A Simple and Convenient Method for the Synthesis of 3,5-disubstituted 1,2,4-thiadiazoles via Oxidative Dimerization of Primary Thioamides

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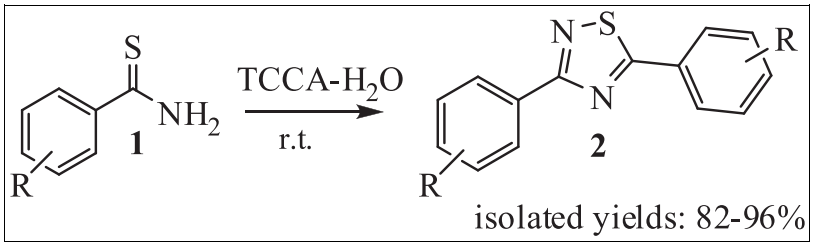

A simple and efficient protocol has been developed for the preparation of 3,5-diaryl-1,2,4-thiadiazoles in high yields through the oxidative dimerization of primary thioamides in aqueous medium at room temperature.

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INTRODUCTION

Nitrogen-containing ring systems are present in widely bioactive natural and synthetic products. The synthesis of the 1,2,4-thiadiazole ring has been the subject of considerable interest as several derivatives of this heterocyclic unit have been found in several natural products to possess useful bilogical activities [1]. Although, currently, the only commercial 1,2,4-thiadiazole drug is the antibiotic cefozopran [2], there are a number of derivatives related to this system often endowed with a wide range of biological activities such as for treatment of human leukemmia cell [3], acetylcholinesterase inhibitory activity [4], G-protein-coupled receptors [5], cardiovascular system [6], central nervous system [4], inflammation [7], or antibiotic activity [8]. In addition to their use as pharmacophores, thiadiazoles are used as thiol trapping agents [9] and the first non-adenosine triphosphate (ATP) competitive glycogen synthase kinase 3β inhibitors [10]. The development of mild and effective methods for the synthesis of symmetrically 3,5-disubstituted 1,2,4-thiadiazoles is thus important in organic synthesis.

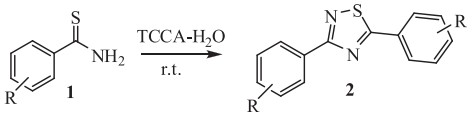
Thioamides are widely used as versatile building blocks in organic synthesis and especially in the construction of heterocyclic compounds [11]. They have been used as important synthons in the synthesis of five, and six-membered heterocycles [12]. Among them, primary thioamides are good intermediates for the synthesis of wide variety of thiazole and thiadiazole derivatives [13]. Traditional methods utilized for the synthesis of 3,5-diaryl-1,2,4-thiadiazoles may be broadly divided into three categories, which include intramolecular cyclization, intermolecular cyclization of two different molecules, and oxidative dimerization of thioamides. 3,5-Unsymmetrically disubstituted 1,2,4-thiadiazoles have generally been synthesized by intramolecular oxidative cyclization of amidinithioureas [14] and 1,3-dipolar cycloaddition of nitrile sulfides to nitriles [15]. The most common approach to the synthesis of 1,2,4-thiadiazoles involves the oxidative dimerization of primary thioamides by using different oxidizing reagents, such as nitrous acid [16], *t*-butyl hypochlorite [17], *N*-bromosuccinimide [18], dimethyl sulfoxide-electrophilic reagents [19], organohypervalent iodine reagents [20], 2,3-dichloro-5,6-dicyano-*p*-benzoquinone [21], polymer-supported diaryl selenoxide and telluroxide [22], Oxone [23]. However, some of these methods are not quite satisfactory in view of using large excess of reagents, long reaction times, harsh reaction conditions, and the formation of nitriles and isothiocyanates as byproducts [24]. Consequently, there is a need to develop a convenient, rapid, and enironmentally friendly method for the synthesis of these important heterocyclic compounds.

RESULTS AND DISCUSSION

In recent years, trichloroisocyanuric acid (1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione, TCCA) is used widely as an industrial disinfectant, bleaching agent, and innocuous oxidant with high stability. TCCA has been employed in various organic transformations [25] that include oxidation of alcohols to their corresponding carbonyl compounds, conversion of alcohols into alkyl halides, dihalogenation of olefins, and halogenation because of its ready availability, inexpensive, and environmentally benign nature. Herein, we wish to report an efficient and practical method by employing TCCA-water as a new promoter system for the one-pot synthesis of 3,5-diaryl-1,2,4-thiadiazoles from arylthioamides as shown in

Scheme 1. The protocol affords a potential route for the access of the target products with wide substrate scope. However, to the best of our knowledge, there is no report on the oxidative dimerization of thioamides to 1,2,4-thiadiazoles with TCCA as catalyst.

Scheme 1

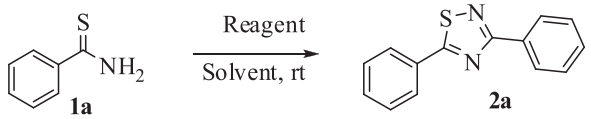


The development of environmentally friendly protocols is very important in chemical research at present, with water emerging as a useful solvent for organic chemistry in recent years [26]. Water is an abundant, inexpensive, and environmentally friendly solvent but also exhibits new reactivity and selectivity, which is different from that of conventional organic solvents [27]. Therefore, we first investigated the optimization of the reaction conditions using thiobenzamide as a model substrate, and the role of various conditions on the reaction system with respect to reagents, appropriate solvents, temperature, and the molar ratio was carried out (Table 1).

Among the various organic solvents studied (EtOH, MeOH, CH_3CN, PEG-400, *N*,*N*-dimethyacetamide, and water), water was found to be the most suitable solvent for this reaction. We found that the optimum ratio of thioamide/TCCA/water is about 1:0.3:5 (Table 1, entry 8). Further investigations revealed that reducing the loading of TCCA to 0.25 equiv gave the desired product in a lower yield of 75% (Table 1, entry 6). The use of 5.0 equiv of H_2O was also found to be necessary for this transformation to proceed smoothly; when H_2O was reduced to 2.5 equiv, a slightly lower yield of 68% product was obtained (Table 1, entry 5). In the similar category, its bromo analog, namely, tribrimoisocyanuric acid, has also been found to be an effective oxidant for this purpose (Table 1, entries 1 and 2). The experiments were run from 0 to 25°C. We found that those conducted at room temperature (23–25°C) were obtained in high yields, whereas at 0°C led to a reduced yield of the product. Under the optimized reaction conditions, we examined the substrate scope for the present oxidative dimerization using 0.3 mmol of TCCA. Various types of primary thioamides including aromatic, heterocyclic, and aliphatic ones could be converted into the corresponding 3,5-disubstituted 1,2,4-thiadiazoles in high

Table 1

Optimization of reagents and reaction conditions.[a]

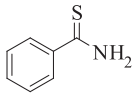
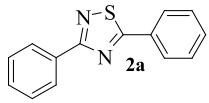
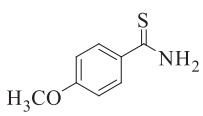
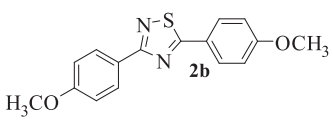


Entry	Reagent (equiv)	Solvent[b]	Time (min)	Yield (%)[c]
1.	TCCA (0.1)	MeOH	2	72
2.	TBCA (0.1)	MeOH	6	74
3.	TCCA (0.2)	EtOH	4	81
4.	TBCA (0.2)	CH_3CN	5	83
5.	TCCA (0.25)	H_2O	8	68
6.	TCCA (0.25)	EtOH	2	75,68[d]
7.	TCCA (0.3)	H_2O	8	81
8.[e]	TCCA (0.3)	PEG-400	2	95,76[f]
9.	TCCA (0.3)	*N*,*N*-Dimenthyl acetamide	10	84
10.	TCCA (0.3)		10	78

TCCA, 1,3,5-trichloro-1,3,5-triazinane-2,4,6-trione; TBCA, tribrimoisocyanuric acid.
[a]Reactions were carried out on a 5-mmol scale in water at room temperature with TCCA/TBCA.
[b]2 mL
[c]Isolated yield after column chromatography.
[d]Reaction was performed at 0°C.
[e]Optimum reaction conditions.
[f]2.5 equiv of H_2O used.

Table 2

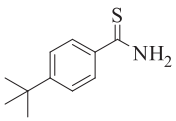
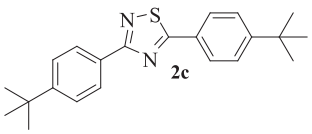
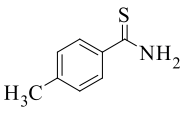
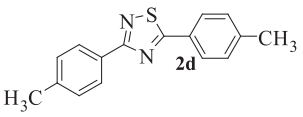
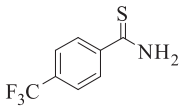
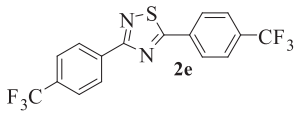
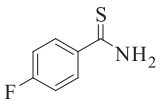
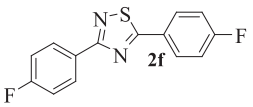
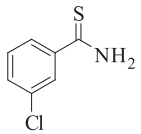
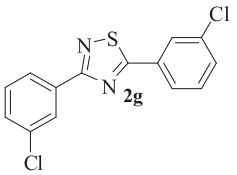
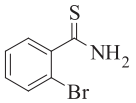
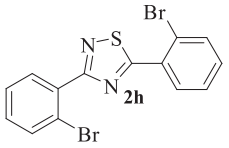
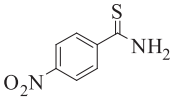
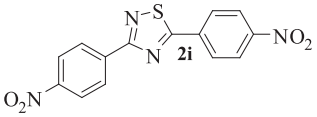
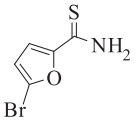
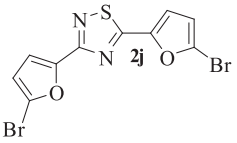
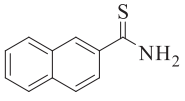
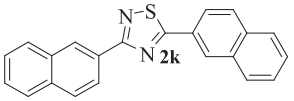
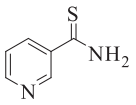
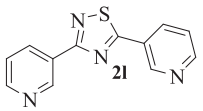
Oxidative dimerization of thioamides to symmetrically 3,5-disubstituted 1,2,4-thiadiazoles.[a]

Entry	Thioamide (1)	Time (min)[b]	Product (2)	mp °C (lit)	Yield (%)[c]
1.		4		90–91 (lit. [18] 89–90)	92
2.		2		137–138 (lit. [18] 139–140)	96

(*Continued*)

Table 2

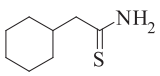
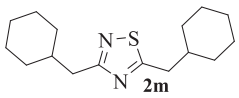
(*Continued*)

Entry	Thioamide (1)	Time (min)[b]	Product (2)	mp °C (lit)	Yield (%)[c]
3.		8	 **2c**	91–92	95
4.		6	 **2d**	129–130 (lit. [18] 135–137)	93
5.		2	 **2e**	80–81	91
6.		2	 **2f**	185–186	90
7.		4	 **2g**	125–127	88
8.		4	 **2h**	97–98	90
9.		8	 **2i**	201–202 (lit. [16] 198–199)	86
10.		4	 **2j**	185–186	89
11.		4	 **2k**	179–180 (lit. [28] 180–180.5)	92
12.		8	 **2l**	132–134 (lit. [16] 136–137)	87

(*Continued*)

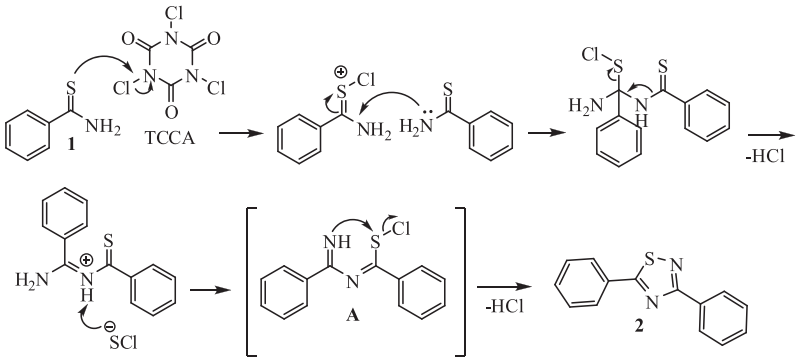
Table 2

(*Continued*)

Entry	Thioamide (1)	Time (min)[b]	Product (2)	mp °C (lit)	Yield (%)[c]
13.		14	 **2m**	—	82

mp, melting point.
[a]All products were characterized by mp's, ^{1}H and ^{13}C NMR, and mass spectral data.
[b]The reaction times were optimized after several experiments.
[c]Yields refer to pure isolated products.

Scheme 2



yields; the results are summarized in Table 2. The experimental procedure for this conversion is straightforward and does not require the use of toxic organic solvents or inert atmosphere. Thiobenzamide derivatives, which contain eletron-donating as well as electron-withdrawing substituents on the aromatic rings, efficiently proceeded to afford the corresponding 3,5-disubstituted 1,2,4-thiadiazoles in high yields without formation of nitriles and isothiocyanates as byproducts [1,24]. The results indicate that no remarkable electronic effects of the substituent on the aromatic ring were observed.

Based on the literature reports, we propose that a tentative mechanism for the condensation of two molecules of the arylthioamides **1** to give 3,5-disubstituted 1,2,4-thiadiazoles **2** via nucleophilic attack by sulfur of another molecule of thioamide gives the intermediate (**A**), which on further oxidation obtained the product (Scheme 2).

CONCLUSIONS

In conclusion, a facile and efficient method is described for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles by the oxidative dimerization of thiobenzamides using TCCA-water as readily available, inexpensive, short reaction times, safe, and environmentally benign oxidant under esentially mild conditions and this protocol should be of further interest in synthetic organic chemistry.

EXPERIMENTAL

Reagents and chemicals were obtained from commercial suppliers and used without further purification. Melting points were determined in open capillaries with a precision digital melting point Veego VMP-DS apparatus and are uncorrected. IR spectra were recorded on a thermo Nicolet Nexus 670 FT-IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker Avance 300 (Bruker, Germany; 300.132 MHz for ^{1}H, 75.473 for ^{13}C) or Varian FT-200 MHz (Gemini) spectrometer in $CDCl_3$. The chemicals shifts (δ) and coupling constants (J) quoted in hertz are reported in parts per million relative to tetramethylsilane ($\delta = 0.00$ ppm) (for ^{1}H) as an internal standard. The resonances of residual proton and those of carbons in deuterated solvents $CDCl_3$ ($\delta_H = 7.26$ ppm, $\delta_c = 77.0$ ppm)

and DMSO-d_6 ($\delta_H = 2.50$ ppm, $\delta_c = 39.52$ ppm) were used as internal standards. Elemental analyses were performed on an Elementar Vario EL microanalyzer. Low-resolution mass spectra (ESI-MS) and HRMS were recorded on Quattro LC, Micromass, and Q STAR XL, Applied Biosystems, respectively. Column chromatography was performed using silica gel (Acme's 60–120 mesh). Solvents for chromatography (*n*-hexane, acetonitrile, cyclohexane, and EtOAc) were distilled prior to use. For analytical thin-layer chromatography, Merck pre-coated silica gel 60 F-254 plates were used; the plates were visualized using UV light (254 nm) or iodine vapor or by dipping the plates in phosphomolybdic acid ceric (IV)sulfate-sulphuric acid (PMA) solution and heating the plates at 100 °C.

General procedure for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles [29]. To a stirred solution of arylthioamide (5.0 mmol) in water (0.5 mL) at room temperature was added TCCA (3.88 g, 1.67 mmol) in one portion. The color of the reaction solution changed to yellow at the beginning of the reaction and it was disappeared after few seconds. The reaction mixture was stirred magnetically at room temperature for the specified time (Table 1) until arylthioamide was completely disappeared (the progress of the reaction was monitored by thin-layer chromatography). After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 5 mL) followed by brine (5 mL). The organic layer was dried over anhy.Na_2SO_4 and concentrated under reduced pressure to give crude product, which was purified by silica gel column chromatography using petroleum ether and ethyl acetate (95:5) to afford analytically pure substituted thiadiazoles in 82–96% yield.

3,5-Diphenyl-1,2,4-thiadiazole (2a). White solid, mp 90–91°C (lit.[18] 89–90°C); IR (KBr) ν_{max}: 3045, 1590, 1475 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.45–8.38 (m, 2*H*), 8.12–8.04 (m, 2*H*), 7.60–7.48 (m, 6*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.0, 173.7, 132.8, 131.9, 130.6, 130.3, 129.2, 128.6, 128.3, 127.4; ESI MS: *m/z* 239 $[M+H]^+$. *Anal*. Calcd. for $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23; N, 11.76; S, 13.46. Found: C, 70.59; H, 4.24; N, 11.74; S, 13.44.

3,5-Bis(4-methoxyphenyl)-1,2,4-thiadiazole (2b). White solid, mp 137–138°C (lit.[18] 139–140°C); IR (KBr) ν_{max}: 2923, 2851, 1607, 1579, 1519, 1475, 1419, 1307, 1275, 1250, 1168, 1027 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.33 (d, *J* = 8.6 Hz, 2*H*), 7.98 (d, *J* = 8.6 Hz, 2*H*), 7.02 (d, *J* = 8.5 Hz, 4*H*), 3.89 (S, 6*H*); ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.3, 173.3, 162.4, 161.2, 129.8, 129.1, 126.0, 123.6, 114.5, 113.9, 55.5, 55.3. HRMS: Calcd. for $C_{16}H_{14}O_2N_2S = 299.0849$ $[M+H]^+$. Found: 299.0845. *Anal*. Calcd. for $C_{16}H_{14}O_2N_2S$: C, 63.98; H, 5.37; N, 9.33; S, 10.67. Found: C, 63.93; H, 5.36; N, 9.31; S, 10.69.

3,5-Bis(4-(t-butyl)phenyl)-1,2,4-thiadiazole (2c). White solid, mp 91–92°C; IR (KBr) ν_{max}: 2957, 2863, 1605, 1465, 1406, 1321, 1110, 839, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.32 (d, *J* = 8.6 Hz, 2*H*), 7.98 (d, *J* = 8.6 Hz, 2*H*), 7.61–7.46 (m, 4*H*), 1.39 (S, 18*H*); ^{13}C NMR (75 MHz, DMSO-d_6): δ 165.4, 152.2, 150.3, 140.75, 120.4, 111.0, 107.3, 56.5, 56.4, 53.0. HRMS: Calcd. for $C_{22}H_{26}N_2S = 351.1889$ $[M+H]^+$. Found: 351.1886.

3,5-Bis(4-methylphenyl)-1,2,4-thiadiazole (2d). White solid, mp 129–130°C (lit.[18] 135–137°C); IR (KBr) ν_{max}: 3040, 2957, 2863, 1605, 1475, 1406, 1321, 1110, 839, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.2 Hz, 2*H*), 7.94 (d, *J* = 8.2 Hz, 2*H*), 7.35–7.24 (m, 4*H*), 2.43 (s, 3*H*); ^{13}C NMR ($CDCl_3$): δ 187.9, 173.7, 142.4, 140.4, 130.3, 129.8, 129.3, 128.2, 127.4, 21.6, 21.5. HRMS: Calcd for $C_{16}H_{14}N_2S = 267.0950$. Found: 267.0946.

3,5-Bis(3-chlorolphenyl)-1,2,4-thiadiazole (2g). White solid, mp 125–127°C; IR (KBr) ν_{max}: 3046, 2950, 2863, 1605, 1470, 1406, 1321, 1110, 839, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.41 (d, *J* = 1.8 Hz, 1*H*), 8.28 (dd, *J* = 7.0 Hz, 1*H*), 8.09 (d, *J* = 1.9 Hz, 1*H*), 7.92 (d, *J* = 7.5 Hz, 1*H*), 7.57–7.43 (m, 4*H*); ^{13}C NMR ($CDCl_3$): δ 186.9, 172.5, 135.4, 134.7, 134.2, 131.9, 130.6, 130.5, 130.0, 128.5, 127.3, 126.4, 125.6; ESI MS: *m/z* 307 $[M+H]^+$. *Anal*. Calcd. for $C_{14}H_8Cl_2N_2S$: C, 54.74; H, 2.61; N, 9.12; S, 10.45. Found: C, 54.68; H, 4.22.61; N, 9.10; S, 10.43.

3,5-Bis(4-nitrophenyl)-1,2,4-thiadiazole (2i). Pale yellow solid, mp 201–202°C (lit.[16] 198–199°C); IR (KBr) ν_{max}: 3075, 2950, 2863, 1605, 1535, 1470, 1406, 1321, 839, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.60 (d, *J* = 8.2 Hz, 1*H*), 8.45–8.33 (m, 4*H*), 8.25 (d, *J* = 8.2 Hz, 1*H*), 7.88 (d, *J* = 8.2 Hz, 2*H*); ^{13}C NMR ($CDCl_3$): δ 191.5, 169.5, 157.1, 154.8, 152.9, 148.7, 147.9, 144.2, 143.7, 143.5, 137.8, 136.2; ESI MS: *m/z* 328 $[M+H]^+$. *Anal*. Calcd. for $C_{14}H_8N_4O_4S$: C, 51.22; H, 2.46; N, 17.07; S, 9.77. Found: C, 51.25; H, 2.42; N, 17.02; S, 9.81.

3,5-Bis(5-bromofuran-2-yl)-1,2,4-thiadiazole (2j). White solid, mp 185–186°C; IR (KBr) ν_{max}: 3060, 2965, 2863, 1605, 1535, 1470, 1406, 1321, 839, 709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, *J* = 3.6 Hz, 1*H*), 7.16 (d, *J* = 3.5 Hz, 1*H*), 6.57 (d, *J* = 3.6 Hz, 1*H*), 6.50 (d, *J* = 3.5 Hz, 1*H*); ^{13}C NMR ($CDCl_3$): δ 175.9, 149.7, 126.9, 125.2, 115.1, 114.9, 114.8, 113.8; ESI MS: *m/z* 376 $[M+H]^+$. *Anal*. Calcd. for $C_{10}H_4Br_2N_2O_2S$: C, 31.94; H, 1.06; N, 7.45; S, 8.53. Found: C, 31.89; H, 1.02; N, 7.38; S, 8.48.

3,5-Cyclohexylmethyl-1,2,4-thiadiazole (2m). Colorless liquid; ^1H NMR (300 MHz, $CDCl_3$): δ 2.96 (d, *J* = 6.5 Hz, 1*H*), 2.84 (d, *J* = 7.2 Hz, 1*H*), 1.74 (dt, *J* = 18.3, 8.5 Hz, 10*H*), 1.37–0.93 (m, 12*H*), 1.39 (S, 18*H*); $^{13}CNMR$ (75 MHz, $CDCl_3$): δ 190.0, 176.4, 40.5, 38.7, 38.6, 37.4, 33.0, 32.9, 30.1, 29.6, 26.0, 25.9. HRMS: Calcd. for $C_{16}H_{26}N_2S = 279.1889$ $[M+H]^+$. Found: 279.1882.

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[29] It is note worthy to mention here that during the preparation of primary thioamide from the corresponding primary amide by using Lawesson's reagent, toluene reflux, we have observed that there is no formation of 3,5-disubstituted 1,2,4-thiadiazoles.