Efficient Synthesis of 1,3,4-Thiadiazoles Using Hydrogen Bond Donor (Thio)urea Derivatives as Organocatalysts

Shahnaz Rostamizadeh,* Reza Aryan, Hamid Reza Ghaieni, and Ali Mohammad Amani

Faculty of Science, Department of Chemistry, K.N. Toosi University of Technology, Tehran, Iran
*E-mail: shrostamizadeh@yahoo.com

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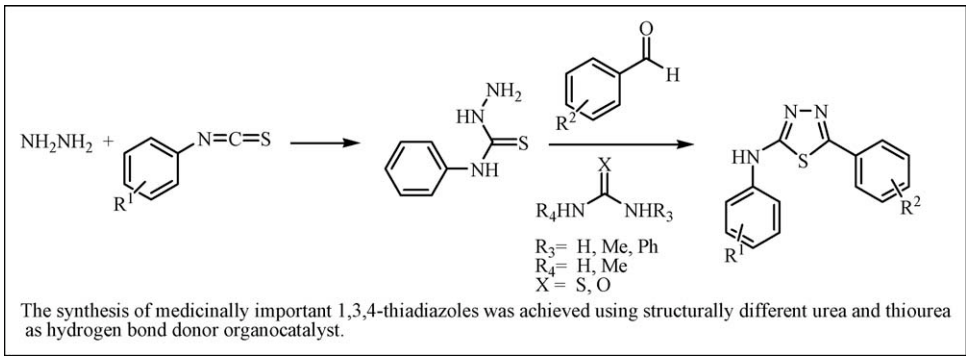

The synthesis of medicinally important 1,3,4-thiadiazoles was achieved using structurally different urea and thiourea as hydrogen bond donor organocatalyst.

A simple and efficient procedure for the synthesis of 1,3,4-thiadiazoles has been achieved using thiourea as organocatalyst. In this study, the steric and electronic effects using structurally different derivatives of urea and thiourea in different solvents were evaluated. The best yields and the rate of the reactions were obtained using 30 mol % of thiourea as catalyst in acetonitrile at room temperature. The molecular structures of the products were established by ^{1}H and ^{13}C NMR spectral data.

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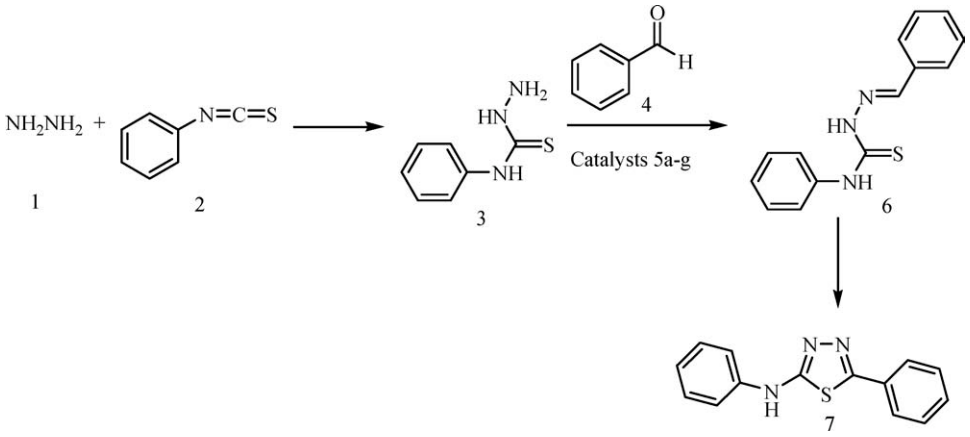
INTRODUCTION

1,3,4-Thiadiazoles are a group of heterocyclic building blocks for which a wide variety of applications have been reported including dyes [1], lubricating agents [2], optically active liquid crystals [3], and photographic materials [4]. In the medicinal field, therapeutic properties such as antitumor [5], hypoglycemic [6], anticonvulsant [7], hypotensive [8], antiproliferative [9] and antituberculosis [10a,b], antileishmanial [11a,b], and anti-*Helicobacter pylori* [12a,b] activities have been assigned to their various derivatives. Moreover, these compounds have recently been the subject of some theoretical and computational studies because of their significance [13,14]. Also, the research on the synthesis and discovery of new 1,3,4-thiadiazole derivatives with specific medicinal properties is still an active area of research [15]. Literature survey of synthetic methods for these interesting compounds indicates that there are three main categories for the synthesis of 1,3,4-thiadiazoles: (1) cyclizations involving one-bond formation [16a–h], (2) cyclizations involving formation of two bonds [16a,d–g], and (3) cyclizations involving formation of three bonds [16a,h]. Very recently, we reported a new three-bond forming one-pot protocol for the synthesis of some 1,3,4-thiadiazoles with potential antituberculosis activity using Brönsted acidic ionic liquid [Bmim]BF_4 as dual solvent and catalyst [17].

With a view to designing more selective, robust, environmentally benign, and functional-group tolerant catalysts, chemists have begun to reconsider using the proton as the simplest Lewis acid. Therefore, taking their cue from natural enzymatic systems, chemists have attempted to explore the development of weak acid–base interactions/hydrogen bonding which is one of the most dominant forces in molecular interaction and recognition in biological systems [18], as a basis for catalyst design and as an impressive option to replace the proton and other commonly known Lewis and Brönsted acids. So, small organic molecules called organocatalysts [19,20], which can form hydrogen bonds, contain no metallic atoms and are favorable in terms of environmental viewpoints that can be used as efficient catalysts for various organic transformations [21]. Recently, thiourea derivatives have been the subject of extensive research in the field of designing hydrogen bond catalyst and several excellent reviews are available on this subject (for example see [22]). Various thiourea catalysts have been utilized to catalyze organic reactions through hydrogen bonding, either for asymmetric or for nonasymmetric catalysis. Herein, we only refer to some of

Scheme 1. Model reaction for the organocatalyzed synthesis of 1,3,4-thiadiazoles.



the most recently reported studies such as chlorohydrins synthesis [23], enantioselective Michael addition [24], asymmetric Bayliss-Hillman reaction [25], Diels-Alder reaction [26], acetallization of aldehydes and ketones [27], nitro-Michael addition [28], nucleophilic addition to acyl imines [29], and enantioselective tandem Michael-Knoevenagel reaction [30]. To the best of our knowledge, there is no report on the role and application of organocatalysts for the preparation of 1,3,4-thiadiazoles in the literature. On the basis of the aforementioned considerations, we decided to investigate the steric and electronic effect of urea and thiourea in different solvents to represent a novel efficient catalytic protocol for the synthesis of some 1,3,4-thiadiazoles derivatives possessing arylamino and aryl moieties on positions 3 and 5 of thiadiazole ring.

RESULTS AND DISCUSSION

At the beginning to determine the appropriate catalyst, we examined the effect of hydrogen bond donor catalyst structure on the synthesis of 1,3,4-thiadiazoles. The model reaction is shown in Scheme 1. For this study, derivatives of urea and thiourea along with two guanidinium salts are used in different solvents and temperatures (Schemes 1 and 2, Tables 1 and 2). As can be deduced from Tables 1 and 2, the best results were obtained when 30 mol % of the thiourea as catalyst was used relative to reactants at room temperature (Table 1, entries 4–6).

The results shown in Tables 1 and 2 indicate an important point about the nature of catalysis and the proper type of solvent used in the process. In water as solvent, no reaction was observed for both urea and thiourea as catalyst (Table 1, entries 1 and 13). So, this solvent was not tested anymore in the case of other catalysts. This means that reactants do not form hydrogen bonds with catalysts in water because the catalysts form very stronger hydrogen bonds with water molecules, especially since the water molecules are present in such a great numbers as solvent [31]. In addition, when we chose ethanol as a hydroxylic solvent capable of forming hydrogen bonds weaker than water, the process did not proceed well either (Table 1, entries 2 and 14). In these two cases, we only obtained the semicarbazone intermediate 6 as the only product and not the desired heterocyclic compound. With a polar aprotic solvent such as acetonitrile, we managed to obtain the thiadiazole product with moderate to good yields and in relatively short reaction times (Table 1, entries 3, 4, and 7–12). This is undoubtedly due to the effective hydrogen bond formation between the substrates and the catalyst in acetonitrile. Solvents such as dimethylformamide (DMF) and dimehtylsulfoxide (DMSO) were also effective in the case of catalysts **5b**, **5c**, **5d**, **5e** but the yields were lower and the reaction times were much longer in these solvents (Table 1, entries 5 and 6, Table 2, entries 6–11), whereas in the case of catalysts **5f** and **5g**, no reaction was observed (Table 2, entries 12–15). Moreover, when the temperature was changed from 30°C to reflux condition, no remarkable change in the yield and the reaction time was observed (Table 1, entries 9–12). It is

Scheme 2. Urea, thiourea, and guanidinium salts as organocatalysts employed in this study.

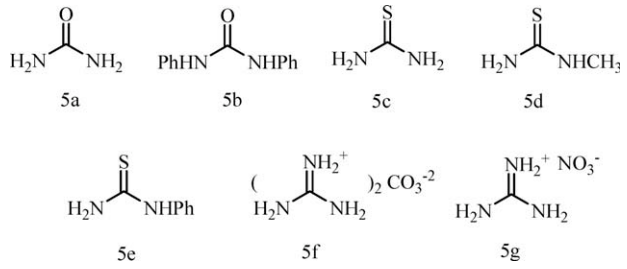


Table 1

Screening of the effect of temperature and the type solvent for the synthesis of 1,3,4-thiadiazoles using simple thiourea and urea.

Entry	Catalyst type	Catalyst loading (%)	Solvent	Temperature (°C)	Reaction time	Comments[a]
1	**5a**	30	Water	30	24 h	No reaction
2	**5a**	30	Ethanol	30	24 h	Only intermediate **6**, Yield 60%
3	**5a**	30	CH_3CN	30	4.5 h	Product **7**, Yield 50%
4	**5c**	30	CH_3CN	30	75 min	Product **7**, Yield 81%
5	**5c**	30	DMF	30	2.5 h	Product **7**, Yield 76%
6	**5c**	30	DMSO	30	2.5 h	Product **7**, Yield 70%
7	**5c**	20	CH_3CN	30	3 h	Product **7**, Yield 40%
8	**5c**	40	CH_3CN	30	70 min	Product **7**, Yield 80%
9	**5c**	30	CH_3CN	40	70 min	Product **7**, Yield 80%
10	**5c**	30	CH_3CN	60	70 min	Product **7**, Yield 83%
11	**5c**	30	CH_3CN	70	70 min	Product **7**, Yield 80%
12	**5c**	30	CH_3CN	reflux	70 min	Product **7**, Yield 77%
13	**5c**	30	Water	30	24 h	No reaction
14	**5c**	30	Ethanol	30	24 h	Only intermediate **6**, Yield 40%

[a] Isolated yield.

worth mentioning that the reaction was best performed at 30°C (Table 1, entry 4).

The amount of 30 mol % of the catalyst was found to be the optimum amount for the present process. When we applied a lower amount of thiourea (20 mol %, Table 1, entry 7), the reaction yield was decreased to nearly half of that found with 30 mol % of the catalyst. Moreover, using higher amounts of catalyst (40 mol %, Table 1, entry 8) did not make any remarkable difference in the yield and the reaction time.

To find out which catalyst could be the most beneficial one for our purpose and what would be the nature of the catalytic effect, we examined five derivatives of urea and thiourea along with two guanidinium salts in this process (Tables 1 and 2, Scheme 2). The chemical nature of catalyst effect here in this process could be both steric and electronic. Taking a precise look at the results in Table 1, upon going from thiourea to *N*-methylthiourea, reveals that even a small change in the structure (replacing H with CH_3) has led to a drastic reduction in the reaction rate and a remarkable decrease in the yield of formation of thiadiazole (Table 1, entry 4 and Table 2, entry 2). This can be better deduced in the case of *N*, *N*′-diphenylurea and *N*-phenylthiourea (Table 2, entries 1 and 2) with their unsubstituted analogs (Table 1, entries 3 and 4). Observing a longer reaction time for *N*-phenylthiourea in comparison with the case of thiourea indicates that steric demands are the major factors governing the formation of the hydrogen bond between catalysts and the substrates. With a more sterically hindered catalyst like *N*-phenylthiourea, the catalyst is not capable of forming effective hydrogen bridges with

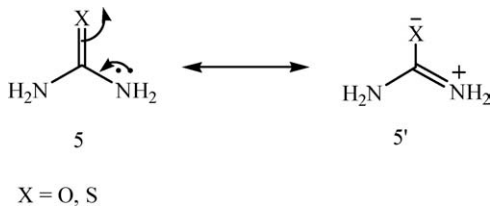
Table 2

Comparison of the urea and thiourea derivatives as organocalysts in the synthesis of 1,3,4-thiadiazoles.

Entry	Catalyst type	Catalyst loading (%)	Solvent	Temperature (°C)	Reaction time (h)	Comments[a]
1	**5b**	30	CH_3CN	30	24	Trace of intermediate **6**
2	**5d**	30	CH_3CN	30	4.5	Product **7**, Yield 45%
3	**5e**	30	CH_3CN	30	24	Product **7**, Yield 40%
4	**5f**	30	CH_3CN	30	24	No reaction
5	**5g**	30	CH_3CN	30	24	No reaction
6	**5b**	30	DMF	30	24	Trace of product **7**
7	**5b**	30	DMSO	30	24	Trace of product **7**
8	**5d**	30	DMF	30	24	Product **7**, Yield 30%
9	**5d**	30	DMSO	30	24	Product **7**, yield 25%
10	**5e**	30	DMF	30	24	Product **7**, Yield 36%
11	**5e**	30	DMSO	30	24	Product **7**, Yield 27%
12	**5f**	30	DMF	30	24	No reaction
13	**5f**	30	DMSO	30	24	No reaction
14	**5g**	30	DMF	30	24	No reaction
15	**5g**	30	DMSO	30	24	No reaction

[a] Isolated yield.

Scheme 3. Resonance structures of urea and thiourea.



substrates. This will result in a decrease in the reactivity of the substrate, much longer reaction time, and much lower yield of the product (Table 2, entry 3). Moreover, the application of *N*,*N*′-diphenylurea, as a catalyst with two very bulky substituents on nitrogen atoms, led to the formation of the intermediate **6** (Scheme 1) in trace amounts and no sign of formation of thiadiazole ring (Table 2, entry 1).

The difference in catalytic activity of thiourea and urea can be clearly seen in Table 1 (entries 3 and 4) as one of the most interesting points of this study. Thiourea has catalyzed the reaction faster than urea in acetonitril as solvent at room temperature. The possible reason for this observation is the fact that in thiourea the sulfur heteroatom has more polarizability in comparison to oxygen. So, when drawing the resonance structures for urea and thiourea, the **5′** contribution in the resonance structure is higher for thiourea because the negative charge could be better stabilized on sulfur than on oxygen atom (Scheme 3). Accordingly, more positive charge on nitrogen and on the hydrogen atom in **5′** resonance structure has lead to stronger hydrogen bonding with the reactants and a more catalytic effect. Moreover, the pK_a value for thiourea is less than the one for urea [32] which means thiourea is more acidic than urea. Therefore, thiourea should be able to catalyze the cyclization step better than urea.

To prove that the electronic effects do not play a distinct role in hydrogen bond catalyzed synthesis of 1,3,4-thiadiazoles, we repeated this process using various phenylisothiocyanate and benzaldehyde derivatives with different electron demands (Scheme 4, Table 3, compounds **7a–n**). Both the reaction times and isolated yields in Table 2 indicate no general pattern for derivatives with electron withdrawing or electron donating substituents. Reaction times are in the range of 30–75 min for all products and the yields vary between 81% and 95%. Taking these facts into consideration, we can only lay emphasis on the role of steric, and not, electronic effects on the preparation of 1,3,4-thiadiazoles using (thio)urea organocatalysts. Then, we performed some control experiments to confirm the role of thiourea as catalyst in this process. Primarily we performed the process by using equivalent amounts of phenylisothiocyanate, hydrazine hydrate, and benzaldehyde and the use of thiourea (30 mol % relative to reactants) in dry acetonitrile as solvent under N_2 inert atmosphere. As expected, we observed the formation of intermediate **6** (Scheme 1) as the only product and no sign of the desired thiadiazole product was observed. When we performed the test experiment in EtOH as solvent and in the absence of any catalyst, only trace amounts of intermediate **6** were obtained. These control experiments show that hydrogen bonds of thiourea are necessary to promote the reaction and solvents such as water and ethanol cannot play the role of a hydrogen bond donor to catalyze this process. According to these results, we proposed a reasonable reaction pathway for the preparation of 1,3,4-thiadiazoles using thiourea as catalyst (Scheme 5).

The main interesting point that can be observed through this proposed reaction pathway is that when one of the hydrogen on nitrogen atom of thiourea (nitrogen atom on the left side of thiourea) is replaced with a more sterically hindered substituent like methyl and phenyl, one of the hydrogen bond connections has actually been removed which prevents self formation of the template between the catalyst with the two reactants. In the case of thiourea as catalyst, this template of hydrogen bridges facilitates the approaching of 4-phenylthiosemicarbazide to benzaldehyde and the formation of 4-phenylthiosemicarbazone intermediate. The ease of hydrogen bond formation also facilitates the cyclization to 2,3-dihydrothiadiazoline intermediate in the second step.

Scheme 4. General reaction pattern used for the synthesis of substituted 1,3,4-thiadiazoles.

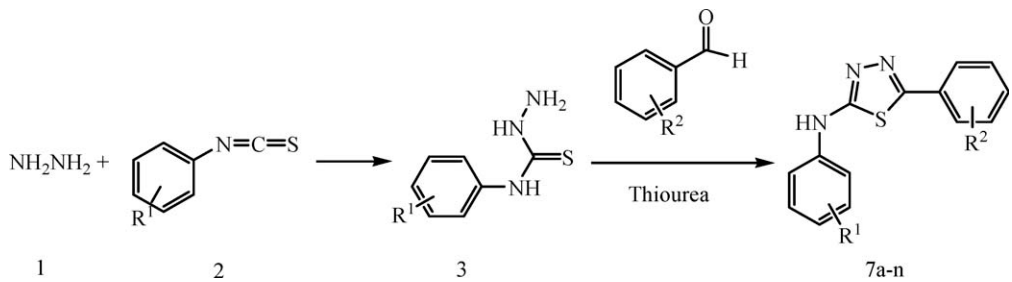


Table 3

Organocatalytic synthesis of 1,3,4-thiadiazoles using thiourea as hydrogen bond catalyst.

Entry	R^1	R^2	Reaction time (min)	Yield[a] (%)	M. P. (°C) (Lit.) [ref.]
7a	H	H	75	81	200–202 (199–200) [10]
7b	H	4-Br	60	95	320–323 (338–339) [10]
7c	H	4-Cl	45	92	217–219 (216–217) [10]
7d	H	4-F	45	87	252–254 (258–262) [10]
7e	H	4-NO_2	30	93	267–269 (275–277) [10]
7f	4-NO_2	H	30	90	207–211 (216–220) [10]
7g	4-NO_2	4-Br	40	95	281–284 (293–294) [10]
7h	4-NO_2	4-Cl	35	92	288–290 (300–302) [10]
7i	4-NO_2	4-NO_2	40	90	343–347 (368) [10]
7j	4-Me	H	60	80	177–179 (176–180) [10]
7k	4-Me	4-Cl	50	89	220–224 (213–214) [10]
7l	4-Me	4-F	60	86	203–207 (210–214) [10]
7m	4-Me	4-NO_2	65	90	270–273 (280–284) [10]
7n	3-Me	H	60	95	180–182 (176) [33]

[a] Isolated yield.

The hydrogen bonding in this step of the reaction is responsible for the activation of C=N double bond and the motivation for cyclization. Herein, the existence of more bulky groups like methyl and phenyl also will result in improper hydrogen bonding of the catalyst to 4-phenylthiosemicarbazone.

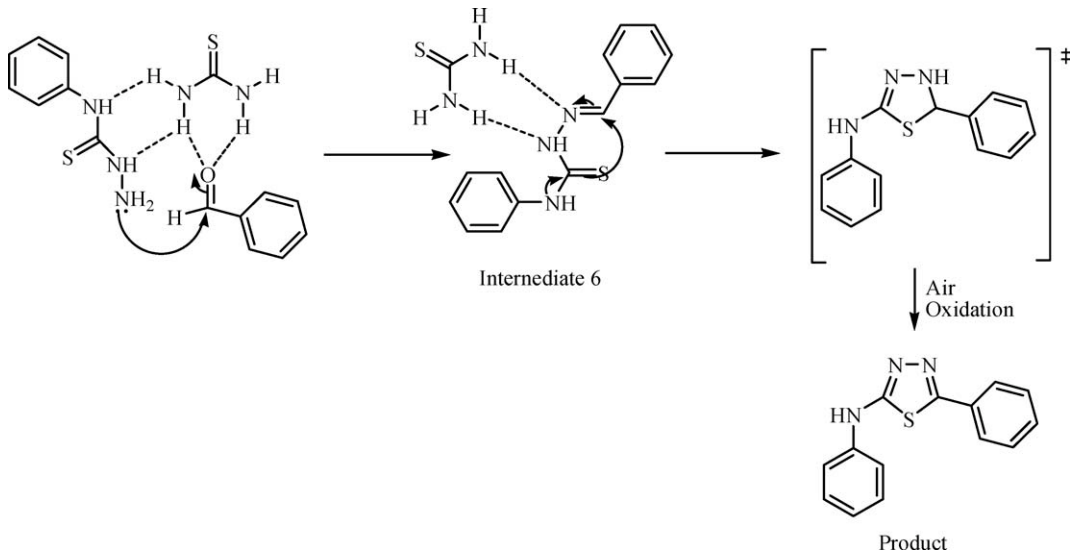
The case of guanidinium salts with no catalytic activity can simply be explained in another way. The guanidinium cations strongly form hydrogen bonds with their counterions carbonates or nitrates, and, consequently will not be able to form such bonds with the substrates in the reaction (Table 1, entries 18 and 19).

In comparison to our previous work [15], this study has several advantages. Apart from the similarity in yields, thiourea derivatives have been used which are cheaper than ionic liquids [bmim]. In addition, ionic liquids [bmim] BF_4 may release HF and decompose after some time, whereas thiourea derivatives do not have such a problem and can also be handled and kept more easily than ionic liquids. The only difference with this study is slightly longer reaction times.

CONCLUSIONS

In summary, we have developed a study on hydrogen bond catalysis in the synthesis of 1,3,4-thiadiazoles as a group of medicinally important heterocyclic

Scheme 5. The proposed reaction pathway for the formation of 1,3,4-thiadiazole in which a template of hydrogen bond thiourea organocatalyst has the main role.



compounds. We examined several urea, thiourea, and gunidinium compounds to realize the major factors governing the catalytic activity of these compounds and realized that the true feature of the catalytic effect is steric, and not, electronic effect because the rates and yields of the reaction are strongly dependent on the steric bulk of the catalyst. Application of *N*-methyl- and *N*-phenylthiourea resulted in lower yields and slower reaction rates in comparison with thiourea. Finally, this process provides easy access to important thiadiazole heterocyclic building block in relatively short reaction times and various derivatives with different electron demands on substituents were prepared. We think that this process has a great potential to be applied for the catalytic purposes of synthetic protocols for other important heterocycles and we are working to develop this idea for the purpose of organic and heterocyclic synthesis.

EXPERIMENTAL

Melting points were measured on a Büchi B-540 apparatus and are uncorrected. IR spectra were measured on Bomem FTIR ABB FTLA200-100 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz using TMS as an internal standard. Chemical shifts are reported (δ) relative to TMS, and coupling constants (*J*) are reported in hertz (Hz). Mass spectra were recorded on a High Resolution Agilent Technology EX mass spectrometer. Chemicals were obtained from Merck, Darmstadt, Germany and Sigma-Aldrich Saint Quentin Falavier, Cedex, France and used without further purification.

Typical experimental procedure for organocatalytic preparation of 1,3,4-thiadiazoles using (thio)urea derivatives. To a round bottomed flask was added phenylisothiocyanate derivative (0.24 mL, 2 mmoles), acetonitrile as solvent (2 mL), and hydrazine hydrate (0.1 mL, 2 mmoles) (Scheme 3). This mixture was stirred at 25–30°C for 10 min, Then thiourea (0.045 g, 0.6 mmoles, 30 mol %) and substituted benzaldehyde (2 mmoles) were added to the reaction vessel. The reaction mixture was then stirred for the specified time at 30°C (Table 2). After completion of reaction (as monitored by TLC, ethyl acetate:petroleum ether, 1:4), the resulting precipitates were vacuum filtered using a Büchi funnel. The results are shown in Table 2. The precipitates were further purified with either ethanol or ethanol/water and were further characterized by mp, IR, NMR, and MS spectroscopy. This procedure was repeated the same in the case of other urea or thiourea derivatives (Table 1).

Analytical data for substituted 1,3,4-thiadiazoles. ***N,5-diphenyl-1,3,4-thiadiazol-2-amine (7a).*** This compound was obtained as white crystalline solid, mp 200–202°C (Lit. mp 199–200°C [10]), ir: 3297, 3148 (NH) 1606 (C=N) 680 cm^{-1} (C—S—C), ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 7.06 (t, 1H, *J* = 9.0 Hz), 7.31 (m, 4H), 7.46 (d, 2H, *J* = 9.0 Hz, ortho to thiadiazole ring), 7.81 (m, 2H, meta to thiadiazole ring), 8.31 (s, 1H, para to thiadiazole ring), 10.33 (1H, NH), 11.62 (1H, NH). (Presence of two tautomeric isomers [34].)

5-(4-Bromopheny)-N-phenyl-1,3,4-thiadiazol-2-amine (7b). This compound was obtained as white crystalline solid, mp 320–323°C (Lit. mp 338–339°C [10]), ir: 3302, 3122 (NH) 1595 (C=N) 679 cm^{-1} (C—S—C); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 7.06 (t, 1H, *J* = 6.5 Hz), 7.29 (t, 2H, *J* = 6.5 Hz, ortho to thiadiazole ring on phenyl), 7.49 (m, 4H, 2H meta to thiadiazole ring and 2H on phenylamino group), 7.76 (m, 2H), 8.04 (s, 2H), 10.21 (1H, NH), 11.79 (1H, NH). (Presence of two tautomeric isomers [34].)

5-(4-Chlorophenyl)-N-phenyl-1,3,4-thiadiazol-2-amine (7c). This compound was obtained as white crystalline solid, mp 217–219°C (Lit. mp 216–217°C [10]), ir 3306, 3132 (NH) 1586 (C=N) 690 cm^{-1} (C—S—C); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 7.21 (t, 1H, *J* = 6.9 Hz), 7.35 (m, 4H), 7.54 (t, 4H, *J* = 7.5 Hz, meta to thiadiazole ring on phenyl group), 10.39 (s, 1H, NH).

5-(4-Fluorophenyl)-N-phenyl-1,3,4-thiadiazol-2-amine (7d). This compound was obtained as white crystalline solid, mp 252–254°C (Lit. mp 258–262°C [10]), ir: 3322, 3132 (NH) 1606 (C=N) 690 cm^{-1} (C—S—C); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 7.25 (t, 1H, *J* = 6.0 Hz), 7.31 (t, 2H, *J* = 6.0 Hz), 7.44 (t, 2H, *J* = 9.0 Hz, ortho to thiadiazole ring on phenyl group), 7.66 (d, 2H, *J* = 6.0 Hz, meta to thiadiazole ring on phenyl group), 8.11 (m, 2H), 10.23 (s, 1H, NH).

5-(4-Nitrophenyl)-N-phenyl-1,3,4-thiadiazol-2-amine (7e). This compound was obtained as light yellow crystalline solid, mp 267–269°C (Lit. mp 275–277°C [10]), ir: 3347, 3137 (NH) 2978 (CH) 1596 (C=N) 695 cm^{-1} (C—S—C); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 7.19 (t, 1H, *J* = 7.5 Hz), 7.51 (t, 2H, *J* = 7.5 Hz), 7.86 (d, 2H, *J* = 8.4 Hz), 8.21 (d, 2H, *J* = 8.4 Hz, ortho to thiadiazole ring on phenyl group), 8.44 (d, 2H, *J* = 8.4 Hz, meta to thiadiazole ring on phenyl group).

N-(4-nitrophenyl)-5-phenyl-1,3,4-thiadiazol-2-amine (7f). This compound was obtained as light yellow crystalline solid, mp 207–211°C (Lit. mp 216–220°C [10]), ir: 3311, 3154 (NH) 2980 (CH) 1601 (C=N) 690 cm^{-1} (C—S—C); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 7.56 (m, 3H), 7.83 (m, 2H), 8.15 (d, 2H, *J* = 9.0 Hz, meta to thiadiazole ring on phenyl group), 8.49 (d, 2H, *J* = 9.0 Hz), 10.66 (s, 1H, NH).

5-(4-Bromophenyl)-N-(4-nitrophenylamino)-1,3,4-thiadiazol-2-amine (7g). This compound was obtained as light yellow crystalline solid, mp 281–284°C (Lit. mp 293–294°C [10]), ir: 3301 3147 (NH) 3003 (CH) 1598 (C=N) 695 cm^{-1} (C—S—C); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 7.66 (d, 2H, *J* = 8.1 Hz, ortho to thiadiazole ring on phenyl group), 7.89 (d, 2H, *J* = 8.1 Hz), 8.21 (m, 2H, meta to thiadiazole ring on phenyl group), 8.77 (br. s, 2H), 10.59 (br. s, 1H, NH).

5-(4-Chlorophenyl)-N-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine (7h). This compound was obtained as light yellow crystalline solid, mp 288–290°C (Lit. mp 300–302°C [10]), ir: 3311, 3167 (NH) 3014 (CH) 1611 (C=N) 690 cm^{-1} (C—S—C); ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 7.59 (d, 2H, *J* = 9.0 Hz, ortho to thiadiazole ring on phenyl group), 7.88 (d, 2H, *J* = 9.0 Hz, meta on thiadiazole ring), 8.11 (d, 2H, *J* = 9.0 Hz), 8.31 (d, 2H, *J* = 9.0 Hz), 10.52 (s, 1H, NH).

N-(4-nitrophenyl)-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine (7i). This compound was obtained as reddish yellow crystalline solid, mp 343–347°C (Lit. mp 368°C [10]), ir: 3302, 3128 (NH) 2990 (CH) 1596 (C=N) 695 cm^{-1} (C—S—C); ^{1}H NMR

(300 MHz, DMSO-d_6): δ 8.12 (d, 2H, J = 9.0 Hz), 8.26 (d, 2H, J = 9.0 Hz), 8.33 (d, 2H, J = 4.2 Hz, ortho to thiadiazole ring on phenyl group), 8.41 (d, 2H, J = 4.2 Hz, meta to thiadiazole ring on phenyl group), 10.53 (br. s, 1H, NH).

N-(4-methylphenyl)-5-phenyl-1,3,4-thiadiazol-2-amine (7j). This compound was obtained as white crystalline solid, mp 177–179°C (Lit. mp 176–180°C [10]), ir: 3260, 3200 (NH) 1615 (C=N) 699 cm^{-1} (C—S—C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.33 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 7.22 (m, 2H), 7.52 (m, 4H, meta to thiadiazole ring), 7.97 (m, 2H, ortho to thiadiazole ring), 8.29 (s, 1H, ortho to thiadiazole ring), 10.19 (1H, NH). (Presence of two tautomeric isomers [34].)

5-(4-Chlorophenyl)-N-(4-methylphenyl)-1,3,4-thiadiazol-2-amine(7k). This compound was obtained as white crystalline solid, mp 220–224°C (Lit. mp 213–214°C [10]), ir: 3342, 3142 (NH) 2978 (CH) 1596 (C=N) 685 cm^{-1} (C—S—C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3), 7.27 (d, 2H, J = 8.1), 7.51 (d, 2H, J = 8.1), 7.63 (d, 2H, J = 6.9, ortho to thiadiazole ring on phenyl group), 8.09 (d, 2H, J = 6.9, meta to thiadiazole ring on phenyl group), 10.22 (s, 1H, NH).

5-(4-Fluorophenyl)-N-(4-methylphenyl)-1,3,4-thiadiazol-2-amine (7l). This compound was obtained as white crystalline solid, mp 203–207°C (Lit. mp 210–214°C [10]), ir: 3322, 3132 (NH) 1606 (C=N) 690 cm^{-1} (C—S—C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.34 (s, 3H, CH_3), 7.27 (d, 2H, J = 8.1 Hz), 7.48 (d, 2H, J = 8.1 Hz), 7.61 (d, 2H, J = 6.0 Hz, ortho to thiadiazole ring on phenyl group) 8.09 (m, 2H, meta to thiadiazole ring on phenyl group), 10.30 (s, 1H, NH).

N-(4-methylphenyl)-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine (7m). This compound was obtained as light yellow crystalline solid, mp 270–273°C (Lit. mp 280–284°C [10]), ir: 3306, 3126 (NH) 2988 (CH) 1591 (C=N) 690 cm^{-1} (C—S—C); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.31 (s, 3H, CH_3), 7.21 (d, 2H, J = 8.4 Hz), 7.44 (d, 2H, J = 8.4 Hz), 8.28 (d, 2H, J = 9.0 Hz, ortho to thiadiazole ring on phenyl group), 8.34 (d, 2H, J = 9.0 Hz, meta to thiadiazole ring on phenyl group).

N-(3-methylphenyl)-5-phenyl-1,3,4-thiadiazol-2-amine (7n). This compound was obtained as white crystalline solid, mp 180–182°C, ir: 3312, 3163 (NH) 1602 (C=N) 699 cm^{-1} (C—S—C), ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.35 (s, 3H, CH_3), 7.12 (d, 1H, J = 6.9 Hz), 7.33 (t, 1H, J = 6.9 Hz), 7.52 (m, 4H), 8.08 (m, 2H, meta to thiadiazole ring on phenyl group), 8.25 (s, 1H, para to thiadiazole ring on phenyl group), 10.15 (1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 23.34, 123.76, 126.77, 127.24, 128.11, 128.35, 129.21, 130.66 (C-para to thiadiazole ring on phenyl group), 134.75 (quaternary carbon on phenyl ring), 137.81, 139.41, 144.11 (C-2 in thiadiazole ring), 178.33 (C-5 in thiadiazole ring); ms m/z = 267; Anal. Calcd. For $C_{15}H_{13}N_3S$ (267.08): C, 67.39; H, 4.90; N, 15.72; S, 11.99; Found: C, 67.69; H, 4.69; N, 15.32; S, 11.72.

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