TCT-DMSO/[bmim]BF_4: A Novel Promoter System for the Synthesis of 3,5-Diaryl-1,2,4-thiadiazoles at Ambient Temperature

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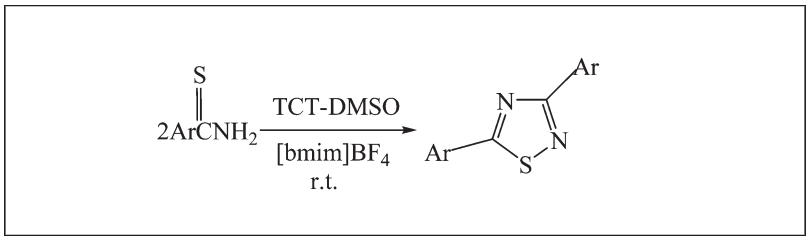

An efficient and practical procedure for direct synthesis of 3,5-diaryl-1,2,4-thiadiazoles by thioamides with 2,4,6-trichloro-1,3,5-triazine (TCT) and dimethylsulfoxide using 1-butyl-3-methylimidazolium tetrafluoroborate as an eco-friendly reaction medium under ambient temperature is described. This protocol can be considered as a new procedure for 3,5-diaryl-1,2,4-thiadiazoles synthesis.

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INTRODUCTION

1,2,4-Thiadiazole nucleus constitutes the core units of many natural products [1]. Although, currently, the only commercial 1,2,4-thiadiazole drug is the antibiotic cefozopram [2], there are a number of synthetic products related to this system with a broad range of biological activities concerning central nervous system (CNS) [3], G-protein coupled receptors [4], inflammation [5], cardiovascular system [6], or antibiotic activity [7]. The antioxidant and muscarinic receptor binding properties of a family of 1,2,4-thiadiazole derivatives has also shown acetylcholinesterase inhibitory activity [3]. A number of derivatives were described as the first non-ATP competitive glycogen synthase kinase 3b inhibitors [8]. Also, the properties of 1,2,4-thiadiazoles as thiol trapping agents have been recently reviewed [9].

Traditional methods for the synthesis of 3,5-diaryl-1,2,4-thiadiazoles limited to the oxidative dimerization reaction of thioamides with 1-methyl pyridinium chloride, benzoyl chloride, or acetyl chloride in chlorinated organic solvents [10]. Recently, these compounds have also been prepared by stoichiometric amount of $PhI(OAC)_2$ at 70°C [11]. However, these methods are not quite satisfactory in view of using large excess of reagents, long reaction times, harsh reaction conditions, and also involvement of toxic solvents such as acetonitrile or dichloromethane. Hence, there is a need to develop a convenient, simple, rapid, and environmentally friendly method for the synthesis of these important heterocyclic compounds.

RESULTS AND DISCUSSION

In recent years, 2,4,6-trichloro-1,3,5-triazine (TCT) has invoked enormous interest in various organic transformations [12]. Moreover, ionic liquids (ILs) have emerged extensively as a novel eco-friendly reaction media for many organic syntheses [13]. In such perspective, in the combination with our recent lies on the design of new synthetic methodologies [14] and development of useful tactics and strategies for the synthesis of heterocyclic compounds [15], especially in ILs [16], we report, herein, a novel and efficient procedure using of TCT-DMSO as a new promoter system in [bmim]BF_4 for direct synthesis of 3,5-diaryl-1,2,4-thiadiazoles from arylthioamids (Scheme 1).

To the best of our knowledge; there is no report on the oxidative dimerization reaction with TCT-DMSO in ionic liquid. At the onset of this work, to explore the scope of this method, we used thiobenzamide as a model, and the role of various conditions on the reaction system was investigated (Table 1). We found that the optima ratio of thioamide/TCT/DMSO is about 1:0.3:1 (Table 1, entry 5). Further investigations revealed that reducing the loading of TCT to 0.25 equiv gave the desired product in a lower yield of 79% (Table 1, entry 4). The use of 1 equiv of DMSO was also found to be necessary for this transformation to proceed smoothly; when DMSO was reduced to 0.9 equiv, a slightly lower product yield of 81% was afforded (Table 1, entry 6).

To determine the most appropriate solvent, the reaction was examined using different ILs and also using

Scheme 1

traditional solvents such as ethanol, acetonitrile, and chloroform. The results are summarized in Table 1. Choosing an appropriate solvent is of crucial importance for successful synthesis. [bmim]BF_4 and [bmim]OTf were the best solvents in terms of yields (Table 1, entries 5 and 7). However, [bmim]BF_4 was favored as water could be used for the work-up. Interestingly, we observed that combination of TCT-DMSO in [bmim]BF_4 is essential for this transformation that attempts to carry out the reactions, in the absence of each of these almost did not yield the product. Another important factor was the reaction temperature.

The experiments were run from 0 to 40°C. We found that those conducted at room temperature (23–25°C) afforded almost quantitative yields, whereas at 40°C some by-products were observed. The experimental procedure for this transformation is remarkably straightforward and does not require the use of toxic organic solvents or inert atmospheres. The structures of the products were established by ^{1}H NMR, ^{13}C NMR, IR, and mass spectrum. The use of these optimal experimental conditions to the reactions of different arylthioamides containing both electron-donating and electron-withdrawing groups in the aromatic rings was found to undergo the conversion smoothly (Table 2, entries a–j). The reaction proceeded at room temperature, and the products were formed within 10–12 min in excellent yields. Acid sensitive thioamides such as 2-furylthioamide also formed the corresponding thiadiazole quantitatively (Table 2, entry k).

Table 1

Optimization of conditions in the synthesis of 3,5-diphenyl-1,2,4-thiadiazole.

Entry	TCT:DMSO equiv	Solvent[a]	Time (min)	Yield (%)[b]
1	0.1:1	[bmim]BF_4	10	18
2	0.15:1	[bmim]BF_4	10	54
3	0.2:1	[bmim]BF_4	10	75
4	0.25:1	[bmim]BF_4	10	79
5	0.3:1	[bmim]BF_4	10	96
6	0.3:0.9	[bmim]BF_4	10	81
7	0.3:1	[bmim]OTf	10	95
8	0.3:1	[bmim]PF_6	10	42
9	0.3:1	PYRTFSI[c]	10	60
10	0.3:0	[bmim]BF_4	60	0
11	0.3:1	CH_3CN	60	65
12	0.3:1	EtOH	60	50
13	0.3:1	$CHCl_3$	60	45

[a] 2 mL.
[b] Isolated yield.
[c] *N*-butyl-*N*-methylpyrrolidinium bi(trifluoromethanesulfonyl)imide.

Table 2

Synthesis of 3,5-diphenyl-1,2,4-thiadiazoles through oxidation condensation reaction promoted with TCT-DMSO in [bmim]BF_4 as a room temperature ionic liquid.

Entry	Ar	Time (min)	Yield (%)[a]
a	C_6H_5	10	96
b	4-FC_6H_4	10	94
c	4-ClC_6H_4	10	95
d	4-BrC_6H_4	10	93
e	3-BrC_6H_4	10	93
f	2,4-$Cl_2C_6H_3$	10	92
g	3-ClC_6H_4	10	94
h	2-ClC_6H_4	10	90
i	4-$CH_3OC_6H_4$	10	93
j	4-$BnOC_6H_4$	10	90
k	2-furyl	12	91

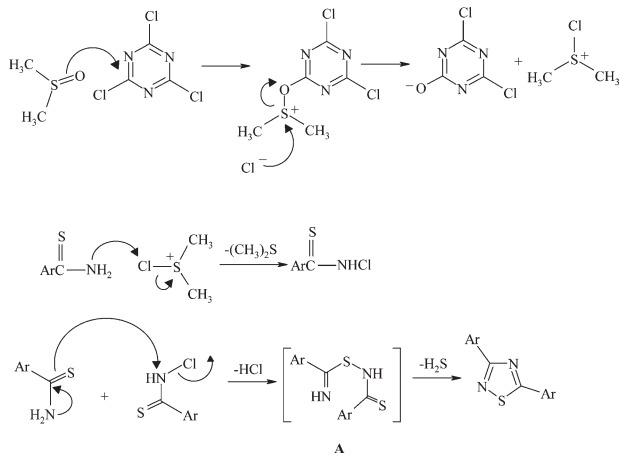
[a] Yields refer to isolated pure products.

Based on the earlier experimental results and the literature [10], we propose a plausible reaction pathway, as shown in Scheme 2.

Addition of DMSO to TCT in [bmim]BF_4 causes the oxidation of thioamide to *N*-chlorothioamide. Nucleophilic attack by sulfur of another molecule of thioamide to *N*-chlorothioamide gives the intermediate (**A**) that on further rapid oxidation gives the product.

In conclusion, we have presented a new, mild, efficient, and convenient method for the preparation of 3,5-diaryl-1,2,4-thiadiazoles through oxidative dimerization using combination of TCT and DMSO in ionic liquid. Moreover, in comparison to the previous methods, this protocol design a unique rut for the efficient synthesis of 3,5-diphenyl-1,2,4-thiadiazoles at room temperature using a novel promoter system. Also, we have shown

Scheme 2



that the method is tolerant to a variety of functional groups. By using this protocol, we synthesized target molecules in excellent yields. The details of synthetic applications of this methodology are being further studied in our laboratory.

EXPERIMENTAL

General procedure for the synthesis of 3,5-diaryl-1,2,4-thiadiazoles by thioamides promoted with TCT and dimethylsulfoxide in [bmim]BF_4. To a stirred solution of arylthioamide (1 mmol) in [bmim]BF_4 (2 mL) at r.t. was added TCT (0.0554 g, 0.3 mmol) and DMSO (0.078 g, 1 mmol). The reaction mixture was stirred magnetically at room temperature for the specified time (see Table 2) until arylthioamide was completely disappeared (the progress of the reaction was followed by TLC). When the reaction was completed, quenched with ice water (10 mL) and stirred at room temperature for 10 min. The above mixture was extracted with ethyl acetate (3 × 5 mL), and the organic layers were combined and washed with brine. After dryness and concentration in vacuo, the residue was chromatographied on silica gel (*n*-heptane/ethyl acetate as eluent) to afford the pure product in 90–96% yield.

3,5-Diphenyl-[1,2,4]thiadiazole. Solid, mp 81–83°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (br s, 2 H), 8.07 (br s, 2 H), 7.54–7.50 (m, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.1, 174.5, 133.5, 130.9, 130.9, 130.6, 131.1, 129.2, 129.2, 128.7, 127.5, 127.5, 129.2, 129.2. Anal. Calcd. For $C_{14}H_{10}N_2S$: C, 70.56; H, 4.23; N, 11.76; S, 13.46. Found: C, 70.60; H, 4.20; N, 11.77; S, 13.43.

3,5-Bis(4-methoxyphenyl)[1,2,4]thiadiazole. Solid, mp 128–130°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J = 8.8 Hz, 2 H), 7.99 (d, J = 8.8 Hz, 2 H), 7.01 (m, 4 H), 3.90 (s, 3 H), 3.89 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.1, 171.5, 162.8, 160.1, 140.3, 140.4, 138.2, 138.3, 128.3, 127.6, 114.6, 114.4, 111.8, 111.6, 59.7, 59.6. Anal. Calcd. For $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33; S, 10.67. Found: C, 63.91; H, 5.39; N, 9.30; S, 10.71.

3,5-Bis(4-benzyloxyphenyl)[1,2,4]thiadiazole. Solid, mp 154–157°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J = 8.6 Hz, 4 H), 7.42–7.36 (m, 10 H), 7.02 (d, J = 8.7 Hz, 4 H), 5.12 (s, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.2, 171.6, 162.1, 162.1, 162.0, 162.0, 134.2, 134.1, 133.4, 133.4, 133.3, 133.2, 132.2, 132.1, 131.6, 128.7, 126.8, 126.8, 123.9, 123.9, 123.8, 123.8, 123.0, 123.0, 122.9, 129.9. Anal. Calcd. For $C_{26}H_{18}N_2O_2S$: C, 73.92; H, 4.29; N, 6.63; S, 7.59. Found: C, 73.89; H, 4.31; N, 6.65; S, 7.57.

3,5-Di(2-furyl)-[1,2,4]thiadiazole. Solid, mp 88–90°C; ^{1}H NMR (500 MHz, CDCl3) δ 7.93 (d, J = 3.5 Hz, 1 H), 7.70 (d, J = 3.7 Hz, 1 H), 7.58 (d, J = 5.1 Hz, 1 H), 7.45 (d, J = 5 Hz, 1 H), 7.18–7.13 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.1, 170.4, 159.0, 151.3, 151.1, 147.9, 117.1, 117.0, 117.0, 112.1. Anal. Calcd. For $C_{10}H_6N_2O_2S$: C, 55.03; H, 2.77; N, 12.84; S, 17.71. Found: C, 55.32; H, 2.41; N, 12.65; S, 17.62.

3,5-Bis(4-chlorophenyl)[1,2,4]thiadiazole. Solid, mp 146–148°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J = 8.5 Hz, 2 H), 7.99 (d, J = 8.5 Hz, 2 H), 7.51 (d, J = 8.5 Hz, 2 H), 7.48 (d, J = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.0, 173.1, 133.3, 133.0, 132.7, 132.5, 132.1, 132.0, 129.8, 129.4, 128.8, 126.6, 125.0. Anal. Calcd. For $C_{14}H_8Cl_2N_2S$: C, 54.74; H, 2.62; N, 9.12; S, 10.44. Found: C, 54.60; H, 2.59; N, 9.04; S, 10.29.

3,5-Bis(3-chlorophenyl)[1,2,4]thiadiazole. Solid, mp 123–125°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (d, J = 1.6 Hz, 1 H), 8.27 (dd, J = 6.9 Hz, 1 H), 8.07 (d, J = 1.7 Hz, 1 H), 7.89 (d, J = 7.6 Hz, 1 H), 7.54–7.42 (m, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.9, 172.5, 135.5, 134.8, 134.2, 132.0, 131.9, 130.6, 130.5, 130.0, 128.5, 127.3, 126.4, 125.6. Anal. Calcd. For $C_{14}H_8Cl_2N_2S$: C, 54.74; H, 2.62; N, 9.12; S, 10.44. Found: C, 54.51; H, 2.62; N, 9.15; S, 10.25.

3,5-Bis(2-chlorophenyl)[1,2,4]thiadiazole. Solid, mp 85–86°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (m, 1 H), 8.05 (m, 1 H), 7.60–7.55 (m, 2 H), 7.48–7.46 (m, 2 H), 7.42–7.40 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.0, 173.2, 133.8, 133.3, 132.2, 132.1, 132.0, 130.9, 130.7, 130.6, 130.4, 129.6, 127.4, 126.7. Anal. Calcd. For $C_{14}H_8Cl_2N_2S$: C, 54.74; H, 2.62; N, 9.12; S, 10.44. Found: C, 54.42; H, 2.82; N, 9.35; S, 10.51.

3,5-Bis(2,4-dichlorophenyl)[1,2,4]thiadiazole. Solid; mp 132–134°C.^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 (1 H, dd, J = 8.2 Hz), 7.46 (1 H, dd, J = 8.4 Hz), 7.58 (1 H, d, J = 2.1 Hz), 7.63 (1 H, d, J = 2.1 Hz), 8.04 (1 H, d, J = 8.4 Hz,), 8.57 (1 H, d, J = 8.6 Hz).^{13}C NMR (125 MHz, $CDCl_3$): δ = 127.1, 128.1, 129.7, 130.2, 130.8, 131.4, 133.1, 134.1, 134.3, 136.3, 136.4, 137.9, 173.2, 182.2. Anal. Calcd. For $C_{14}H_6Cl_4N_2S$: C, 44.71; H, 1.61; N, 7.45; S, 8.52. Found: C, 44.36; H, 1.82; N, 7.33; S, 8.75.

3,5-Bis(4-bromophenyl)[1,2,4]thiadiazole. Solid, mp 149–154°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (d, J = 8.5 Hz, 2 H), 7.90 (dd, J = 6.6 Hz, 2 H), 7.66 (dd, J = 6.7 Hz, 2 H), 7.63 (dd, J = 6.7 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.1, 173.2, 132.8, 132.5, 132.3, 132.2, 131.9, 131.6, 129.8, 129.4, 128.8, 126.6, 125.0. Anal. Calcd. For $C_{14}H_8Br_2N_2S$: C, 42.45; H, 2.04; N, 7.07; S, 8.10. Found: C, 42.27; H, 2.03; N, 7.17; S, 8.31.

3,5-Bis(3-bromophenyl)[1,2,4]thiadiazole. Solid, mp 137–140°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (s, 1 H), 8.32 (m, 1 H), 8.21 (s, 1 H) 7.93–7.91 (m, 1 H), 7.68–7.60 (m, 2 H), 7.42-7.35 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.7, 172.3, 134.8, 134.4, 133.4, 132.2, 131.4, 130.7, 130.3, 130.2, 126.8, 126.1, 123.4, 122.8. Anal. Calcd. For $C_{14}H_8Br_2N_2S$: C, 42.45; H, 2.04; N, 7.07; S, 8.10. Found: C, 42.52; H, 2.15; N, 7.01; S, 8.02.

3,5-Bis(4-fluoroophenyl)[1,2,4]thiadiazole. Solid, mp 185–188°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (m, 2 H), 8.05 (m, 2 H), 7.24–7.16 (m, 4 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.9, 172.8, 165.9, 165.2, 163.9, 163.2, 130.4, 130.3, 129.6, 129.5, 116.6, 116.4, 115.8, 115.6. Anal. Calcd. For $C_{14}H_8F_2N_2S$: C, 61.30; H, 2.94; N, 10.21; S, 11.69. Found: C, 61.24; H, 2.92; N, 10.17; S, 11.49.

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