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o-Iodoxybenzoic Acid Mediated Oxidative Desulfurization Initiated Domino Reactions for Synthesis of Azoles

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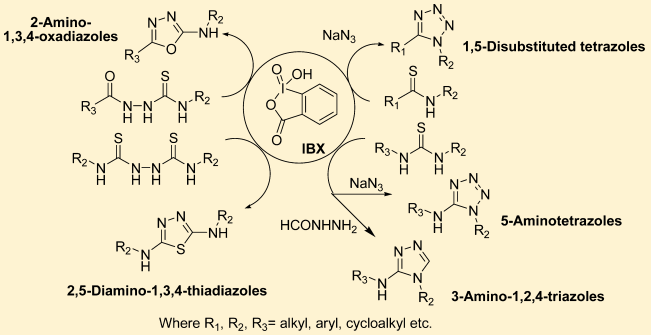
Supporting Information

ABSTRACT: A systematic exploration of thiophilic ability of *o*-iodoxybenzoic acid (IBX) for oxidative desulfurization to trigger domino reactions leading to new methodologies for synthesis of different azoles is described. A variety of highly substituted oxadiazoles, thiadiazoles, triazoles, and tetrazoles have been successfully synthesized in good to excellent yields, starting from readily accessible thiosemicarbazides, *bis*-diarylthiourea, 1,3-disubtituted thiourea, and thioamides.



INTRODUCTION

Azoles are of paramount importance to medicinal chemistry and pharmaceutical industry in numerous ways and find wide applications in agricultural and material research.[1] Despite myriad synthetic methods available in the literature, the advent of new efficient and short routes to access them is of practical significance and is most welcome. In the past two decades, hypervalent organoiodine(V) reagents have emerged as versatile reagents for organic transformations with far reaching synthetic applicability.[2] They find wide applications in the field of medicinal and natural product research due to their mild oxidative property and carbon−carbon and carbon−heteroatom bond-forming ability.[3] According to recent literature, hypervalent iodine reagents have been used for desulfurization purposes,[4] but *o*-iodoxybenzoic acid (IBX)−sulfur chemistry, in particular, is less explored, and few significant transformations reported are deprotection of dithianes.[5] New transformations revealed by our group include oxidation of sulfides to sulfoxides,[6] ring expansion of dihydro-1,4-dithiins and dihydro-1,4-dithiepines to the corresponding 1,3-dithiolanes and 1,3-dithianes,[7] oxidative dimerization of thioamides to 1,2,4-thiadiazoles,[8] and more recently, oxidative desulfurization of 1,3-disubstituted thioureas to carbodiimides.[9] With the knowledge acquired through these investigations on IBX−sulfur interactions and considerable potential of carbodiimide methodology for construction of various nitrogen containing heterocycles, we envisaged and developed a one-pot synthesis of azoles.

RESULTS AND DISCUSSION

We reasoned that intra- and intermolecular trapping of generated carbodiimide by different nucleophiles could lead to construction of azoles. With this reasoning, present work was planned and various methods were developed, as summarized in Scheme 1, and are discussed here case by case.

2-Amino-1,3,4-oxadiazoles 3. It was envisaged that intramolecular oxidative cyclization reactions on to carbodiimide **A**, generated from thiosemicarbazides **2**, could lead to formation of 2-amino-1,3,4-oxadiazoles **3** due to favorable entropy requirement (Scheme 1, Route I). Under similar conditions, *bis*-diarylthioureas **4** could lead to formation of 2,5-diamino-1,3,4-thiadiazoles **5** through intramolecular cyclization reaction via carbodiimide intermediate **B** (Scheme 1, Route II).

2-Amino-1,3,4-oxadiazoles are useful chemical entities and exhibit a broad spectrum of biological activities such as anti-inflammatory,[10a] analgesic,[10a] hypertensive,[10a] diuretic,[10a] anticonvulsant,[10b] muscle relaxant,[10c] antineoplastic,[10d] insecticidal,[10e] and herbicidal activities.[10f] Apart from their latent potential in medicinal and agricultural chemistry, they also find applications in the field of materials science such as photosensitizers, liquid crystals, and electron-transporting layers in organic light emitting diodes (LEDs).[11] Despite wide applications, the development of mild and efficient methods for their synthesis has received less attention. General methods reported in the literature for synthesis of 2-amino-1,3,4-oxadiazoles can be classified into two categories: (i) cyclodehydration of semicarbazides,[12] including use of dehydrating agents such as $POCl_3$, $SOCl_2$, concentrated H_2SO_4, the Burgess reagent, Appel conditions, and phosphonium reagents and (ii) cyclodesulfurization of thiosemicarbazides,[13] by use of I_2/NaOH, tosyl chloride, alkylating agents such as methyl iodide and ethyl bromoacetate, carbodiimides, mercuric salt, and lead oxide. These approaches suffer from one or the other drawbacks such as harsh reaction conditions,

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Scheme 1. IBX-Mediated Domino Reactions and Synthesis of Azoles

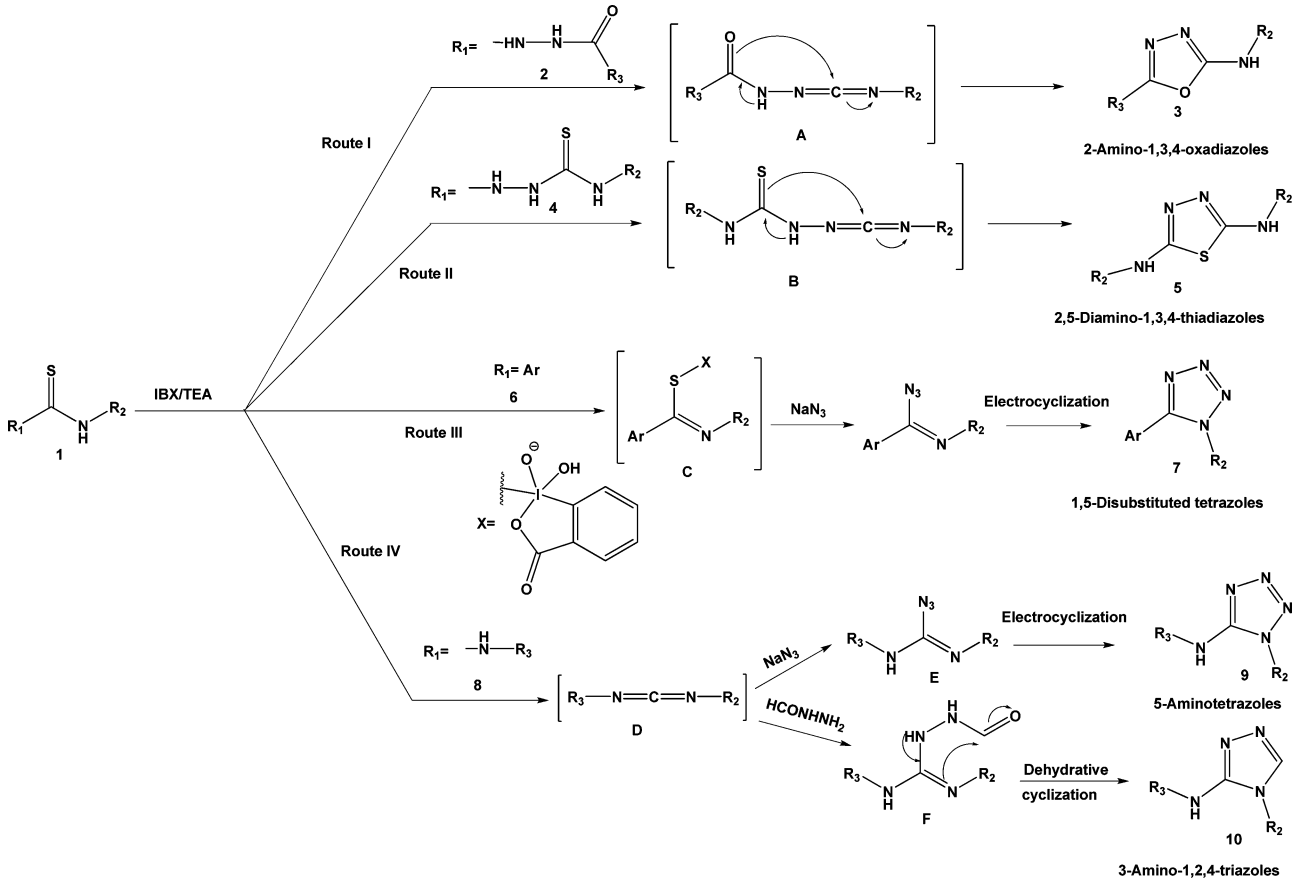
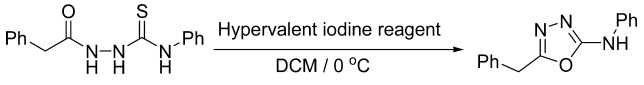


Table 1. Optimization of Reaction Conditions for Preparation of 3d[a]



2d 3d

entry	hypervalent iodine reagent	TEA (equiv)	time (min)	yield[b] (%)
1	DIB	nil	360	78
2	IBX	nil	360	68
3	DMP	nil	360	65
4	DIB	2	10	84
5	**IBX**	**2**	**10**	**96**
6	DMP	2	10	80
7	IBX	1	60	70

[a]Reaction conditions: thiosemicarbazide **2d** (0.5 g, 1.75 mmol), hypervalent iodine reagent (1.75 mmol), and triethylamine in an appropriate amount in DCM (10 mL) were stirred for the mentioned time, and temperature was maintained at 0 °C. [b]Isolated yield.

multiple byproduct formation, and use of corrosive and toxic reagents. The use of a *o*-iodoxybenzoic acid (IBX)/triethylamine (TEA) system addresses many of these problems.

4-Pheny-1-(2-phenylacetyl) thiosemicarbazide **2d** was used as a model substrate, and reaction conditions were optimized with different hypervalent iodine reagents, moles of TEA, time, and results, as summarized in Table 1.

Suitability of other solvents such as DMSO, acetonitrile, ethyl acetate, and THF were investigated, and all were found suitable; however, the reaction was clean in the case of DCM. We tested other hypervalent reagents viz. Dess−Martin periodinane (DMP) and diacetoxyiodobenzene (DIB) with or without combination of triethylamine, and in all cases yield of **3d** was lower compared to that obtained with IBX (Table 1, entries 1, 3, 4, and 6). It should be noted that yield of reaction was significantly reduced with decrease in equivalents of triethylamine employed (Table 1, entries 5 and 7). The overall results reflected the IBX/TEA system to be superior for this transformation.

To explore the scope of the reaction, several 2-amino-1,3,4-oxadiazoles **3** were successfully synthesized in good to excellent yields, and results are given in Table 2. In general, all the reactions were fast and completed in just 10 min, giving comparable yields irrespective of the nature of substituent on the aromatic rings (Table 2, entries **3f−3i**). It is well-known that IBX can oxidize phenol to corresponding quinone (even at

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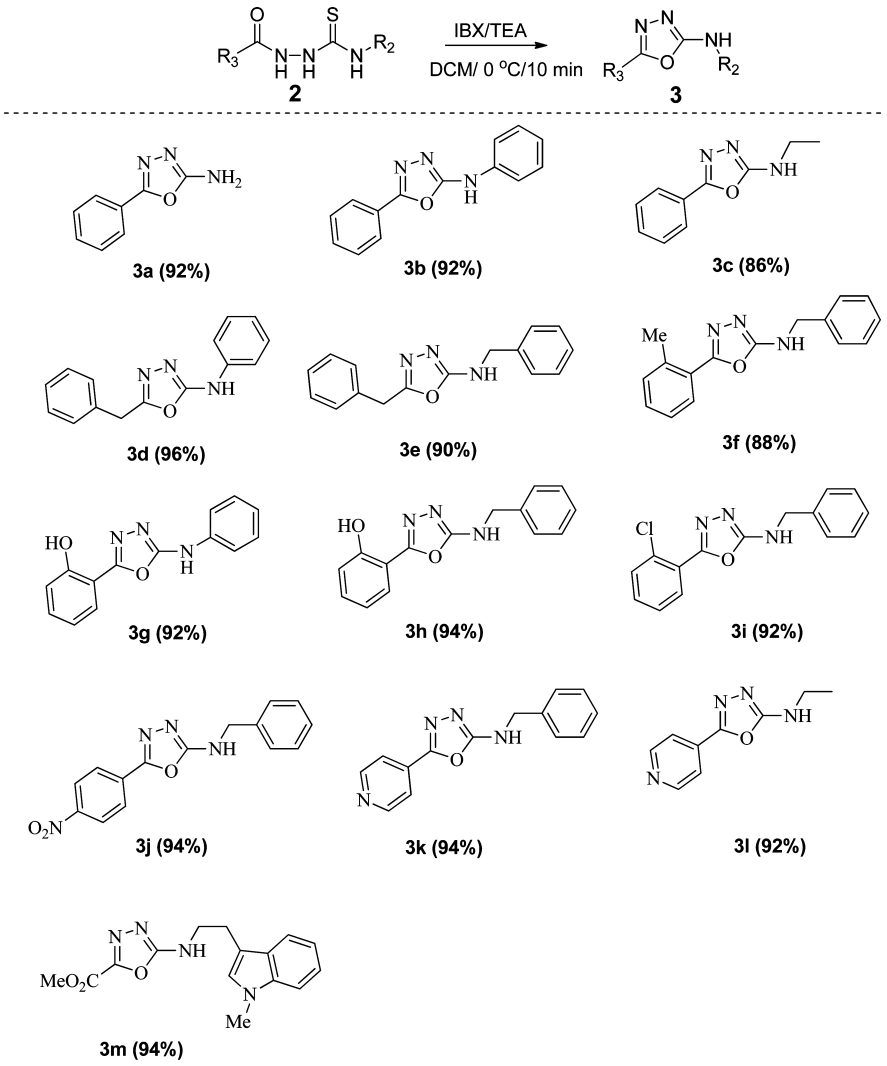
Table 2. Substrate Scope for 2-Amino-1,3,4-oxadiazoles[a] 3



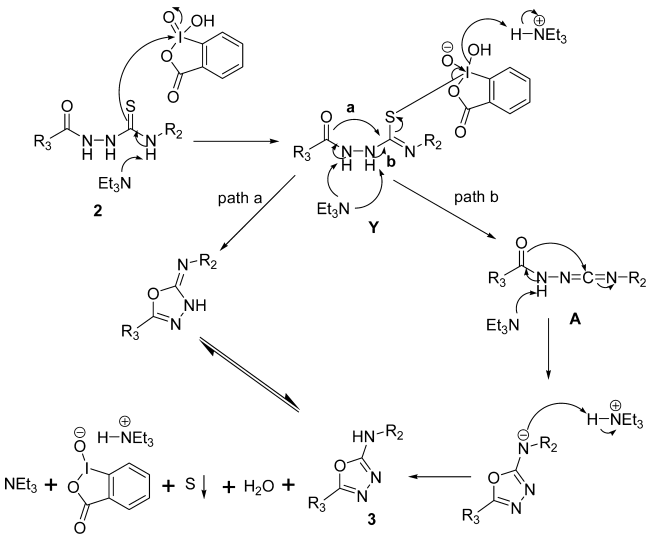
[a]Optimized reaction conditions: thiosemicarbazide (1 equiv), IBX (1 equiv), and TEA (2 equiv) were stirred in DCM for 10 min at 0 °C. Yields are isolated; products were characterized by mp, IR, ^{1}H NMR, and MS (ESI).

0 °C); however, we did not observe any such oxidation product (Table 2, entries **3g** and **3h**) indicating high chemoselectivity. The present method efficiently extended for synthesis of methyl 5-(2-(1-methyl-1*H*-indol-3-yl)ethylamino)-1,3,4-oxadiazole-2-carboxylate (Table 2, entry **3m**), a common intermediate employed as heterodiene by Boger et al. for synthesis of vinca alkaloids.[14]

According to recent literature on desulfurization by hypervalent iodine reagents,[4,9] herein, we would postulate representative reaction mechanism of desulfurization for synthesis of 2-amino-1,3,4-oxadiazoles **3** as shown in Scheme 2.

Initially, intermediate **Y** is formed by nucleophilic attack of sulfur on electrophilic iodine assisted by triethylamine. Then, intermediate **Y** could follow two paths, i.e., path "a", where nucleophilic displacement of sulfur by oxygen leading to cyclization followed by tautomerization giving oxadiazole, or in the case of path "b", formation of carbodiimide intermediate **A** followed by cyclization. The precipitation of elemental sulfur supports the proposed mechanism. The role of TEA, a base, was considered to be dual: to solublize IBX in DCM and facilitate transformations at different steps by activation of hydrazides/thisemicarbazides.

Scheme 2. Representative Postulated Mechanism of Desulfurization for Synthesis of 2-Amino-1,3,4-oxadiazoles and Role of TEA



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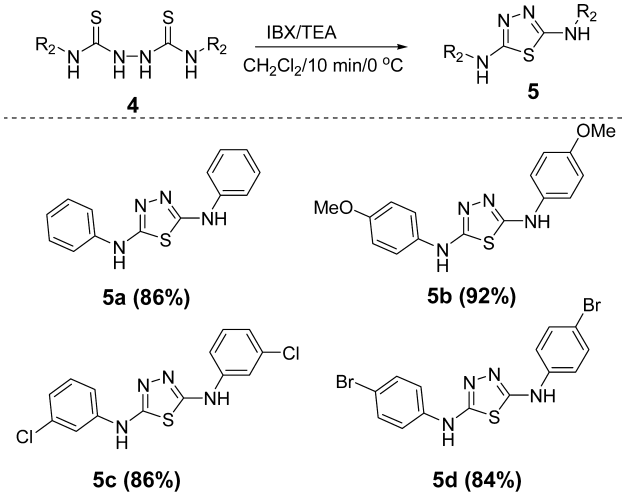
2,5-Diamino-1,3,4-thiadiazoles 5. Drug resistance has become a serious problem in the treatment of infectious diseases caused by bacteria, fungi, and viruses. The search for new antimicrobial agents is one of the most challenging tasks to medicinal chemists. In particular, 1,3,4-thiadiazoles have been widely employed in drug discovery programs because of their versatile biological properties such as antimicrobial, antituberculosis, anti-inflammatory, anticonvulsant, antioxidant, and antifungal properties.[15] Numerous methods are available in the literature[16] for preparation of 1,3,4-thiadiazoles employing different precursors. However, there are only a few methods based on oxidative cyclization of *bis*-diaryl thioureas **4** because formation of number of byproducts is a major concern. Methods based on alkali-catalyzed thermal cyclization of *bis*-diaryl thiourea **4** results in very low yield of 2,5-diamino-1,3,4-thiadiazole **5**, and modification using microwave heating did not show any improvement; instead, the reaction mass was messy, posing difficulty in separation.[17] In the past few years, desulfurizing agents viz. chloranil, bromonil,[18] and very recently iodine[19] are utilized for this transformation; however, good yields have been observed only in the case of iodine-based methods. In our approach, we utilized IBX/TEA system for desulfurization leading to a new method for preparation of 2,5-diamino-1,3,4-thiadiazoles **5** starting from *bis*-diaryl thioureas **4**, and the results are summarized in Table 3.

Table 3. Representative Examples for 2,5-Diamino-1,3,4-thiadiazoles[a] 5

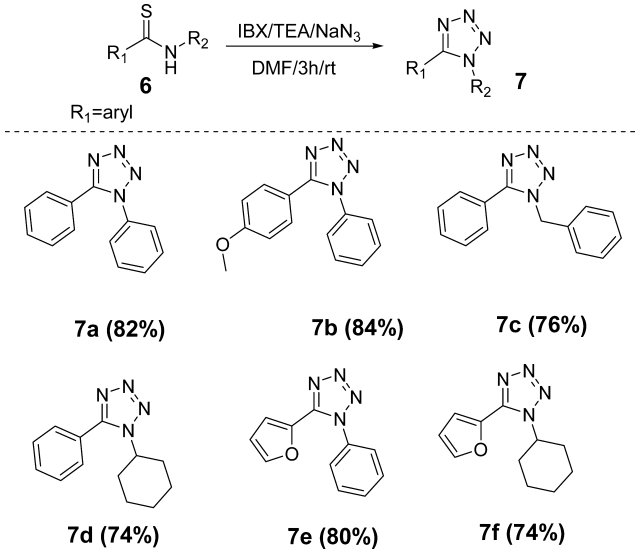


[a]Optimized reaction conditions: *bis*-diarylthiourea **4** (1 equiv), IBX (1 equiv), and TEA (2 equiv) were stirred in DCM for 10 min at 0 °C. Yields are isolated, and products are characterized by mp, IR, ^{1}H NMR, and MS (ESI).

The reactions were carried out under the same conditions employed for synthesis of 2-amino-1,3,4-oxadiazoles **3**. High yield was observed with *bis*-diaryl thiourea containing electron-donating substituent (Table 3, entry **5b**), while yield was somewhat lower observed with electron-withdrawing substituent (Table 3, entry **5d**).

Synthesis of Tetrazoles. *1,5-Disubstituted Tetrazoles 7.* It is quite logical that desulfurization of thioamides **6** with IBX/TEA system would be expected to give 1,5-disubstituted tetrazoles **7** via nucleophilic displacement of IBX activated complex **C** by azide ion and subsequent electrocyclization (Scheme 1, Route III). Tetrazoles are considered as bioisosteres of *cis* amides and carboxylic acids in medicinal chemistry with tunable liphophilicity. This class of compounds has great potential as NAD(P)H oxidase inhibitors,[20] glucokinase activators,[21] hepatitis C virus (HCV) protease S3 inhibitors,[22] calcitonine gene-related peptide receptor antagonist,[23] and synthetic intermediates for bioactive molecules.[24] Synthetic methods for 1,5-disubstituted tetrazoles based on metal catalyzed coupling reactions of 5-chloro-1-phenyltetrazole via Suzuki–Miyaura–Negishi pathway and more recently by direct C–H arylation/alkenylation of 1-substituted tetrazoles show promising results.[25] Other methods include reaction of secondary amides or thioamides with PCl_5/HN_3, $TMSN_3/Ph_3P/DEAD$, and $TMSN_3/Et_3N/Hg(II)$; however, these methods suffer from long reaction times, tedious workup, and use of toxic metals.[26] A good number of methods are known for synthesis of 1,5-disubtituted tetrazoles; however, because of their importance, development of new and efficient synthetic methods remains an attractive area of research. We explored our approach and scope of the reaction with synthesis of aryl and heteroaryl tetrazoles, and results are given in Table 4. High

Table 4. Substrate Scope for 1,5-Disubstituted Tetrazoles[a] 7



[a]Optimized reaction conditions: thiourea (1 equiv) was added to a stirred solution of IBX (1 equiv)/TEA (3 equiv) in DMF for 10 min, and then NaN_3 (3 equiv) was added portionwise, and stirring was continued for 3 h at rt. Yields are isolated; products are characterized by mp, IR, ^{1}H NMR, and MS (ESI).

yields were observed in the case of 1,5-diaryl tetrazoles (Table 4, entries **7a**, **7b**, and **7e**), whereas yields were on the lower side in the case of tetrazoles when one of the substituent R_1 is alkyl (Table 4, entries **7d** and **7f**). A noteworthy feature is the stability of the acid-sensitive furan moiety under the reaction conditions (Table 4, entries **7e** and **7f**).

5-Aminotetrazoles 9. After successful synthesis of 1,5-disubstituted tetrazoles, we premised that intermolecular trapping of carbodiimide intermediate **D**, generated by oxidative desulfurization of 1,3-disubstituted thioureas, by external nucleophiles such as sodium azide and hydrazides could lead to corresponding 5-aminotetrazoles **9** and 1,2,4-triazoles **10** (Scheme 1, Route IV), respectively. 5-Aminotetrazoles constitute an important class of compounds that possess widespread applications such as high energy density materials,[27] useful ligands,[28] and important synthetic inter-

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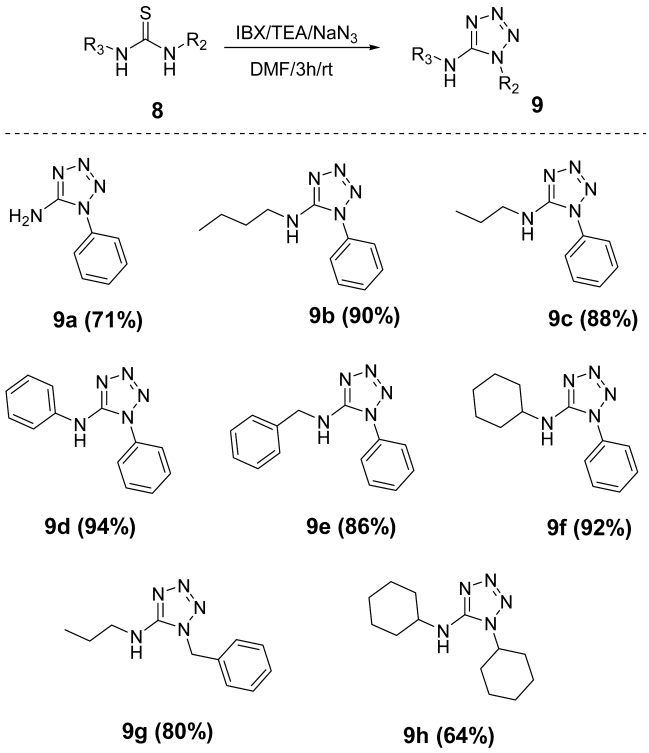
mediates in pharmaceutical and natural product research.[29] Methods for synthesis of 5-(substituted amino) tetrazoles are divided into four main categories:[30] (i) amino group or ring functionalization of 5-aminotetrazole, (ii) the nucleophilic substitution of a leaving group in the 5-position of tetrazole with amines, (iii) reactions of aminoguanidine derivatives with sodium nitrite, and (iv) various azide-mediated tetrazole ring constructions including addition of azide to carbodiimides, cynamides, and nucleophilic substitution by azide ion on chloroformamidines, aminoiminomethanesulfonic acid, and di- and trisubstituted (benzotriazolyl)-carboximidamides. Our approach falls under the category viz. azide-mediated tetrazole ring construction starting from 1,3-disubstituted thiourea via carbodiimide intermediacy, whereas those approaches reported in the literature totally relied on the use of mercury or lead salts for desulfurization. More recently, the same transformation has been reported by using molecular iodine. It shows promising results but with the limitation of not being applicable for synthesis of molecules such as *N*,1-dialiphatic-1*H*-tetrazol-5-amines.[18] For the development of our method, the reaction was optimized, taking 1-butyl-3-phenylthiourea **8b** (R_2 = phenyl and R_3 = butyl, Table 5) as a model substrate with respect to

Table 5. Substrate Scope for 5-Aminotetrazoles[a] 9



[a]Optimized reaction conditions: thiourea (1 equiv) was added to a stirred solution of IBX (1 equiv)/triethylamine (3 equiv) in DMF for 10 min, and then NaN_3 (3 equiv) was added portionwise, and stirring was continued for 3 h at rt. In the cases of **9e** and **9g**, a mixture of regioisomeric tetrazoles was obtained. Yields are isolated, and products are characterized by mp, IR, ^{1}H NMR, and MS (ESI).

moles of TEA and NaN_3 and time (refer to Table S1, Supporting Information (SI)). We screened different solvents such as DMSO, DMF, acetonitrile, DCM, and THF, but the reaction was clean and high yielding in DMF. With the optimized conditions of reacting thiourea (1 equiv), IBX (1 equiv), and triethylamine (3 equiv) in DMF for 10 min followed by addition of NaN_3 (3 equiv) portionwise with continued stirring for 3 h at rt, we synthesized various 5-aminotetrazoles **9** in good to excellent yields, as shown in Table 5.

1-Phenyl-5-aminotetrazole from the terminal phenylthiourea was obtained in good yield (Table 5, entry **9a**). High yields of *N*,1-disubstituted tetrazoles were observed in cases where thioureas were substituted at least with one aromatic nucleus (Table 5, entries **9b**−**9f**), while yields were moderate in the case of dialiphatic substituted thioureas (Table 5, entries **9g** and **9h**). It should be mentioned here that formation of regioisomeric tetrazoles is possible in the case of unsymmetrically substituted thioureas. The possible preponderance of the observed regioisomers, *N*-aryl substituted tertrazoles (Table 5, entries **9a**−**9f**) and others, could be due to the difference in the pK_as of the precursor amines attached to the thioureas.[19] The guanidyl intermediate **E** (Scheme 1, Route IV), formed with protonation of more basic amine (higher pK_a) with imine group on the other side and vice versa following the attack by azide group on to the first formed unsymmetrical carbodiimide, undergoes electrocyclization giving products 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.

Synthesis of 3-Amino-1,2,4-triazoles 10. As an extension of this study, we explored the preparation of 3-amino-1,2,4-triazoles **10** from 1,3-disubtituted thioureas **8** (Scheme 1, Route IV). Triazoles show a wide range of biological activities such as antifungal,[31] antimicrobial,[32] antiviral,[33] anti-inflammatory,[34] antiasthmatic,[35] and antiproliferative[36] activities and are also used as amide bond isostere for design of receptor ligands in order to enhance their pharmacokinetic properties.[37] Synthesis of 3-amino-1,2,4-triazole has been accomplished from thiourea using mercury(II) and more recently silver salts as a key reagent for the desulfurization purpose.[38] Other methods, based on solid phase synthesis strategy using acid hydrazide resin and amidines in the presence of molecular sieves, acylated amidrazones obtained from *N*-resin bound thioamides on subsequent cyclization in presence of acetic acid, suffer from drawbacks such as harsh reaction conditions and longer reaction times.[39] To explore the scope of our method, we tested various 1,3-disubstituted thioureas **8** with formyl hydrazide, and results are shown in Table 6. Good yields of triazoles were observed with electron-donating substituent (Table 6, entry **10b**) as compared to electron-withdrawing substituent (Table 6, entry **10c**). Further exploration of this transformation to exploit its potential is underway.

In conclusion, we have demonstrated the multifaceted use of a homogeneous IBX/TEA system for construction of azoles in one pot via oxidative desulfurization approach from easy to prepare starting materials. In the literature, many of these reactions were carried out by using toxic heavy metals. In the present approaches, (i) intramolecular trapping of in situ generated carbodiimide-like intermediate from thiosemicarbazides and *bis*-diarylthioureas by oxygen and sulfur nucleophile, respectively, provide an access to a range of 2-amino/thio-1,3,4-oxadiazoles and 2,5-diamino-1,3,4-oxadiazoles in an excellent yield, and (ii) intermolecular trapping of in situ generated carbodiimide from thioamide and thiourea by azide and hydrazide nucleophiles leads to highly substituted tetrazoles and triazoles in moderate to good yields. Because of rapid access to highly substituted *N*-containing heterocycles by these approaches and occurrence of these heterocycles in natural

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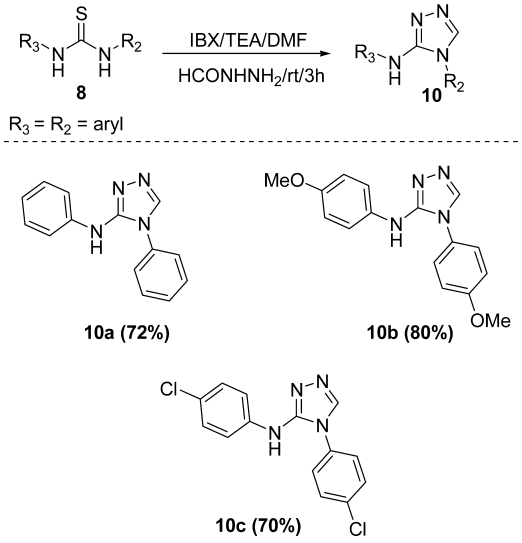
Table 6. Representative Examples for 3-(Substituted Amino)-1,2,4-triazoles[a] 10



[a]Optimized reaction conditions: thiourea (1 equiv) was added to a stirred solution of IBX (1 equiv)/triethylamine (3 equiv) in DMF for 10 min, and then $HCONHNH_2$ (3 equiv) was added portionwise, and stirring was continued for 3 h at rt. Yields are isolated, and products are characterized by mp, IR, ^1H NMR, and MS (ESI).

products and active pharmaceutical ingredients, we are hopeful that these one-pot methods will hold great potential.

EXPERIMENTAL SECTION

General Methods. All products are well-known compounds and were characterized by comparing physical and spectral properties with literature values. ^1H NMR spectra were recorded on 300 and 400 MHz spectrometer in $CDCl_3$ and DMSO-d_6.

General Experimental Procedure for Preparation of 2-Amino/thio-1,3,4-oxadiazole (3a−3m). Thiosemicarbazide **2d** (0.5 g, 1.75 mmol) was added over a cooled, temperature ~0 °C, and stirred solution of IBX (0.49 g, 1.75 mmol) and TEA (0.5 mL, 3.5 mmol) in dichloromethane (10 mL). The mixture was stirred at 0 °C for 10 min. The reaction was then quenched with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to afford the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate combination) or recrystallization to afford 0.42 g of **3d** as a white solid in 96% yield. The product was confirmed by mp, IR, ^1H NMR, and ESI-MS.

General Experimental Procedure for Preparation of 2,5-Diamino-1,3,4-thiadiazole (5a−5d). *Bis*-diaryl thiurea **4a** (0.5 g, 1.65 mmol) was added over a cooled, temperature ~0 °C, and stirred solution of IBX (0.49 g, 1.65 mmol) and TEA (0.5 mL, 3.5 mmol) in dichloromethane (10 mL). The mixture was stirred at 0 °C for 10 min. The reaction was then quenched with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to afford the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate combination) to afford 0.38 g of **5a** as a white solid in 86% yield. The product was confirmed by mp, IR, ^1H NMR, and ESI-MS.

General Experimental Procedure for Preparation of 1,5-Disubstituted Tetrazole (7a−7f). Thioamide **6a** (0.5 g, 2.34 mmol) was added to a stirred solution of IBX (0.65 g, 2.34 mmol)/TEA (1 mL, 7.11 mmol) in DMF (10 mL) for 5 min. Then, NaN_3 (0.45 g, 7.04 mmol) was slowly added to the reaction mixture with continued stirring for 3 h at rt. After completion, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to afford the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate combination) to afford 0.42 g of **7a** as a white solid in 82% yield. The product was confirmed by mp, IR, ^1H NMR, and ESI-MS.

General Experimental Procedure for Preparation of 5-Aminotetrazole (9a−9h). 1,3-Disubstituted thiourea **8b** (0.5 g, 2.59 mmol) was added to a stirred solution of IBX (0.72 g, 2.59 mmol)/TEA (1 mL, 7.77 mmol) in DMF (10 mL) for 5 min. Then, NaN_3 (0.5 g, 7.77 mmol) was slowly added to the reaction mixture with continued stirring for 3 h at rt. After completion, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to afford the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate combination) to afford 0.5 g of **4b** as a white solid in 90% yield. The product was confirmed by mp, IR, ^1H NMR, and ESI-MS.

General Experimental Procedure for Preparation of 3-Amino-1,2,4-triazole (10a−10c). 1,3-Diphenyl thiourea (0.5 g, 2.19 mmol) was added to a stirred solution of IBX (0.65 g, 2.19 mmol)/TEA (1 mL, 7.11 mmol) in DMF (10 mL) for 5 min. Then, NaN_3 (0.45 g, 7.04 mmol) was slowly added to the reaction mixture with continued stirring for 3 h at rt. After completion, the reaction mixture was poured into a saturated solution of $NaHCO_3$ (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to afford the crude product, which was purified by column chromatography on silica gel (petroleum ether/ethyl acetate combination) to afford 0.37 g of **10a** as a white solid in 72% yield. The product was confirmed by mp, IR, ^1H NMR, and ESI-MS.

5-Phenyl-1,3,4-oxadiazole-2-amine (3a). Yield 92%: white solid, mp 246−248 °C (lit. 244−247 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3365, 3290, 3059, 1596, 1490, 1448; ^1H NMR (300 MHz, DMSO-d_6) δ 7.81 (br s, 2H, NH_2), 7.64 (m, 1H), 7.58 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H); MS (ESI) m/z $(M + H)^+$ 161.87.

***N*,5-Diphenyl-1,3,4-oxadiazole-2-amine (3b).** Yield 92%: white solid, mp 218−220 °C (lit. 218−220 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3385, 3059, 1560, 1495, 1440; ^1H NMR (400 MHz, DMSO-d_6) δ 7.02 (t, J = 7.3 Hz, 1H), 7.33 (dd, J = 7.3, 7.5 Hz, 2H), 7.40 (m, 3H), 7.60−7.65 (m, 2H), 7.95 (m, 2H), 9.66 (s, 1H, NH); MS (ESI) m/z $(M + H)^+$ 237.90.

***N*-Ethyl-5-phenyl-1,3,4-oxadiazole-2-amine (3c).** Yield 86%: white solid, mp 129−130 °C (lit. 128−130 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3305, 3050, 1560, 1475, 1420; ^1H NMR (400 MHz, $CDCl_3$) δ 1.42 (t, J = 8.2 Hz, 3H), 3.50 (q, J = 8.2 Hz, 2H), 5.41 (bs, 1H), 7.45 (m, 3H), 7.91 (d, J = 7.3 Hz, 2H); MS (ESI) m/z $(M + H)^+$ 190.20.

5-Benzyl-*N*-phenyl-1,3,4-oxadiazole-2-amine (3d). Yield 96%: white solid, mp 179−180 °C (178−180 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3325, 3030, 1540, 1485, 1440; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (1H, m), 7.45−7.50 (m, 7H), 7.93 (d, J = 7.4 Hz, 2H), 4.61 (d, 2H), 5.20 (bs, 1H); MS (ESI) m/z $(M + H)^+$ 252.13.

***N*,5-Dibenzyl-1,3,4-oxadiazol-2-amine (3e).** Yield 90%: white solid, mp 122−124 °C (lit. 120−122); IR (KBr, thin film) ν_{max} (cm^{-1}) 3332, 3030, 1545, 1465, 1420; ^1H NMR (300 MHz, DMSO-d_6) δ 4.01 (s, 2H), 4.33 (s, 2H), 7.22 (dd, J = 7.5, 8.3 Hz, 2H), 7.52 (m, 3H), 7.26 - 7.29 (dd, J = 7.5, 8.4 Hz, 2H), 7.34 −7.37 (m, 3H), 8.01 (t, 1H, NH); MS (ESI) m/z $(M + 1)^+$ 266.28.

***N*-Benzyl-5-*o*-tolyl-1,3,4-oxadiazol-2-amine (3f).** Yield 88%: white solid, mp 125−127 °C (lit. 126−128 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3325, 3025, 1570, 1445, 1428; ^1H NMR (300 MHz, DMSO-d_6) δ 2.53 (s, 3H), 4.45 (s, 2H), 7.25−7.29 (dd, J = 6.8, 3.6, 2H), 7.41−7.34 (m, 2H), 7.35−7.37 (d, J = 7.2, 8.2 Hz, 2H), 7.40 (m, 1H), 7.68−7.70 (d, J = 7.2 Hz, 2H), 8.3 (t, 1H); MS (ESI) m/z $(M)^+$ 265.20 $(M)^+$.

2-(5-(Phenylamino)-1,3,4-oxadiazol-yl)phenol (3g). Yield 92%: white solid, mp 223−224 °C (lit. 223−224 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3325, 3020, 1560, 1485, 1440; ^1H NMR (300 MHz, DMSO-d_6) δ 6.97−7.03 (dd, J = 7.4, 3 Hz, 2H), 7.04−7.07 (m, 1H),

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7.32 (m, 1H), 7.35−7.38 (m, J = 7.6, 2 Hz, 1H), 7.38−7.43 (dd, J = 7.6, 2 Hz, 2H), 7.59−7.67 (m, 2H), 10.20 (s, 1H) 10.74 (s, 1H); MS (ESI) m/z $(M - H)^+$ 252.73.

2-(5-(Benzylamino)-1,3,4-oxadiazol-yl)phenol (3h). Yield 94%: white solid, mp 129−130 °C (lit. 128−130 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3315, 3040, 1530, 1485, 1428; ^1H NMR (300 MHz, DMSO-d_6) δ 4.49 (s, 2H), 6.93−7.03 (dd, J = 7.8, 3.2 Hz, 2H), 7.24 (m, 1H), 7.30 (m, 1H), 7.33−7.37 (m, J = 8.2, 7.4 Hz, 1H), 7.55−7.69 (dd, J = 8.2, 2.2 Hz, 2H), 7.95−7.97 (m, 2H), 8.53 (s, 1H), 10.10 (s, 1H); MS (ESI) m/z $(M - H)^+$ 266.20.

***N*-Benzyl-5-(2-chlorophenyl)-1,3,4-oxadiazol-2-amine (3i).** Yield 92%: white solid, mp 119−120 °C (lit. 118−120 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3345, 3030, 1540, 1475, 1430; ^1H NMR (300 MHz, DMSO-d_6) δ 8.46 (br s, 1H), 4.45 (s, 2H), 7.25−7.33 (dd, J = 6.8, 1.8 Hz, 2H), 7.36−7.47 (m, J = 6.8, 1.8, 8.2 Hz, 2H), 7.50 (dd, J = 8.2, 2.1 Hz, 2H), 7.60−7.82 (m, 3H); MS (ESI) m/z $(M + H)^+$ 286.00.

***N*-Benzyl-5-(2-nitrophenyl)-1,3,4-oxadiazol-2-amine (3j).** Yield 94%: yellow solid, mp 123−125 °C (123−126 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3365, 3050, 1545, 1459, 1420, 1350; ^1H NMR (300 MHz, DMSO-d_6) δ 4.48 (s, 2H), 7.25 (dd, J = 6.8, 3 Hz, 2H), 7.39 (m, 3H), 8.00−8.03 (d, J = 9 Hz, 2H), 8.32−8.35 (d, J = 9 Hz, 2H), 8.62 (t, 1H); MS (ESI) m/z $(M - H)^+$ 295.27.

***N*-Benzyl-5-(pyridine-4-yl)-1,3,4-oxadiazol-2-amine (3k).** Yield 94%: white solid, mp 139−140 °C (lit. 137−139 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3345, 3030, 1540, 1475, 1430; ^1H NMR (300 MHz, DMSO-d_6) δ 4.47 (s, 2H), 7.23−7.25 (dd, J = 6.9, 3.1 Hz, 2H), 7.28−7.39 (m, 3H), 7.69−7.71 (d, J = 5.7 Hz, 2H), 8.70−8.72 (d, J = 5.7 Hz, 2H), 8.63 (t, 1H); MS (ESI) m/z $(M + H)^+$ 253.10.

***N*-Ethyl-5-(pyridine-4-yl)-1,3,4-oxadiazol-2-amine (3l).** Yield 92%: white solid, mp 131−132 °C (131−132 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3350, 3030, 1567, 1460, 1410; ^1H NMR (300 MHz, DMSO-d_6) δ 3.23−3.30 (q, J = 7.2 Hz, 2H), 1.14−1.19 (t, J = 7.2 Hz, 3H), 7.68−7.70 (d, J = 5.7 Hz, 2H), 8.69−8.71 (d, J = 5.7 Hz, 2H), 7.98 (t, 1H); MS (ESI) m/z $(M - H)^+$ 189.07.

Methyl 5-[(2-(1-Methyl-1*H*-indol-3-yl)ethyl)amino]-1,3,4-oxadiazole-2-carboxylate (3m). Yield 94% white solid, mp143−145 °C (lit. 144−146 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3430, 1740, 1635, 1515, 1068; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.4 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.26 (m, 1H), 7.18 (t, 1H), 6.95 (s, 1H), 5.45 (s, 1H), 3.95 (s, 3H), 3.74 (s, 3H), 3.73 (m, 2H), 3.15 (t, 2H); MS (ESI) m/z $(M - H)^+$ 298.90.

***N*^{2},*N*^{5}-Diphenyl-1,3,4-thiadiazole-2,5-diamine (5a).** Yield 86%: white solid, mp 239−241 °C (lit. 239−242 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3341, 1556, 1470, 1420, 1152; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 6.80 (dd, J = 7.2, 2.1 Hz, 1H), 7.20 (m, 3H), 8.45 (s, 2H); MS (ESI) m/z $(M + H)^+$ 269.16.

***N*^{2},*N*^{5}-Bis(4-methoxyphenyl)-1,3,4-thiadiazole-2,5-diamine (5b).** Yield 92%: white solid, mp 235−238 °C (lit. 235−237 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3331, 1540, 1450, 1440, 1050, 1152; ^1H NMR (300 MH, $CDCl_3$+DMSO-d_6) δ 3.80 (s, 6H), 6.80 (d, J = 8.2 Hz, 4H), 7.45 (d, J = 8.2 Hz, 4H), 8.15 (s, 2H); MS (ESI) m/z $(M + H)^+$ 329.41.

1,5-Diphenyl-1*H*-tetrazole (7a). Yield 82%: white solid, mp 142−143 °C (lit. 142−143 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 1640, 1510, 1145, 1030; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (dd, J = 8.1, 2.8 Hz, 1H), 7.40 (dd, J = 8.2, 7.5 Hz, 2H), 7.67 (dd, J = 8.2, 2.8 Hz, 2H), 7.45 (m, 3H), 7.90 (dd, J = 8.1, 2.3 Hz, 2H); MS (ESI) m/z $(M + H)^+$ 223.93.

5-(4-Methoxyphenyl)-1-phenyl-1*H*-tetrazole (7b). Yield 84%; IR (KBr, thin film) ν_{max} (cm^{-1}) 1660, 1550, 1125, 1010; ^1H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6. 95 (d, J = 7.6 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H), 7.55 (d, J = 8.1 Hz, 2H), 7.90 (m, 3H); MS (ESI) m/z $(M + H)^+$ 253.20.

1-Benzyl-5-phenyl-1*H*-tetrazole (7c). Yield 76%: white solid, mp 90−92 °C (lit. 88−90 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 1660, 1550, 1135, 1010; ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (s, 2H), 7.20 (m, 2H), 7.40−7.50 (m, 5H), 7.75−7.80 (m, 3H); MS (ESI) m/z $(M - H)^+$ 236.90.

1-Cyclohexyl-5-phenyl-1*H*-tetrazole (7d). Yield 74%: mp 131−133 °C (lit. 131−133 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 2928, 1640, 1520, 1165, 1040; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25−1.40 (m, 4H), 1.60 (m, 2H), 1. 95−2.14 (q, J = 8.3 Hz, 4H), 4.20 (quin, J = 8.4 Hz, 1H), 7.40 (dd, 1H), 7.60 (m, 2H), 7.85 (m, 1H); MS (ESI) m/z $(M + H)^+$ 229.27.

5-(Furan-2-yl)-1-phenyl-1*H*-tetrazole (7e). Yield 80%: IR (KBr, thin film) ν_{max} (cm^{-1}) 3030, 1650, 1545, 1170, 1020, 1069; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55−7.68 (m, 3H), 7.45−7.52 (m, 3H), 7.20−7.28 (m, 1H), 7.0−7.1 (m, 1H); MS (ESI) m/z $(M + H)^+$ 213.62.

1-Cyclohexyl-5-(furan-2-yl)-1*H*-tetrazole (7f). Yield 74%: mp 58−60 °C (lit. 58−60 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 2928, 1650, 1510, 1145, 1020; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20−1.40 (m, 4H), 1.75−1.80 (m, 2H), 1. 95−2.14 (m, 4H), 4.80 (m, 1H), 6.45 (m, 1H), 6.65 (m, 1H), 7.25 (m, 1H); MS (ESI) m/z $(M - H)^+$ 217.74.

1-Phenyl-1*H*-tetrazol-5-amine (9a). Yield 71%: white solid, mp 165−168 °C (lit. 166−168 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3329, 3158, 2983, 1659, 1594, 1578, 1498, 1460, 1317, 1141, 1130, 1093; ^1H NMR (400 MHz, DMSO-d_6 + $CDCl_3$) δ 6.82 (bs, 2H), 7.51−7.55 (m, 5H); MS (ESI) m/z $(M + H)^+$ 162.07.

***N*-Butyl-1-phenyl-1*H*-tetrazol-5-amine (9b).** Yield 90%: white solid, mp 105−107 °C (lit. 104−105 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3320, 1652, 1530, 1560, 1468, 1315, 1160, 1043; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 8.4 Hz, 3H), 1.4 (m, J = 8.4 Hz, 2H), 1.65 (m, J = 8.2 Hz, 2H), 3.45 (t, J = 8.2 Hz, 2H), 4.30 (bs, 1H), 7.45−7.60 (m, 5H); MS (ESI) m/z $(M)^+$ 218.50.

1-Phenyl-*N*-propyl-1*H*-tetrazol-5-amine (9c). Yield 88%: IR (KBr, thin film) ν_{max} (cm^{-1}) 3310, 1620, 1545, 1440, 1325, 1110, 1020; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 8.3 Hz, 3H), 1.65 (m, J = 8.3, 2H), 3.50 (t, J = 8.1 Hz, 2H), 4.25 (bs, 1H), 7.50−7.65 (m, 5H); MS (ESI) m/z $(M + H)^+$ 204.10.

***N*,1-Diphenyl-1*H*-tetrazol-5-amine (9d).** Yield 94%: white solid, mp 158−160 °C (lit. 158−159 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3340, 1650, 1520, 1430, 1340, 1145, 1050; ^1H NMR (400 MHz, $CDCl_3$) δ 6.35 (bs, 1H), 7.10 (dd, J = 7.5, 3.1 Hz, 2H), 7.40 (dd, J = 7.4, 2.8 Hz, 2H), 7.50 (m, 3H), 7.70 (m, 3H); MS (ESI) m/z $(M + H)^+$ 238.93 $(M + H)^+$.

***N*-Benzyl-1-phenyl-1*H*-tetrazol-5-amine (9e).** Yield 86%: IR (KBr, thin film) ν_{max} (cm^{-1}) 3330, 1650, 1525, 1460, 1342, 1125, 1010; ^1H NMR (400 MHz, $CDCl_3$) δ 4.70 (m, 2H), 6.25 (bs, 1H), 7.20 (dd, J = 7.6, 2.6 Hz, 2H), 7.30 (m, 3H), 7.35 (m, 3H), 7.50 (dd, J = 7.2, 3.1 Hz, 2H); MS (ESI) m/z $(M + H)^+$ 252.73.

***N*-Cyclohexyl-1-phenyl-1*H*-tetrazol-5-amine (9f).** Yield 92%: white solid, mp 129−131 °C (lit. 128−130 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3332, 1670, 1550, 1430, 1310, 1165, 1030; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (m, 2H), 1.40−1.45 (m, J = 8.1, 8.5 Hz, 4H), 1.65−1.80 (m, J = 8.1, 8.5 Hz, 4H), 3.80 (quin, J = 8,1 Hz, 1H), 4.10 (bs, 1H), 7.45 (dd, J = 7.6 Hz, 2.9 Hz, 2H), 7.60 (m, J = 7.6, 7.6, 2.9 Hz, 3H); MS (ESI) m/z $(M - H)^+$ 242.16.

1-Benzyl-*N*-propyl-1*H*-tetrazol-5-amine (9g). Yield 80%: IR (KBr, thin film) ν_{max} (cm^{-1}) 3345, 1650, 1550, 1430, 1310, 1135, 1050; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (m, 5H), 5.32 (s, 2H), 3.74 (bs, 1H), 3.31 (m, 2H), 1.51 (m, 2H), 0.8 (m, 3H); MS (ESI) m/z $(M + H)^+$ 218.62.

***N*,1-Dicyclohexyl-1*H*-tetrazol-5-amine (9h).** Yield 92%: white solid, mp 202−204 °C (lit. 204−2−5 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3340, 1442, 1350, 1120, 1040; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (m, J = 8.1, 6H), 1.40 (m, J = 8.2 Hz, 4H), 1.45−1.60 (m, J = 8.5 Hz, 6H), 1.70−1.85 (m, J = 7.9 Hz, 4H), 3.50 (m, 2H), 4.10 (bs, 1H); MS (ESI) m/z $(M + H)^+$ 250.80.

***N*-4-Diphenyl-4*H*-1,2,4-triazole-3-amine (10a).** Yield 72%: mp 216−218 °C (lit. 214−216 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3315, 1650, 1548, 1492, 1453, 1020; ^1H NMR (400 MHz, DMSO-d_6) δ 6.85 (dd, J = 7.2, 3.1 Hz, 1H), 7.20 (d, J = 7.4 Hz, 2H), 7.40 (dd, J = 7.2, 7.4 Hz, 2H), 7.60 (m, 5H), 8.50 (bs, 1H); MS (ESI) m/z $(M + H)^+$ 237.47.

***N*-4-Bis(4-methoxyphenyl)-4*H*-1,2,4-triazol-3amine (10b).** Yield 80%: mp 184−186 °C (lit. 183−184 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3335, 1630, 1560, 1478, 1460, 1046; ^1H NMR (400 MHz,

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DMSO-d_6) δ 3.70 (s, 3H), 3.80 (s, 3H), 6.80 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 7.40 (m, 3H), 8.20 (s, 1H), 8.16 (d, 2H); MS (ESI) m/z $(M + H)^+$ 297.43.

***N*,4-Bis(4-chlorophenyl)-4*H*-1,2,4-triazol-3-amine (10c).** Yield 70%: mp 224−226 °C (lit. 226−228 °C); IR (KBr, thin film) ν_{max} (cm^{-1}) 3345, 1660, 1510, 1458, 1430, 1056; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.30 (d, J = 7.3 Hz, 2H), 7.50 (m, 4H), 7.70 (d, J = 7.6 Hz, 2H), 8.80 (s, 1H); MS (ESI) m/z $(M + H)^+$ 306.20.

■ ASSOCIATED CONTENT

Supporting Information

Table S1, spectroscopic data of all product entries in Tables 1−4 with their ^{1}H NMR, MS (ESI) copies, and supporting references. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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