 F_{254} (0.25 mm) with detection by UV or iodine. Chromatography was performed using Merck silica gel (60–120) mesh size with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Varian FT-400 MHz instrument using TMS as an internal standard. Data are presented as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, b = broad, br s = broad singlet, br m = broad multiplet, coupling constant *J* (Hz). Elemental analyses were carried out on a Perkin–Elmer 2400 automatic carbon, hydrogen, nitrogen and sulfur analyser. Melting points were recorded on Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded in KBr or neat on a Nicolet Impact 410 spectrophotometer. Mass data were obtained with a WATERS MS system, Q-tof premier and data analyzed using Mass Lynx4.1.

Crystallographic analysis. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite by using graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) at 298 K. Cell parameters were retrieved using SMART [39] software and refined with SAINT[39] for all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentzian and polarization effects. Absorption corrections were applied with the SADABS program.[40] The structures were solved by direct methods implemented in the SHELX-97[41] program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atom positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. The crystals were isolated in rectangular shape from ethyl acetate and hexane mixture at room temperature.

General experimental procedure

General procedure for the preparation of 1-phenyl-1*H*-tetrazol-5-ylamine (3a). Aqueous ammonia (25%, 2 mL) was added to phenyl isothiocyanate **1a** (270 mg, 2 mmol.) in an ice-cold condition and the reaction mixture was stirred for 20 min at room temperature. During this time complete formation of 1-phenyl thiourea **2a** was observed. Excess of ammonia was removed in a rotary evaporator and the reaction mixture was admixed with DMF (2 mL) followed by the sequential addition of NaN_3

(390 mg, 6 mmol.), I_2 (559 mg, 2.2 mmol.) and a drop wise addition of triethylamine (835 μL, 6 mmol.) over a period of 5 min. During the addition of triethylamine the reaction was exothermic. After complete addition of triethylamine, the reaction mixture was stirred for an additional 3 h. Complete conversion of the *in situ* generated 1-phenylthiourea **2a** to 1-phenyl-1*H*-tetrazol-5-ylamine **3a** was observed by thin layer chromatography (TLC). The reaction mixture was treated with a 5% hypo solution (5 mL) and the product was extracted with ethylacetate (3 × 10 mL). The combined ethylacetate layer was washed with water (3 × 5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The product was purified over a column of silica gel (saturated with 1% triethyl amine) and eluted with (8 : 2 hexane/ethylacetate) to give **3a** (242 mg, 75% yield). mp: 168 °C (Lit.[22a] 162–163 °C); ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 6.82 (br s, 2H), 7.50–7.63 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 123.6, 129.4, 129.8, 133.3, 154.2; IR (KBr): 3411, 3321, 3160, 1632, 1597, 1570, 1560, 1504, 1456, 1324, 1128, 1067, 1017, 770, 755 cm^{-1}; Elemental analysis: $C_7H_7N_5$ (161.16): calcd. C, 52.17; H, 4.38; N, 43.45; found: C, 52.11; H, 4.42; N, 43.34.

Spectral data of selected compounds

1-(3-Chloro-phenyl)-1*H*-tetrazol-5-ylamine (3c). mp: 177–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 6.65 (br s, 2H), 7.27–7.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 121.1, 122.9, 128.4, 130.3, 133.8, 134.1, 153.9; IR (KBr): 3355, 3151, 1651, 1593, 1489, 1458, 1422, 1322, 1140, 1102, 1080, 866, 791 cm^{-1}; Elemental analysis: $C_7H_6ClN_5$ (195.60): calcd. C, 42.98; H, 3.09; N, 35.80; found: C, 42.94; H, 3.03; N, 35.91.

1-(3-Nitro-phenyl)-1*H*-tetrazol-5-ylamine (3d). mp: 161–163 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 7.12 (br s, 2H), 7.90 (t, J = 8.0 Hz, 1H), 8.05 (d, J = 8.0 Hz, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 117.9, 122.9, 128.8, 130.4, 133.9, 147.9, 154.2; IR (KBr): 3318, 3142, 3091, 1660, 1596, 1574, 1532, 1497, 1351, 1307, 1139, 1079, 909, 813, 780, 743 cm^{-1}; HRMS (ESI): 207.0630 (MH$^+$).

(3-Chloro-phenyl)-[1-(3-chloro-phenyl)-1*H*-tetrazol-5-yl]-amine (7c). mp: 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.62 (br s, 1H), 7.08 (d, J = 8.0 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.46 (m, 2H), 7.55–7.62 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 116.6, 118.2, 122.1, 123.5, 125.2, 129.8, 130.9, 133.8, 134.7, 140.6, 151.8; IR (KBr): 3445, 2922, 2847, 1615, 1595, 1566, 1473, 1322, 1248, 1122, 1085, 834, 782 cm^{-1}; Elemental analysis: calcd. $C_{13}H_9Cl_2N_5$ (306.15): C, 51.00, H, 2.96, N, 22.88; found: C, 50.94, H, 2.92, N, 23.00.

(3-Nitro-phenyl)-[1-(3-nitro-phenyl)-1*H*-tetrazol-5-yl]-amine (7d). mp: 188–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 7.56 (t, J = 8.0 Hz, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.95 (t, J = 8.4 Hz, 1H), 8.05–8.13 (m, 2H), 8.47 (d, J = 8.0 Hz, 1H), 8.51 (s, 1H), 8.60 (s, 1H), 9.96 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 112.8, 116.6, 120.2, 123.8, 124.1, 129.4, 130.6, 131.0, 133.4, 140.2, 147.9, 148.2, 151.6; IR (KBr): 3444, 3258, 3089, 2925, 2857, 1622, 1574, 1524, 1393, 1353, 1245, 1119, 1081, 880, 803, 739 cm^{-1}; HRMS (ESI): 328.0794 (MH$^+$).

(2-Methoxy-phenyl)-(1-phenyl-1*H*-tetrazol-5-yl)-amine (9b). mp: 128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.82 (s, 3H), 6.88 (d, J = 7.4 Hz, 1H), 7.04 (m, 2H), 7.26 (s, 1H), 7.63 (m, 4H), 8.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 56.1, 110.1, 117.8, 121.7, 123.0, 124.4, 127.9, 130.5, 130.7, 133.2, 147.3, 151.4; IR (KBr): 3399, 3022, 2925, 1609, 1593, 1570, 1507, 1485, 1466, 1455, 1390, 1252, 1240, 1211, 1107, 1092, 1050, 1016, 765, 752 cm^{-1}; Elemental analysis: $C_{14}H_{13}N_5O$ (267.28): calcd. C, 62.91; H, 4.90; N, 26.20; found: C, 62.96; H, 4.96; N, 26.11.

[1-(2-Methoxy-phenyl)-1*H*-tetrazol-5-yl]-phenyl-amine (10b). mp: 178 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 3.87 (s, 3H), 7.02 (d, J = 6.0 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 6.0 Hz, 2H), 7.45 (d, J = 7.6 Hz, 1H), 7.54–7.65 (m, 3H), 8.30 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 55.7, 112.4, 118.1, 120.7, 122.1, 122.8, 128.2, 128.5, 131.7, 139.0, 152.7, 153.8; IR (KBr): 3250, 3200, 3168, 3115, 3088, 3052, 3012, 2971, 2926, 2842, 1614, 1574, 1532, 1499, 1471, 1406, 1384, 1318, 1305, 1280, 1260, 1240, 1185, 1163, 1113, 1087, 1043, 1020, 980, 785, 754 cm^{-1}; Elemental analysis: $C_{14}H_{13}N_5O$ (267.28): calcd. C, 62.91; H, 4.90; N, 26.20; found: C, 62.95; H, 4.94; N, 26.08.

[1-(2-Chloro-phenyl)-1*H*-tetrazol-5-yl]-phenyl-amine (9f). mp: 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 5.93 (br s, 1H), 7.03 (d, J = 6.4 Hz, 1H), 7.30 (s, 2H), 7.53–7.66 (m, 5H), 8.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ (ppm) 118.4, 122.4, 123.9, 124.8, 128.1, 128.5, 129.6, 130.5, 132.0, 139.1, 152.9; IR (KBr): 3241, 3078, 3038, 2997, 2926, 1603, 1614, 1593, 1529, 1489, 1454, 1318, 1245, 1120, 1087, 1077, 1020, 756, 748 cm^{-1}; HRMS (ESI): 272.0703 (MH$^+$).

***N*-((*E*)-Morpholino(phenylimino)methyl)-*N*-phenyl morpholine-4-carbothioamide (13b).** mp: 150 °C (Lit.[28c] 150 °C), ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 2.62–3.80 (m, 16H), 6.81 (brm, 1H), 6.95–7.10 (m, 4H), 7.13 (t, J = 7.6 Hz, 1H), 7.21 (t, J = 7.6 Hz, 2H), 7.28–7.48 (brm, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 46.8, 50.7, 65.5, 66.2, 120.4, 121.4, 122.2, 122.9, 124.8, 128.8, 129.8, 142.8, 149.3, 185.2; IR (KBr): 2979, 2904, 2894, 2856, 1634, 1586, 1485, 1453, 1351, 1301, 1277, 1239, 1206, 1157, 1109, 1062, 1022, 994, 937, 855, 765, 753 cm^{-1}; HRMS (ESI): 411.1854 (MH$^+$).

***N*^{2},*N*^{5}-Bis(3-chlorophenyl)-1,3,4-thiadiazole-2,5-diamine (17b).** mp: 217–219 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 5.20 (br s, 1H), 6.90 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 7.74 (s, 2H), 9.69 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 114.7, 116.2, 120.3, 129.2, 133.5, 141.6, 155.6; IR (KBr): 3280, 3075, 1600, 1567, 1541, 1528, 1478, 1451, 1407, 1079, 773 cm^{-1}; Elemental analysis: $C_{14}H_{10}Cl_2N_4$ (337.23): calcd. C, 49.86; H, 2.99; N, 16.61; S, 9.51; found: C, 49.81; H, 3.03; N, 16.66; S 9.46.

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33 Crystallographic data for **9b**: $C_{14}H_{13}N_5O$, crystal dimension (mm): $0.32 \times 0.24 \times 0.16$, $M_r = 267.29$, monoclinic, space group P21/c, $a = 10.8360(4)$, $b = 16.3772(6)$, $c = 7.6105(3)$ Å; $\alpha = \gamma = 90°$, $\beta = 107.280(2)°$, $V = 1289.63(9)$ Å^3, $Z = 4$, $\rho_{cal} = 1.377$ mg m^{-3}, $\mu = 0.093$ mm^{-1}, $F(000) = 560$, reflection collected/unique = 3221/1965, refinement method = full-matrix least-squares on F^2, final R indices [$I > 2\sigma_I$] $R_1 = 0.0442$, $wR_2 = 0.1203$, R indices (all data) $R_1 = 0.0672$, $wR_2 = 0.1327$, goodness of fit = 0.953. CCDC-787038 (for **9b**) contains 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.

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