Solvent-free synthesis of 3,5-di(hetero)aryl-1,2,4-thiadiazoles by grinding of thioamides under oxidative conditions

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An efficient and facile synthesis of 3,5-di(hetero)aryl-1,2,4-thiadiazoles by oxidative dimerisation of thioamides by grinding with NBS under solvent-free conditions at room temperature has been developed. The efficiency of this reaction was demonstrated by the compatibility with trifluoromethyl, methyl, methoxy, chloro, pyridyl and thienyl groups. This method has notable advantages in terms of short reaction times, high yields and is a more practical alternative to the existing methods to access these compounds.

Keywords: thioamides, thiadiazoles, grinding, solvent-free synthesis

Thiadiazoles play a important part in the synthesis of many bioactive molecules belonging to various therapeutic categories, such as bactericides,[1] fungicides,[2] herbicides[3] and antibiotics.[4] Various approaches toward the synthesis of thiadiazoles derivatives have been explored during the past years. One of the most common methods for the synthesis of 1,2,4-thiadiazoles involves the oxidative dimerisation of thioamides in the presence of various promoting agents, such as nitrous acid,[5] tertiary butyl hypochlorite,[6] DMSO/electrophilic regent,[7] polystyrene-bound diaryl selenoxide and telluroxide,[8] organotellurium,[9] *p*-toluenesulfinic acid,[10] polystyrene-supported iodobenzene diacetate (PIBD)[11] and PIBD/ionic liquids.[12] Recently, Akamanchi and co-worker reported that IBX/TEAB–mediated oxidative dimerisation of thioamides for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles in acetonitrile.[13] Some other methods include intramolecular cyclisation[14–16] and intermolecular cyclisation.[17–19] Although these methods are suitable for certain synthetic conditions, many of these procedures are associated with one or more disadvantages such as long reaction time, use of hazardous organic solvents and harsh reaction conditions, which leaves scope for further development of new environmentally clean syntheses.

In recent years, significant articles have appeared reporting solid-state reactions by grinding.[20–24] Most of these reactions are carried out at room temperature in a completely solvent-free environment using only a mortar and pestle, and therefore the common merit of these processes is that they are efficient, economical, and environmentally friendly.

In continuation of our interest in green chemistry,[24–34] we here describe a green, simple and practical method for the synthesis of 3,5-diaryl-1,2,4-thiadiazole by oxidative dimerisation of thioamides under solvent-free conditions.

To optimise the reaction conditions, initial studies were concentrated on treatment of thiobenzamide **1a** with NBS (*N*-bromosuccinimide) as a model reaction. Different reaction media were tested to find the optimal conditions. As shown in Table 1, basic Al_2O_3 was determined to be the more suitable medium, which afforded the desired product **2a** with excellent yield (Table 1, entry 3). When the amount of NBS was decreased to 1.05 equiv, the reaction proceeded smoothly within just 5 min without decreasing the yields (Table 1, entries 5–7).

Furthermore, the present route to 3,5-diphenyl-1,2,4-thiadiazole **2a** was successfully applied to a large-scale reaction. For instance, the oxidative dimerisation reaction of thiobenzamide **1a** (5 mmol) using basic Al_2O_3 (5 g) as reaction medium in the presence of NBS (5.25 mmol, 1.05 equiv.) provided the desired product **2a** in 93% (Table 1, entry 7).

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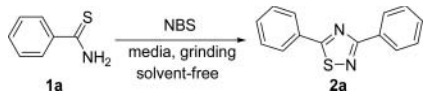
Table 1 Effect of reaction condition on synthesis of 3,5-disubstituted 1,2,4-thiadiazoles[a]



1a 2a

Entry	NBS/equiv	Media	Time/min	Yield/%[b]
1	1.2	Silica gel	15	77
2	1.2	Neutral Al_2O_3	15	78
3	1.2	Basic Al_2O_3	15	93
4	–	Basic Al_2O_3	15	Trace
5	1.05	Silica gel	5	73
6	1.05	Basic Al_2O_3	15	92
7	1.05	Basic Al_2O_3	5	92 (93)[c]

[a]Reactions conditions: thiobenzamide **1a** (0.5 mmol) and media (0.5g) in the presence of NBS on grinding at room temperature under solvent-free conditions.
[b]Isolated yields.
[c]Thiobenzamide **1a** (0.686 g, 5 mmol), NBS (0.935 g, 5.25 mmol) and basic Al_2O_3 (5 g).

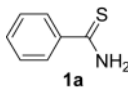
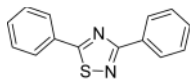
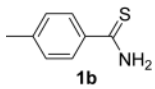
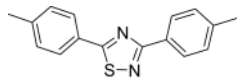
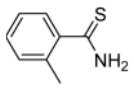
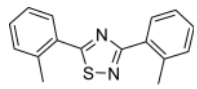
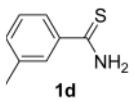
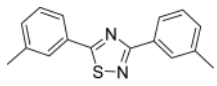
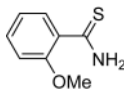
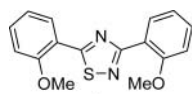
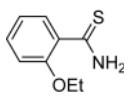
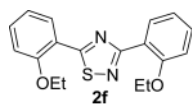
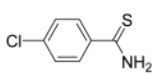
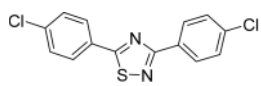
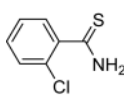
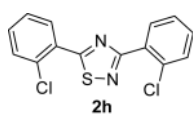
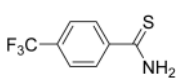
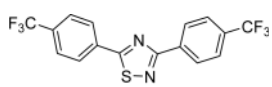
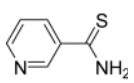
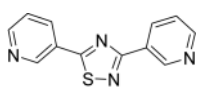
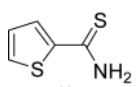
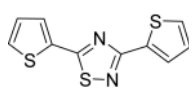
On the basis of the above results, to extend the scope and generality of this method, a variety of aromatic and heteroaromatic thioamides were subjected to oxidative dimerisation to give various 3,5-disubstituted 1,2,4-thiadiazoles by grinding with NBS and the results are summarised in Table 2.

As shown in Table 2, a series of aromatic thioamides were investigated. Thioamides containing electron-donating groups, such as 4-methylthiobenzamide **1b** and 3-methylthiobenzamide **1d** afforded the corresponding thiadiazoles **2b** and **2d** in 94% and 96%, respectively (Table 2, entries 2 and 4). Similarly, thioamides containing electron-withdrawing groups, such as 4-(trifluoromethyl) thiobenzamide afforded the corresponding thiadiazole **2i** in 91% (Table 2, entry 9), and showed no deleterious electronic effect.

Next, we examined the steric effect of phenyl-ring substituents on the reactions. Good yields were obtained when the sizes of the *ortho*-substituent groups were small, such as 2-methylthiobenzamide **1b**, 2-methoxythiobenzamide **1c** and 2-chlorothiobenzamide **1h** (Table 2, entries 3, 5, 8). However, it was found that yields were significantly decreased when the sizes of the *ortho*-substituent groups were large. For example, 2-ethoxybenzothioamide was found to be less active and gave the corresponding thiadiazole **2f** in moderate yield even after 30 min (Table 2, entry 6).

Finally, we also examined the reactivity of heterocyclic thioamides, such as pyridine-3-carbothioamide **1j** and thiophene-2-carbothioamide **1k** using the present protocol. It was found that the desired products **2j** and **2k** were obtained in 92% and 99% yields, respectively (Table 2, entries 10 and 11).

Table 2 Synthesis of 3,5-disubstituted 1,2,4-thiadiazoles[a]

Entry	Substrate (**1**)	Product (**2**)	Time/min	Yield/%[b]
1	 **1a**	 **2a**	5	92
2	 **1b**	 **2b**	5	94
3	 **1c**	 **2c**	5	93
4	 **1d**	 **2d**	5	96
5	 **1e**	 **2e**	5	91
6	 **1f**	 **2f**	15	57 (62)[c]
7	 **1g**	 **2g**	10	94
8	 **1h**	 **2h**	5	90
9	 **1i**	 **2i**	5	91
10	 **1j**	 **2j**	15	92
11	 **1k**	 **2k**	5	99

[a] Reactions were carried out on a 0.5-mmol scale with NBS (1.05 equiv) by grinding at room temperature under solvent-free conditions.
[b] Isolated yields.
[c] For 30 min.

In conclusion, we have developed a highly effcient and facile method for the synthesis of 3,5-di(hetero)aryl-1,2,4-thiadiazoles on grinding under solvent-free conditions. Good yields, short reaction times and neat conditions are the notable advantages of this method. We believe that this method has provided better scope for the synthesis of 3,5-di(hetero)aryl-1,2,4-thiadiazoles and will be a more practical alternative to the existing methods for accessing these compounds.

Experimental

Chemicals were purchased and used without further purification. All the melting points were uncorrected. NMR spectroscopy was performed on a Bruker-300 spectrometer or Bruker-500 spectrometer using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ units relative to TMS, the coupling constants J = are given in Hz. Mass spectra (MS) were measured with a Thermo Finnigan LCQ-Advantage. Elemental analyses were carried out using a Carlo-Erba EA1112 instrument. Column chromatography was performed using EM Silica gel 60 (300–400 mesh).

Typical procedure for preparation of thiobenzamides

A three-necked and round-bottomed flask is fitted with a rubber septum, thermometer, magnetic stirring bar, and reflux condenser equipped with a nitrogen bubbler. The flask is charged with thiophene-2-carboxamide (1.02 g 8 mmol) and Lawesson's reagent (1.62 g 4 mmol) and then the reaction mixture is purged with N_2, whereupon

the temperature of the reaction mixture increased to 95 °C. After 10 min dry toluene (15 mL) was added by syringe. The mixture was stirred for 14 h. and then cooled to room temperature. The toluene is removed with the aid of a rotary evaporator and the resulting yellow mixture was separated by silica gel column chromatography to provide 0.584 g (51%) of thiophene-2-carbothioamide as a yellow solid, m.p. 106–107 °C. Other thiobenzamide compounds were synthesised by a similar method.

Typical procedure for preparation of 1,2,4-thiadiazoles

The following components were added to the glass mortar: basic Al_2O_3 (200–300mesh, 500 mg), thiobenzamide **1a** (68.6 mg, 0.5 mmol) and NBS (93.5 mg, 0.525 mmol). The mixture was then ground at room temperature with a glass pestle in the glass mortar. When the mixture became pale yellow, a sample was dissolved in ethyl acetate to monitor the progress of the reaction using TLC. After completion of the reaction, the mixture was washed with ethyl acetate. The combined washings were removed under vacuum. The pure product was obtained by silica gel column chromatography. The physical and spectral data of compounds **2a**–**k** are as follows.

3,5-Diphenyl-1,2,4-thiadiazole (**2a**): Solid, m.p. 88–89 °C, (lit.[13] 90–92 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.56 (m, 6H), 8.04–8.08 (m, 2H), 8.38–8.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 127.4, 128.3, 128.6, 129.1, 130.3, 130.6, 131.8, 173.7, 188.0.

3,5-Bis(4-methylphenyl)-1,2,4-thiadiazole (**2b**): Solid, m.p. 119–121 °C, (lit.[13] 130–131 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.43 (s, 3H), 2.48 (s, 3H), 7.29–7.32 (m, 4H), 7.91–7.94 (m, 2H), 8.27–8.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.5, 21.7, 127.4, 128.2, 128.3, 129.4, 129.9, 130.4, 140.5, 142.5, 173.8, 188.0.

3,5-Bis(2-methylphenyl)-1,2,4-thiadiazole (**2c**): Solid, m.p. 45–46 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.69 (s, 3H), 2.74 (s, 3H), 7.33–7.45 (m, 6H), 8.04–8.06 (m, 2H), 8.16–8.18 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.9, 22.1, 125.9, 126.4, 127.8, 129.7, 129.8, 130.2, 131.0, 131.4, 131.7, 132.4, 137.0, 137.9, 173.7, 186.5. ESI-MS: *m/z* (%): 267 ([M+H]$^+$, 100) Anal. Calcd for $C_{16}H_{14}N_2S$: C, 72.15; H, 5.30; N, 10.52. Found: C, 72.20; H, 5.34; N, 10.57%.

3,5-Bis(3-methylphenyl)-1,2,4-thiadiazole (**2d**): Solid, m.p. 45–47 °C, (lit.[19] 55–56 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (s, 3H), 2.46 (s, 3H), 7.27–7.41 (m, 4H), 7.81–7.86 (m, 2H), 8.18–8.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 21.4, 124.7, 125.5, 127.9, 128.5, 128.9, 129.1, 130.6, 131.1, 132.6, 132.8, 138.3, 139.1, 173.9, 188.2.

3,5-Bis(2-methoxyphenyl)-1,2,4-thiadiazole (**2e**): Solid, m.p. 108–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.97 (s, 3H), 4.11 (s, 3H), 7.07–7.18 (m, 4H), 7.44–7.50 (m, 2H), 8.15–8.18 (m, 1H), 8.54–8.57 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.8, 56.2, 111.1, 112.2, 120.2, 120.6, 121.3, 122.9, 128.5, 131.1, 132.3, 132.5, 157.6, 158.0, 169.6, 180.5. ESI-MS: *m/z* (%): 299 ([M+H]$^+$, 100)Anal. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39. Found: C, 64.36; H, 4.77; N, 9.43%.

3,5-Bis(4-ethoxyphenyl)-1,2,4-thiadiazole (**2f**): Solid, m.p. 110–112°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (t, J = 7.0), 1.65 (t, J = 7.0), 4.17 (q, J = 7.0), 4.32 (q, J = 7.0), 7.02–7.13 (m, 4H), 7.36–7.45 (m, 2H), 8.04–8.07 (m, 1H), 8.51–8.54 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.7, 14.8, 64.7, 64.9, 111.5, 113.8, 120.2, 120.5, 120.9, 123.5, 128.3, 130.7, 131.9, 132.2, 156.8, 157.3, 169.5, 180.4. ESI-MS: *m/z* (%): 327 ([M+H]$^+$, 100). Anal. Calcd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56; N, 8.58. Found: C, 66.29; H, 5.61; N, 8.64%.

3,5-Bis(4-chlorophenyl)-1,2,4-thiadiazole (**2g**): Solid, m.p. 154–155°C, (lit.[13] 161–162 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45–7.50 (m, 4H), 7.94–7.97 (m, 2H), 8.28–8.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 128.6, 128.9, 129.0, 129.5, 129.6, 131.1, 136.6, 138.1, 172.8, 187.0.

3,5-Bis(2-chlorophenyl)-1,2,4-thiadiazole (**2h**): Solid, m.p. 84–86°C, (lit.[13] 92–95 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.46 (m, 4H), 7.53–7.58 (m, 2H), 8.03–8.06 (m, 1H), 8.61–8.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 126.7, 127.4, 129.5, 130.3, 130.6, 130.7, 130.8, 131.9, 132.1, 132.2, 133.2, 133.8, 169.7, 183.0.

3,5-Bis(4-trifluoromethylphenyl)-1,2,4-thiadiazole (**2i**): Solid, m.p. 92–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74–7.80 (m, 4H), 8.12–8.15 (m, 2H), 8.47–8.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 120.3, 120.7, 122.5, 122.9, 124.6, 125.0, 125.6, 125.7, 126.3, 126.8, 127.2, 127.8, 128.6, 128.8, 131.8, 132.1, 132.3, 132.6, 133.3, 133.5, 133.8, 134.0, 135.5, 172.6, 186.9. ESI-MS: *m/z* (%): 375 ([M+H]$^+$, 100). Anal. Calcd for $C_{16}H_8F_6N_2S$: C, 51.34; H, 2.15; N, 7.48. Found: C, 51.28; H, 2.11; N, 7.56%.

3,5-Bis(3-pyridyl)-1,2,4-thiadiazole (**2j**): Solid, m.p. 128–129 °C, (lit.[13] 133–135 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.48 (m, 2H), 8.28–8.31 (m, 1H), 8.56–8.59 (m, 1H), 8.68–8.75 (m, 2H), 9.21 (s, 1H), 9.55 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 123.5, 124.0, 126.5, 128.3, 134.4, 135.4, 148.4, 149.6, 151.2, 152.7, 171.5, 185.4.

3,5-Bis(2-thienyl)-1,2,4-thiadiazole (**2k**): Solid, m.p. 87–89 °C, (lit.[35] 84–86 °C).^{1}H NMR (300 MHz, $CDCl_3$): δ 7.03–7.06 (m, 2H), 7.34–7.36 (m, 1H), 7.45–7.47 (m, 1H), 7.56–7.58 (m, 1H), 7.82–7.84 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 127.8, 128.4, 128.8, 129.2, 129.8, 130.5, 133.0, 136.2, 168.3, 180.6. ESI-MS: *m/z* (%): 251 ([M+H]$^+$, 100). Anal. Calcd for $C_{10}H_6N_2S_3$: C, 47.97; H, 2.42; N, 11.19. Found: C, 47.91; H, 2.37; N, 11.25%.

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