Heteroatom Chemistry
Volume 19, Number 6, 2008

A New Convenient Way to Synthesize 1,3,4-Thiadiazol-2-yl Urea Derivatives under Microwave Irradiation

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Received 7 November 2006; revised 9 March 2008

ABSTRACT: *A simple and efficient method was developed for the synthesis of 1-(substituted)-3-(5-(substituted)-1,3,4-thiadiazol-2-yl) ureas from heterocyclic amino compounds and phenyl-5-(pyridine-3-yl)-1,3,4-thiadiazol-2-ylcarbamate(***2***) or phenyl-5-(trifluoro-methyl)-1,3,4-thiadiazol-2-ylcarbamate(***5***) under solvent conditions using microwave irradiation. The products were obtained in satisfactory yield as we expected. The reactions can be realized by conventional heating, but we find that the condition of microwave is better according to the reaction time. New 1-(substituted)-3-(5-(substituted)-1,3,4-thiadiazol-2-yl) urea derivatives are reported. The products were characterized by* ^{1}*H NMR, ESI-MS, and Elemental analysis. The crystal structure of compound* **6h** *was determined by X-ray single crystal diffraction.*
 Heteroatom Chem 19:621–629, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20489

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Contract grant sponsor: National Natural Science Foundation of China.
Contract grant number: 20432010.
Contract grant sponsor: Ministry of Science and Technology of the People's Republic of China.
Contract grant number: 2003CB114400.
Contract grant sponsor: Ministry of Education of China.

INTRODUCTION

Microwave-assisted organic chemistry (MAOC) has been developed to be a valuable tool for chemistry research during the past 20 years [1–2] and has received widespread acceptance [3]. The recent availability of commercial microwave systems specific for synthesis makes this technique more convenient and accessible, because of the improved opportunities for reproducibility, rapid synthesis, rapid reaction optimization, and the potential discovery of new chemistries. Therefore, the beneficial effects of microwave irradiation are becoming more and more remarkable, especially when ordinary reactions require forcing conditions or prolonged reaction times.

The 1-(substituted)-3-(5-(substituted)-1,3,4-thiadiazol-2-yl) urea is an important heterocyclic scaffold in the field of medicinal and pesticide chemistry as the derivatives are well known for their diverse biological activities [4–6]. Although there are many feasible routes for the synthesis of 1,3,4-thiadiazol-2-yl urea derivatives, the products are often limited to 5-(substituted)-1,3,4-thiadiazol-2-amine and heterocyclic isocyanates [7–10]. To develop multifunctional libraries of 1-(substituted)-3–5-(substituted)-1,3,4-thiadiazol-2-yl) urea derivatives, we herein report a new convenient way to synthesize 1,3,4-thiadiazol-2-yl urea derivatives from heterocyclic amino compounds using MAOC condition.

RESULTS AND DISCUSSION

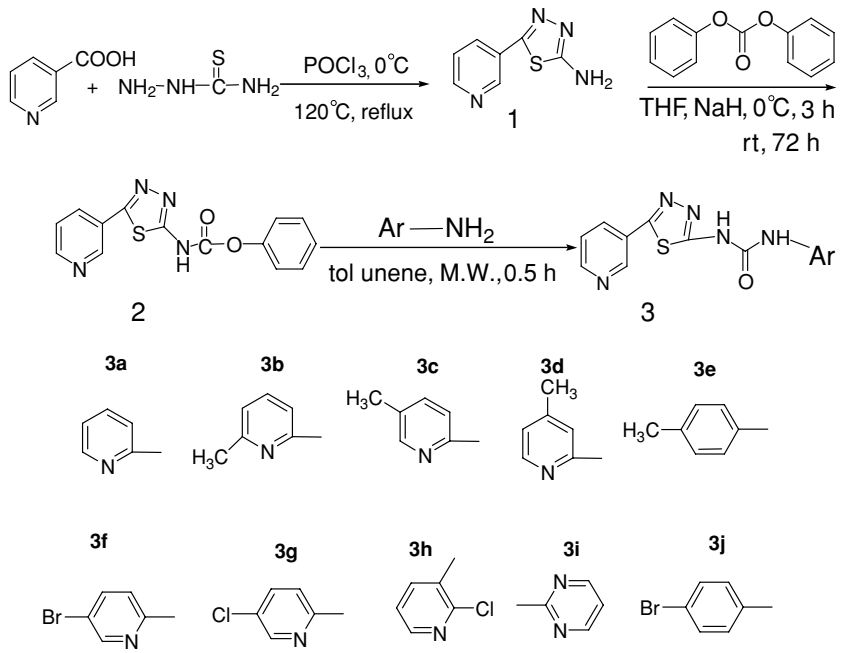
Previously, a preparation of the 1,3,4-thiadiazol-2-yl urea derivatives has been reported. The synthesis is accomplished by the reaction of heterocyclic amino compounds with heterocyclic isocyanato compounds in the presence of anhydrous solvent [11–15]. In this report, we find that the heterocyclic isocyanato compounds must be freshly made because these compounds are unstable and the reaction is very sensitive to water. To get the 1,3,4-thiadiazol-2-yl urea derivatives in a convenient way, we make an effort to prepare relatively stable compounds **2** and **5** as the intermediates from compounds **1** and **4**.

The compounds **1** and **4** were synthesized from the thiosemicarbazide and their carboxylic acids, respectively. Because of the violent reaction condition of preparing compound **1**, we use 1,4-dioxane as solvent and drop $POCl_3$ slowly into the reaction mixture. Then, the reaction was kept at 120°C for 5 h. The reaction of preparing the compound **4** was relatively mild compared with the first reaction. Then, we performed the reaction in polyphosphoric acid. Both of the two reactions gave reasonable yield, and we successfully got the two compounds. Compound **1** or **4** was then treated with diphenyl carbonate and NaH in anhydrous THF to give phenyl-5-(substituted)-1,3,4-thiadiazol-2-ylcarbamate(**2** or **5**) in acceptable yield. We found that this substance is stable at room temperature and can be stored for a long time. (Schemes 1 and 2)

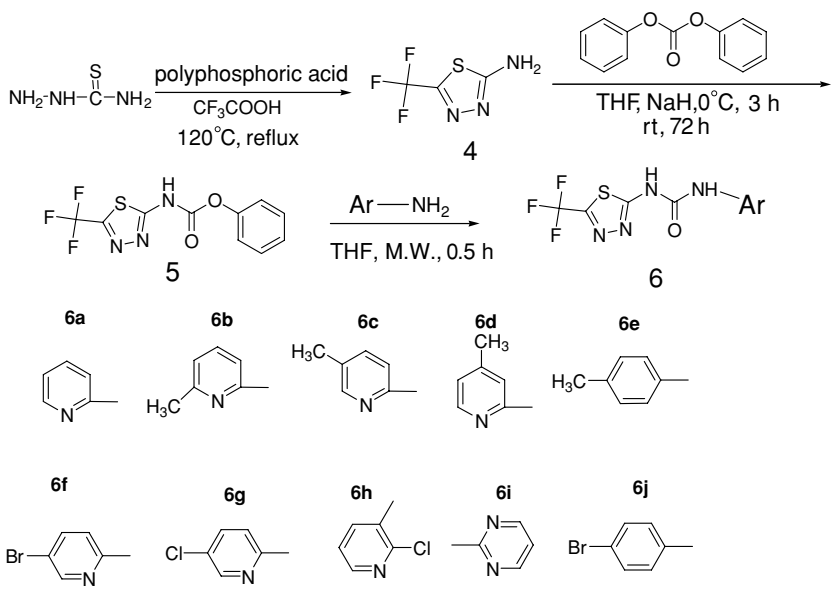
Pyridines, pyrimidines, and their derivatives have been studied for more than one century due to their diverse biological activities [16–18]. They possess antibacterial, antiviral, antitumor, antihypertensive, and anti-inflammatory activities [19–28]. Because of the potential bioactivity of pyridines and pyrimidines, we designed 20 compounds, **3a–j** and **6a–j**, including these groups, which are listed in Schemes 1 and 2.

The compound **2** or **5** could be converted into the target molecule **3** or **6** by simple aminolysis. We first attempted this aminolysis reaction in the conventional heating condition. The mixture must be refluxed in THF or toluene for 24 h to give an acceptable yield. The product could crystallize from the solution. After a simple recrystallization, we got 20 pure products (**3a–j** and **6a–j**) (Table 1).

To improve the reaction condition, we attempted to use MAOC. When compound **2** or **5** reacted with amines under the condition of MAOC, the reaction was accomplished within only 30 min and gave similar product yields from the former condition. Table 1 lists the reaction time and product yields of different derivatives in the two different reaction conditions. We can see that the aminolysis process can be treated under either conventional heating or MAOC. Yet performing the process under MAOC, the reaction can be completed in much less time.



SCHEME 1



SCHEME 2

Structures of the Products

The structures of all the 1,3,4-thiadiazol-2-yl ureas were confirmed by elemental analysis, ^{1}H NMR, and ESI-MS. One structure of the products, compound **6h**, was confirmed by X-ray. Single-crystal structure of 1-(2-chloropyridin-3-yl)-3-(5-(trifluoromethyl)-1,3,4-thiadiazol-2-yl) urea (**6h**) was obtained by slow evaporation of an ethyl acetate solution. The crystal data, data collection, and refinement parameter for the compound are listed in Table 2. Data were collected with a crystal-clear detector, graphite monochromatized MoKα radiation ($\lambda = 0.71073$Å) being used. The structure was solved by direct methods, using the SHELXS-97 package and refined on F^2, using the data ($I > 2\sigma\ (I)$) by the full-matrix least-squares procedures using the SHELXL-97 package.

TABLE 1 Preparation of the Title Compounds (**3, 6**)

		Conventional Heating		*Microwave Irradiation*	
Entry	*Compound*	*Time (h)*	*Yield (%)*	*Time (min)*	*Yield (%)*
1	**3a**	24	87.0	30	86.0
2	**3b**	24	80.2	30	83.3
3	**3c**	24	80.0	30	84.1
4	**3d**	24	85.0	30	91.7
5	**3e**	24	76.5	30	80.5
6	**3f**	24	80.3	30	81.5
7	**3g**	24	85.5	30	91.1
8	**3h**	24	83.3	30	86.1
9	**3i**	24	82.7	30	83.7
10	**3j**	24	85.6	30	87.5
11	**6a**	24	55.3	30	56.4
12	**6b**	24	56.3	30	55.0
13	**6c**	24	60.0	30	61.8
14	**6d**	24	55.7	30	58.2
15	**6e**	24	56.0	30	58.2
16	**6f**	24	85.3	30	86.4
17	**6g**	24	80.0	30	79.5
18	**6h**	24	57.3	30	58.9
19	**6i**	24	63.2	30	66.7
20	**6j**	24	57.0	30	58.1

TABLE 2 Crystallographic Data for Compound **6h**

Empirical formula	$C_9H_5ClF_3N_5OS$
CCDC deposit no.	293781
Color	Colorless
Crystal size (mm)	0.24 × 0.20 × 0.18
Crystal system	Monoclinic
Space group	*P*2(1)/*c*
Unit-cell dimensions (Å)	8.642 (2)
a (Å)	7.7641 (17)
b (Å)	17.923 (4)
c (Å)	90
α (deg)	100.953 (4)
β (deg)	90
γ (deg)	1180.7 (5)
Volume (Å^3)	4
Z	323.69
Formula weight	1.821
Density (calcd.) (mg/m^3)	0.543
Absorption coefficient (mm^{-1})	648
F(000)	SMART CCD 1000
Diffractometer scan wavelength (Å)	0.71070
Temperature (K)	113 (2)
θRange for data collection (deg)	2.31–27.88
Index ranges	$-10 <= h <= 11$, $-10 <= k <= 10$, $-20 <= l <= 23$ 14282
No. of data collected	14,282
No. of unique data	2,820
No. of refined parameters	191
Absorption correction	Semiempirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters Goodness-of-fit on F^2	2820/0/191
Final *R* indices [$I > 2\sigma(I)$]	1.065
R indices (all data)	$R1 = 0.0272$
Largest diff. peak and hole (e Å^3)	$wR2 = 0.0735$
	$R1 = 0.0357$
	$wR2 = 0.0769$
	0.331/−0.282

The crystal structure of **6h** is shown in Figs. 1 and 2. Figure 1 is a perspective view of the compound showing the atomic numbering scheme, whereas Fig. 2 is the unit cell of complex **6h**. All no hydrogen atoms were refined anisotropically. Hydrogen atoms were located from difference maps and then added geometrically, refined isotropically with a riding model. The fractional coordinates of non-hydrogen atoms and equivalent isotropic thermal parameters are given in Table 3, and selected bond

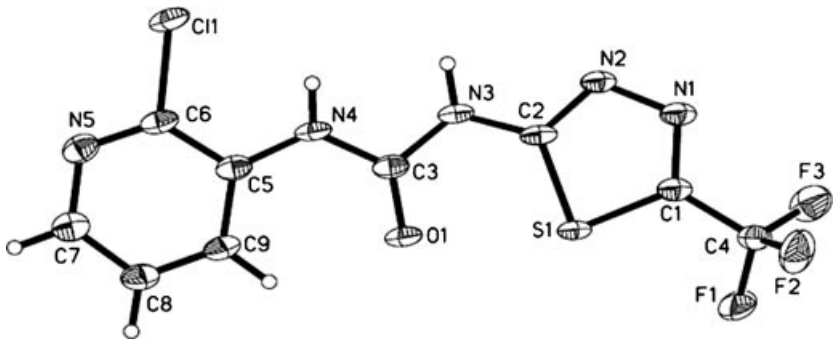


FIGURE 1 The molecular structure of complex **6h**.

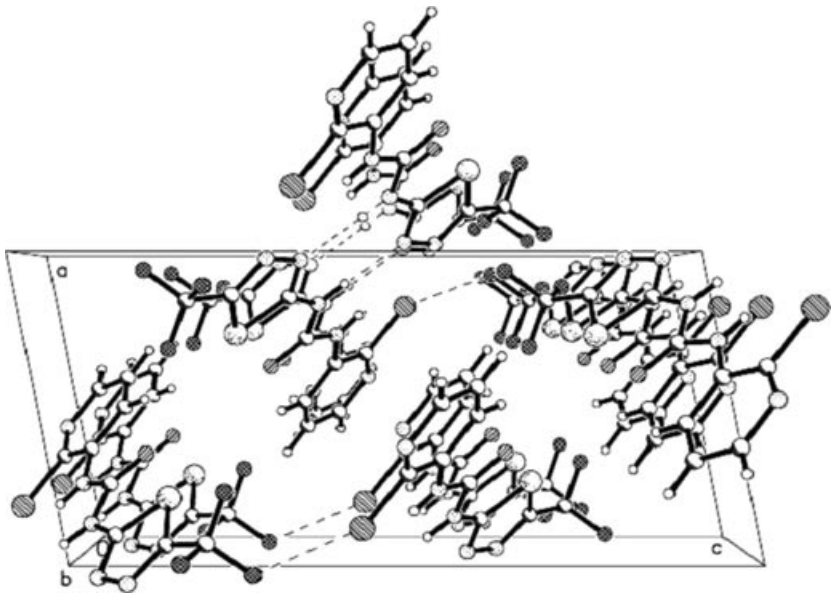


FIGURE 2 The unit cell of complex **6h**.

lengths and angles are listed in Table 4. The bond length of C(3)–N(4)[1.3696(18) Å] is shorter than that of C(5)–N(4)[1.3983(19) Å] that is closed to the value of C(3)–O(1)[1.2172(15) Å] and C(3)–N(3)[1.3796(18) Å] bond. Similarly, the bond length of C(2)–N(3)[1.3605(18) Å] is shorter than that of C(5)–N(4)[1.3983(19) Å] that is closed to the thiadiazol ring.

In summary, we have synthesized twenty 1-(substituted)-3-(5-(substituted)-1,3,4-thiadiazol-2-yl) urea derivatives, using a simple efficient procedure from the heterocyclic amino compounds and phenyl-5-(substituted)-1,3,4-thiadiazol-2-yl-carbamate under solvent conditions. The reaction can be realized in similar yield under conventional heating condition or MAOC condition. In addition,

TABLE 3 Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($10^3 Å^2$) for Compound **6h**

Atom	*x*	*y*	*z*	*U (equiv)*
Cl (1)	1779 (1)	−1557 (1)	−598 (1)	31 (1)
S (1)	2620 (1)	5974 (1)	1900 (1)	22 (1)
F (1)	3039 (1)	9279 (2)	2773 (1)	59 (1)
F (2)	660 (1)	8872 (1)	2910 (1)	43 (1)
F (3)	1144 (1)	10679 (1)	2092 (1)	45 (1)
O (1)	3728 (1)	2867 (1)	1567 (1)	27 (1)
N (1)	286 (1)	7803 (2)	1218 (1)	26 (1)
N (2)	318 (1)	6376 (2)	769 (1)	24 (1)
N (3)	1682 (1)	3838 (2)	678 (1)	23 (1)
N (4)	2727 (1)	1193 (2)	525 (1)	25 (1)
N (5)	4231 (1)	3090 (2)	197 (1)	28 (1)
C (1)	1401 (2)	7751 (2)	1814 (1)	23 (1)
C (2)	1466 (2)	5316 (2)	1053 (1)	21 (1)
C (3)	2808 (2)	2634 (2)	972 (1)	23 (1)
C (4)	1572 (2)	9156 (2)	2397 (1)	29 (1)
C (5)	3706 (2)	253 (2)	649 (1)	23 (1)
C (6)	3397 (2)	−1667 (2)	154 (1)	24 (1)
C (7)	5488 (2)	−3218 (2)	769 (1)	28 (1)
C (8)	5899 (2)	−1906 (2)	1292 (1)	30 (1)
C (9)	5009 (2)	−414 (2)	1234 (1)	27 (1)

TABLE 4 Selected Bond Lengths and Bond Angles for Compound **6h**

Atoms	*Bond Lengths (Å)*	*Atoms*	*Bond Angels (deg)*
C(1)–C(6)	1.7500(14)	C(1)–S(1)–C(2)	85.24(7)
S(1)–C(1)	1.7249(15)	C(1)–N(1)–N(2)	111.26(11)
S(1)–C(2)	1.7274(13)	C(2)–N(2)–N(1)	112.14(11)
F(1)–C(4)	1.3212(16)	C(2)–N(3)–C(3)	122.47(12)
F(2)–C(4)	1.3386(17)	C(3)–N(4)–C(5)	126.90(12)
F(3)–C(4)	1.3261(18)	C(6)–N(5)–C(7)	117.44(13)
O(1)–C(3)	1.2172(15)	N(1)–C(1)–C(4)	120.76(13)
N(1)–C(1)	1.2959(17)	N(1)–C(1)–S(1)	116.40(11)
N(1)–N(2)	1.3723(17)	C(4)–C(1)–S(1)	122.82(10)
N(2)–C(2)	1.3144(17)	N(2)–C(2)–N(3)	120.12(12)
N(3)–C(2)	1.3605(18)	N(2)–C(2)–S(1)	114.96(11)
N(3)–C(3)	1.3796(18)	N(3)–C(2)–S(1)	124.92(11)
N(3)–H(1)	0.880(17)	O(1)–C(3)–N(4)	125.93(13)
N(4)–C(3)	1.3696(18)	O(1)–C(3)–N(3)	121.95(13)
N(4)–C(5)	1.3983(19)	N(4)–C(3)–N(3)	112.11(11)
N(5)–C(6)	1.313(2)	F(1)–C(4)–F(3)	108.10(13)
N(5)–C(7)	1.3479(19)	F(1)–C(4)–F(2)	107.20(12)
C(1)–C(4)	1.499(2)	F(3)–C(4)–F(2)	106.00(12)
C(5)–C(9)	1.3907(19)	F(1)–C(4)–C(1)	111.47(12)
C(5)–C(6)	1.404(2)	F(3)–C(4)–C(1)	112.25(12)
C(7)–C(8)	1.385(2)	F(2)–C(4)–C(1)	111.52(13)
C(8)–C(9)	1.384(2)	C(9)–C(5)–N(4)	124.80(13)
		C(9)–C(5)–C(6)	115.83(14)
		N(4)–C(5)–C(6)	119.37(12)
		N(5)–C(6)–C(5)	125.73(13)
		N(5)–C(6)–C(1)	115.81(11)
		C(5)–C(6)–C(1)	118.46(12)
		N(5)–C(7)–C(8)	121.76(14)
		C(9)–C(8)–C(7)	119.86(14)
		C(8)–C(9)–C(5)	119.37(14)

the MAOC allows us to obtain target compounds in relative good yields within a short time. The bioactivity studies of these compounds are under way.

EXPERIMENTAL

Microwave irradiation is initiator 8 (Biotage). Melting points were determined using Yanaco MP-500 apparatus and were incorrect. Nuclear magnetic resonance spectra were recorded on Varian Mercury Plus 400 NMR and Bruker AVANCE-300 NMR instrument in $(CD_3)_2SO$. Tetramethylsilane (TMS) was used as an internal standard for ^1H NMR spectroscopy. Elemental analysis was carried out on a Yana MT-3 instrument.

*5-(Pyridin-3-yl)-1,3,4-thiadiazol-2-amine (**1**)*

$POCl_3$ of 138 g (0.9 mole, 3 equiv) was added slowly to the ice-bathed mixture of 37 g (0.3 mole, 1 equiv) of nicotinic acid, 27.3 g (0.3 mole, 1 equiv) of thiosemicarbazide, and 180 mL 1,4-dioxane. The mixture was then heated to and held at a temperature of about 120°C for about 5 h. Then the mixture was poured into 1 L ice water. Fifty percent of NaOH solution was added until the solution became basic. Yellow solid precipitated and was filtered off, washed with water, and air-dried. The dried solid was recrystallized from aqueous ethanol to yield yellow products as 5-(pyridin-3-yl)-1,3,4-thiadiazol-2-amine in 63.5% yield. mp 232–233°C, ^1H NMR: [300 MHz] δ: 8.944(d, $J = 2.1$ Hz, 1H), 8.622–8.602 (m, 1H), 8.157–8.125 (m, 1H), 7.548 (s, 2H, NH), 7.523–7.481(m, 1H); ESI-MS: (M^+) $m/z(\%) = 179.36(100)$.

*Phenyl-5-(pyridin-3-yl)-1,3,4-thiadiazol-2-ylcarbamate (**2**)*

NaH (8.1 g, 0.337 mole, 3 equiv) in anhydrous THF (300 mL) was slowly added to an ice-bathed solution of 5-(pyridin-3-yl)-1,3,4-thiadiazol-2-amine (**1**) (20 g, 0.112 mol, 1 equiv). The mixture was stirred for 2 h. Then the diphenyl carbonate (29 g, 0.134 mol, 1.2 equiv) was added to the flask. The resulting mixture was stirred at 0°C for 30 min and then warmed to room temperature and stirred for additional 2 days. About 300 mL of ethyl acetate was then added. The

organic layer was wash with saturated salt water and dried by anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure, and the residue was subjected to chromatography on silica gel using ethyl acetate/methanol (20:1) as eluent. The yield was 70.5%. ^{1}H NMR [300M Hz] δ: 13.013 (s, 1H, NH), 9.081 (s, 1H), 8.075 (s, 1H), 8.295–8.275 (m, 1H), 7.544–7.524 (t, $J = 4.0$ Hz, 1H), 7.433 (d, $J = 7.2$ Hz, 2H), 7.278 (d, $J = 7.6$ Hz, 2H). ESI-MS: (M^+) m/z (%) = 297.3 (100).

*2-Amino-5-trifluoromethyl-1,3,4-thiadiazole (**4**)*

Trifluoroacetic acid of 114.02 g (0.73 mole) was added to 47.42 g (0.52 mol) of thiosemicarbazide in 135 g of polyphosphoric acid. The mixture was heated to and held at a temperature of about 110°C for about 8 h. It was then poured into 1 kg of ice. The yellow solid was filtered off, washed with water, and air-dried. The dried solid was recrystallized from aqueous ethanol to yield yellow product as 2-amino-5-trifluoromethyl-1,3,4-thiadiazole [5] in 63.2% yield. mp 230–232°C, ESI-MS: (M^+) m/z(%) = 168.37.

*Phenyl 5-(trifluoromethyl)-1,3,4-thiadiazol-2-ylcarbamate (**5**)*

5-(Trifluoromethyl)-1,3,4-thiadiazol-2-amine (**4**) was dissolved in 60 mL dry THF and added to 6 g (0.355 mol, 3 equiv) of NaH in 25 mL of dry THF under ice-bath. Then diphenyl carbonate was added to the flask slowly under ice-bath. After 2 days, it was then poured onto 250 mL filler. Ethyl acetate of 60 mL was added. The organic layer was washed with saturated salt water and dried by anhydrous Na_2SO_4. The solvent was evaporated at reduced pressure, and the residue was subjected to chromatography on silica gel, using petroleum ether/ethyl acetate (1:1) as eluent. The yield was 61.3%. ^{1}H NMR [400 MHz] δ: 7.401–7.362 (t, $J = 7.8$ Hz, 2H), 7.218 (d, $J = 7.2$ Hz, 1H), 7.182–7.160 (t, $J = 4.4$ Hz, 2H); ESI-MS: (M^+) m/z (%) = 288.06(100).

*General Procedure for the Synthesis of 1-(Substituted)-3-(5-(substituted)-1,3,4 -thiadiazol-2-yl) Urea Derivatives (**6a–j** and **3a–j**)*

General Procedure

Method A. A mixture of equimolar amounts (1 equiv) of either **2** or **5** and heterocyclic amino compounds (2 equiv) in toluene or THF (15 mL), was oil-heated under reflux for 24 h. When the solution was cooled at room temperature, many precipitated solid products were deposited from the solvent, which were filtered off, dried, and crystallized from the appropriate solvents.

Method B. A mixture of equimolar amounts (1 equiv) of either **2** or **5** and heterocyclic amino compounds (2 equiv) in toluene or THF (15 mL) was treated in a microwave synthetic reactor under these reaction conditions: The temperature was 150°C, the absorption level was normal, and the reaction time was 30 min. When the solution was cooled at room temperature, many precipitated solid products were deposited from the solvent. After the yellow solvent was removed under reduced pressure, the residue was gained and washed with ethanol. The residue was recrystallized from the appropriate solvents to yield a pure product as solid.

3a: White solid, yield 86%, mp >300°C, ^{1}H NMR (400 MHz) δ: 10.018 (s, 1H, NH), 9.094 (d, $J = 1.6$ Hz, 1H), 8.680–8.665 (m, $J = 2.0$ Hz, 1H), 8.348–8.296 (m, $J = 5.6$ Hz, 2H), 7.843–7.800 (m, $J = 3.3$ Hz, 1H), 7.561–7.530 (m, $J = 4.0$ Hz, 2H), 7.124–7.033 (m, 1H). ESI-MS (M^-) m/z (%): 297 (100), 298.2 (20); Anal. Calcd. for $C_{13}H_{10}N_6OS$. (298.3): C, 52.34; H, 3.38; N, 28.17. Found: C, 52.32; H, 3.48; N, 28.17.

3b: White solid, yield 86%, mp >300°C, ^{1}H NMR (400 MHz) δ: 12.674 (s, 1H, NH), 9.992 (s, 1H), 9.075 (s, 1H), 8.659 (s, 1H), 8.283 (d, J = 6.4 Hz, 1H), 7.698–7.662 (m, $J = 4.8$ Hz, 1H), 7.533 (d, $J = 4.0$ Hz, 1H), 7.287 (d, $J = 2.8$ Hz, 1H), 6.948 (d, $J = 6.8$ Hz, 1H), 2.433 (s, 3H). ESI-MS (M^-) m/z (%): 313.2 (100), 314.2 (15); Anal. Calcd. for $C_{14}H_{12}N_6OS$. (312.3): C, 53.83; H, 3.87; N, 26.91. Found: C, 53.82; H, 3.80; N, 26.89.

3c: White solid, yield 84%, mp >300°C, ^{1}H NMR (400 MHz) δ: 9.893 (d, $J = 3.6$ Hz, 1H), 9.088 (s, 1H), 8.674–7.665 (m, $J = 1.8$ Hz, 1H), 8.309–8.288 (t, $J = 4.2$ Hz, 1H), 8.168 (s, 1H), 7.658–7.637 (m, 1H), 7.555–7.475 (m, 2H), 2.234 (s, 3H). ESI-MS: (M^-) m/z (%) = 313 (100); Anal. Calcd. for $C_{14}H_{12}N_6OS$. (312.3): C, 53.83; H, 3.87; N, 26.91. Found: C, 53.89; H,3.99; N, 26.83.

3d: White solid, yield 92%, mp >300°C, ^{1}H NMR (300 MHz) δ: 10.017 (s, 1H), 9.087 (s, 1H), 8.672 (d, $J = 4.8$ Hz, 1H), 8.312–8.289 (m, $J = 3.8$ Hz, 1H), 8.198 (d, $J = 4.8$ Hz, 1H), 7.558–7.528 (m, 1H), 7.313 (s, 1H), 6.954 (d, $J = 5.2$ Hz, 1H), 2.305 (s, 3H); ESI-MS: (M^-) m/z(%) = 312 (100); Anal. Calcd. for $C_{14}H_{12}N_6OS$. (312.3): C, 53.83; H, 3.87; N, 26.91. Found: C, 53.61; H, 3.85; N, 26.90.

3e: White solid, yield 81%, mp >300°C, ^{1}H NMR (400 MHz) δ: 11.107 (s, 1H, NH), 9.064 (s, 1H), 8.957 (s, 1H), 8.659 (d, $J = 4.4$ Hz, 1H), 8.263 (d, $J = 8.0$

Hz, 1H), 7.546–7.514 (m, $J = 4.3$ Hz, 1H), 7.358 (d, $J = 8.0$ Hz, 2H), 7.109 (d, $J = 8.0$ Hz, 2H), 2.231 (s, 3H, CH_3); ESI-MS: (M^-) m/z (%) = 312.0 (100).

3f: White solid, yield 82%, mp >300°C, ^{1}H NMR (400 MHz) δ: 11.912 (s, 1H, NH), 9.890 (s, 1H), 8.667 (s, 1H), 8.443 (s, 1H), 8.287 (d, $J = 6.8$ Hz, 1H), 8.019 (d, $J = 8.4$ Hz, 1H), 7.707 (d, $J = 8.8$ Hz, 1H), 7.541 (d, $J = 4$ Hz, 1H). ESI-MS (M^-) m/z (%): 375.3(100), 376.1(96), 378.1(50); Anal. Calcd. for $C_{13}H_9BrN_6OS$. (377.2): C, 41.39; H, 2.40; N, 22.28. Found: C, 41.43; H, 2.63; N, 22.41.

3g: White solid, yield 91%, mp >300°C, ^{1}H NMR (400 MHz) δ: 11.835 (s, 1H, NH), 9.888 (s, 1H), 9.087 (s, 1H), 8.675 (d, $J = 3.6$ Hz, 1H), 8.384 (d, $J = 1.6$ Hz, 1H), 8.298 (d, $J = 8.0$ Hz, 1H), 7.943–7.916 (m, 1H), 7.746 (d, $J = 8.4$ Hz, 1H), 7.560–7.529 (m, $J = 4.4$ Hz, 1H); ESI-MS (M^-) m/z (%): 330.4 (100), 332.4 (30); Anal. Calcd. for $C_{13}H_9ClN_6OS$ (332.8): C, 46.92; H, 2.73; N, 25.25; Found: C, 46.80; H, 2.97; N, 25.37.

3h: White solid, yield 86%, mp >300°C, ^{1}H NMR (400 MHz) δ (ppm): 11.871 (s, 1H, NH), 9.084 (s, 1H), 8.885 (s, 1H), 8.684 (d, $J = 4.4$ Hz, 1H), 8.493 (d, $J = 8.0$ Hz, 1H), 8.290 (d, $J = 8.0$ Hz, 1H), 8.127 (d, $J = 4.4$ Hz, 1H), 7.559–7.528 (m, $J = 4.1$ Hz, 1H), 7.459–7.427 (m, $J = 4.4$ Hz, 1H). ESI-MS (M^-) m/z (%): 331.3 (100), 333.2 (35). Anal. Calcd. for $C_{13}H_9ClN_6OS$ (332.8): C, 46.92; H, 2.73; N, 25.25; Found: C, 47.05; H, 2.78; N, 24.82.

3i: White solid, yield 84%, mp >300°C, ^{1}H NMR (400 MHz) δ: 11.835 (s, 1H, NH), 9.888 (s, 1H), 9.087 (s, 1H), 8.675 (d, $J = 3.6$ Hz, 1H), 8.384 (d, $J = 1.6$ Hz, 1H), 8.298 (d, $J = 8.0$ Hz, 1H), 7.943–7.916 (m, 1H), 7.746 (d, $J = 8.4$ Hz, 1H), 7.560–7.529 (m, $J = 4.4$ Hz, 1H); ESI-MS (M^+) m/z (%): 330.4 (100), 332.4 (30).

3j: White solid, yield 88%, mp >300°C. ^{1}H NMR [400 MHz] δ: 11.268 (s, 1H, NH), 9.237 (s, 1H), 9.006 (s, 1H), 8.668 (t, $J = 2.2$ Hz, 1H), 8.264 (t, $J = 3.8$ Hz, 1H), 7.553–7.521 (m, $J = 4.3$ Hz, 1H), 7.472 (s, 4H); ESI-MS (M^-) m/z (%): 374.5 (85), 376.4 (100), 377.3 (20).

6a: White solid, yield 56%, mp 225–227°C; ^{1}H NMR (400 MHz) δ: 12.859 (s, 1H, NH), 10.123 (s, 1H, NH), 8.35 (d, $J = 4$ Hz, 1H), 7.861–7.817 (m, 1H), 7.528 (d, $J = 8.4$ Hz, 1H), 7.149–7.118 (t, $J = 6.2$ Hz, 1H); ESI-MS: (M^-) m/z (%) = 287 (100); Anal. Calcd. for $C_9H_6F_3N_5OS$. (289.2): C, 37.37; H, 2.09; N, 24.21; Found: C, 37.27; H, 2.11; N, 24.25.

6b: White solid, yield 35%, mp 238–240°C; ^{1}H NMR [300 MHz] δ: 13.056 (s, 1H, NH), 10.130 (s, 1H, NH), 7.746 (t, $J = 10.6$ Hz, 1H), 7.330 (d, $J = 11.2$ Hz, 1H), 7.016 (d, $J = 10.0$ Hz, 1H), 2.476 (s, 3H, $-CH_3$). ESI-MS: (M^-) m/z (%) = 302 (100); Anal. Calcd. for $C_{10}H_8F_3N_5OS$. (303.3): C, 39.6; H, 2.66; N, 23.09; Found: C, 39.77; H, 2.51; N, 23.13.

6c: White solid, yield 62%, mp 234–236°C; ^{1}H NMR (300 MHz) δ: 12.864 (s, 1H, NH), 10.037 (s, 1H, NH), 8.202 (s, 1H), 7.712–7.677 (m, 1H), 7.467 (d, $J = 11.2$ Hz, 1H), 2.267 (s, 3H, $-CH_3$). ESI-MS: (M^-) m/z (%) = 301(100); Anal. Calcd. for $C_{10}H_8F_3N_5OS$. (303.3): C, 39.6; H, 2.66; N, 23.09; Found: C, 39.50; H, 2.72; N, 23.13.

6d: White solid, yield 58%, mp 250–252°C. ^{1}H NMR (300 MHz) δ: 13.065 (s, 1H, NH), 10.148 (s, 1H, NH), 8.233 (d, $J = 7.2$ Hz, 1H), 7.334 (s, 1H), 7.006 (d, $J = 6.8$ Hz, 1H), 2.339 (s, 3H, $-CH_3$). ESI-MS: (M^-) m/z (%) = 301(100); Anal. Calcd for $C_{10}H_8F_3N_5OS$. (303.3): C, 39.6; H, 2.66; N, 23.09; Found: C, 40.06; H, 2.61; N, 23.11.

6e: White solid, yield 58%, mp 238–240°C. ^{1}H NMR (300 MHz) δ: 11.63 (s, 1H, NH), 9.084 (s, 1H, NH), 7.381 (d, $J = 6.8$ Hz, 2H), 7.154 (d, $J = 11.2$ Hz, 2H), 2.270 (s, 3H, $-CH_3$). ESI-MS: (M^-) m/z (%) = 301(100); Anal. Calcd. for $C_{11}H_9F_3N_4OS$. (302.3): C, 43.71; H, 3.00; N, 18.54; Found: C, 43.61; H, 2.90; N, 18.82.

6f: White solid, yield 86%, mp 258–260°C, ^{1}H NMR [400 MHz] δ: 12.224 (s, 1H, NH), 9.936 (s, 1H, NH), 8.447 (s, 1H), 8.027 (d, $J = 8.4$ Hz, 1H), 7.695 (d, $J = 8.4$ Hz, 1H). ESI-MS (M^-) m/z (%): 365 (100), 368 (85); Anal. Calcd. for $C_9H_5BrF_3N_5OS$. (368.1): C, 29.36; H,1.37; N, 19.02; Found: C, 29.57; H, 1.57; N, 19.10.

6g: White solid, yield 80%, mp 262–265°C, ^{1}H NMR [400 MHz] δ: 12.178 (s, 1H, NH), 9.945 (s, 1H, NH), 8.383 (s, 1H), 7.938 (d, $J = 8.8$ Hz, 1H), 7.732 (d, $J = 8.8$ Hz, 1H). ESI-MS: (M^-) m/z (%) = 323(100); Anal. Calcd. for $C_9H_5ClF_3N_5OS$. (323.7): C, 33.40; H, 1.56; N, 21.64; Found: C, 33.39; H, 1.72; N, 21.56.

6h: White solid, yield 59%, mp 242–245°C. ^{1}H NMR (300 MHz) δ: 12.286 (s, 1H, NH), 8.965 (s, 1H, NH), 8.465 (d, $J = 10.8$ Hz, 1H), 8.165 (d, $J = 4.8$ Hz, 1H), 7.488–7.446 (m, $J = 5.3$ Hz, 1H). ESI-MS: (M^-) m/z (%) = 322 (100); Anal. Calcd. for $C_9H_5ClF_3N_5OS$. (323.7): C, 33.40; H, 1.56; N, 21.64; Found: C, 33.59; H, 1.42; N, 21.41.

6i: White solid, yield 67%, mp 240–241°C. ^{1}H NMR (300 MHz_ δ: 13.365 (s, 1H, NH), 11.249 (s, 1H, NH), 8.792 (d, $J = 6.8$ Hz, 2H), 7.302–7.270 (t, $J = 6.4$ Hz, 1H). ESI-MS: (M^-) m/z (%) = 289(100); Anal. Calcd. for $C_8H_5F_3N_6OS$. (290.0): C, 33.11; H, 1.74; N, 28.96; Found: C, 32.95; H, 1.93; N, 28.90.

6j: White solid, yield 28%, mp 248–250°C, ^{1}H NMR (300 MHz) δ: 11.778 (s, 1H, NH), 9.330 (s, 1H, NH), 7.507–7.444 (q, $J = 11.2$ Hz, 4H); ESI-MS: (M^+) m/z (%) = 368(100); Anal. Calcd. for $C_{10}H_6BrF_3N_4OS$. (367.1): C, 32.71; H, 1.65; N, 15.26; Found: C, 32.81; H, 1.60; N, 15.19.

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