



scales.

Herein, a very rapid, clean and efficient procedure for the synthesis of symmetrical 3,5-diaryl-1,2,4-thiadiazole derivatives from the corresponding thiobenzamides is reported.

## EXPERIMENTAL

### Modified Procedure for the Preparation of N-Benzyl-DABCO-tribromide

To a stirred solution of DABCO (50 mmol, 5.6 g) in chloroform (40 ml), a solution of benzyl bromide (10 mmol, 1.71 g) in chloroform (10 ml) was added for 4 min. The reaction mixture was stirred for further 30 min at ambient temperature and liquid bromine (10 mmol, 1.60 g) was added dropwise for 2 min. Then the resulting yellowish orange precipitate was filtered, washed with chloroform (3 × 5 ml), and dried under vacuum.

### General Procedure for the Preparation of 1,2,4-Thiadiazoles in DMSO as a Solvent

To a stirred solution of thiobenzamide derivative (1 mmol) in DMSO (1.5 ml), N-benzyl-DABCO-tribromide (1 mmol, 443 mg) was added portionwise for over 1 min. Then the reaction mixture was stirred and heated to the mentioned temperatures and for the times noted in Table 1. After completion of the reaction, a solution of ethanol/water (30:70, 4 ml) was added to the reaction mixture. The precipitated compound was filtered and crystallized in ethanol (or ethanol-chloroform) to obtain pure product in moderate to good yields.

### General Procedure for the Preparation of 1,2,4-Thiadiazoles in Wet Solid-Solid Conditions

Finely pulverized thiobenzamide (10 mmol) and N-benzyl-DABCO-tribromide (10 mmol, 4.43 g) were mixed and wetted with water (4 ml). The resulting pasty reaction mixture was stirred using a mechanical stirrer for the times noted in Table 1. Then a solution of ethanol/water (50:50, 30 ml) was added to the reaction mixture. The precipitated compound was filtered and crystallized in ethanol (or ethanol-chloroform) to obtain the corresponding thiadiazoles as pure compounds in good to excellent yields.

**3,5-Bis(4-nitrophenyl)-1,2,4-thiadiazole (2e).** Pale yellow

solid; m.p.: 208-210 °C; IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>) 3083, 2743, 1454, 1263, 1095, 785. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  (ppm) = 8.30 (d, 2H, J = 8.3 Hz), 8.43 (d, 2H, J = 8.2 Hz), 8.47 (d, 2H, J = 8.2 Hz), 8.65 (d, 2H, J = 8.3 Hz). MS: m/z 328 (M<sup>+</sup>). Anal. Calcd. For C<sub>14</sub>H<sub>8</sub>N<sub>4</sub>O<sub>4</sub>S: C, 51.22; H, 2.46; N, 17.07. Found: C, 51.42; H, 2.41; N, 16.98.

**3,5-Bis(3-pyridyl)-1,2,4-thiadiazole (2h).** Off white solid; m.p.: 131-132 °C; IR (KBr)  $\nu_{\max}$  (cm<sup>-1</sup>) 3097, 2751, 1461, 1257, 1089, 777. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  (ppm) = 7.53-7.56 (m, 4H), 7.61-7.63 (m, 2H), 7.91 (s, 1H) 9.18 (s, 1H). MS: m/z 240 (M<sup>+</sup>). Anal. Calcd. For C<sub>12</sub>H<sub>8</sub>N<sub>4</sub>S: C, 59.98, H, 3.36; N, 23.32. Found: C, 60.15; H, 3.33; N, 23.13.

## RESULTS AND DISCUSSION

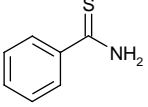
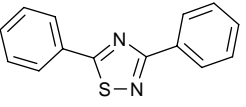
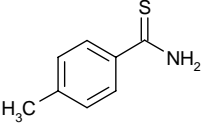
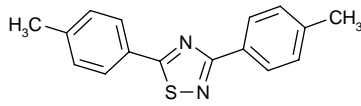
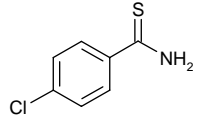
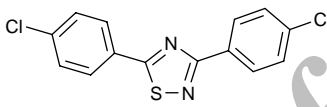
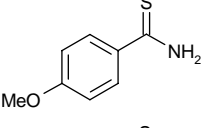
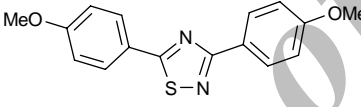
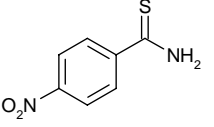
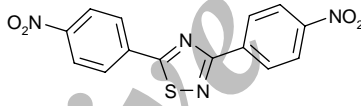
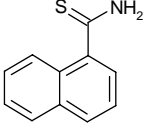
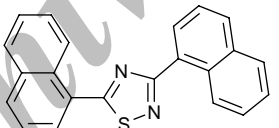
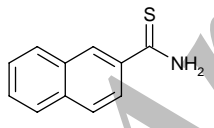
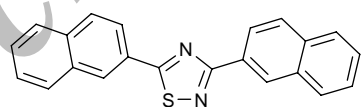
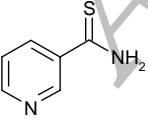
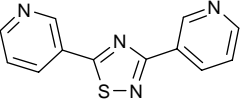
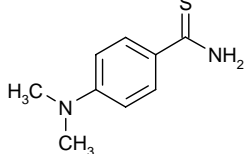
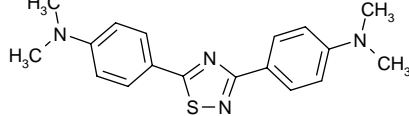
In this work, thiobenzamides were subjected to oxidation and cyclization to the 3,5-diaryl-1,2,4-thiadiazoles using N-benzyl-DABCO-tribromide in DMSO or in solvent-free conditions. As an alternative reagent to liquid bromine, organic ammonium tribromides (OATBs) which are of high molecular weight, stable, crystalline solids and also capable to release a stoichiometric amount of bromine (where small quantities of bromine are necessary for microscale reactions). OATBs have been largely used in organic synthesis as mild and effective brominating agents [19].

We introduced for the first time N-benzyl-DABCO-tribromide as a new OATB reagent. We found that N-benzyl-DABCO-tribromide is an effective reagent for the oxidative cyclization of thiobenzanilides to benzothiazoles [20], and for the deprotection of dithioacetals to the corresponding carbonyl compounds [21]. It was also found that, oxidation reaction of thiobenzamides following the cyclization to 1,2,4-thiadiazole derivatives rapidly occurs by N-benzyl-DABCO-tribromide in DMSO as solvent or in the solvent-free and in mild conditions with good to excellent yields (Scheme 1).

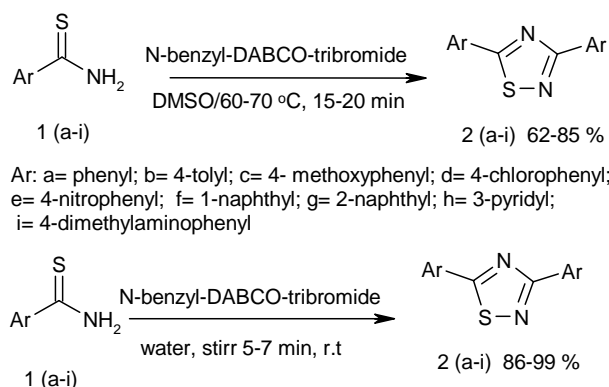
In a typical procedure, thiobenzamide **1a** was treated with equimolar amount of N-benzyl-DABCO-tribromide in DMSO and stirred for 15 min at 60 °C. After conventional work-up the corresponding 3,5-diphenyl-1,2,4-thiadiazole **2a** was obtained in good (85%) yield. It is worth noting that the resulting thiadiazole derivatives were simply isolated from the reaction mixture by precipitation with small amount of ethanol/water (30:70) and filtration in a pure

## Green Protocol for Synthesis of the 3,5-Disubstituted 1,2,4-Thiadiazoles

**Table 1.** Rapid and Efficient Conversion of Thioamides to 1,2,4-Thiadiazole Derivatives

Entry	Thioamide	Product <sup>a</sup>	Time (min) <sup>b</sup>	Temp. (°C)	M.P. (lit.)	Yield <sup>c</sup> DMSO/solid-solid
1			15	60	90-91	85
			5	r.t.	(89-90)	99
2			15	60	130-131	82
			5	r.t.	(130.5-131)	98
3			17	65	160-161	81
			6	r.t.	(161.5-162)	94
4			15	65	139-140	71
			6	r.t.	(139-139.5)	89
5			20	70	208-210	75
			7	r.t.	-	88
6			20	70	100-101.5	62
			6	r.t.	(99-100)	87
7			17	70	179-181	80
			6	r.t.	(180-180.5)	90
8			17	65	131-132	66
			6	r.t.	-	88
9			20	70	222-224	63
			7	r.t.	(223)	86

<sup>a</sup>All products were characterized by melting points, IR, <sup>1</sup>H NMR and their spectroscopic data, which were the same as those reported in the literature. <sup>b</sup>The reaction times were optimized after several experiments. <sup>c</sup>All yields refer to isolated products.



Scheme 1

form.

However, when the reaction course was performed in solvent-free conditions, the reaction products were produced at room temperature, in shorter times (5-7 min), and in higher yields (86-99%). Therefore, thioamide was mixed with equimolar quantity of the reagent and the reaction mixture was ground using a crucible mortar and pestle. Finally, the corresponding thiadiazole was precipitated with addition of aqueous ethanol and filtered. It was found that the grinding process takes place with difficulty due to formation of gummy mixture. Interestingly, the reaction course undergoes drastic favorable changes when the reaction mixture is made wet with a small amount of water.

Thus, an equimolar blend of 4-methyl-thio benzamide **1b** and N-benzyl-DABCO-tribromide was soaked in a small amount of water. Then the resulting pasty reaction mixture was stirred for 5 min at room temperature. After the addition of aqueous ethanol to the reaction mixture, the corresponding thiadiazole was precipitated, filtered, and crystallized to obtain pure product **2b** in high quantity (98%) yield. In both procedures, the reaction proceeds easily and cleanly and no tarry materials are produced. Another advantage of this method lies in the regeneration of the reagent. After the work-up, the aqueous layer of the reaction mixture was washed with ether and treated with bromine. Then the precipitated N-benzyl-DABCO-tribromide was filtered and washed twice with a small amount of water (10 ml) and dried under vacuum. It is also remarkable that no bromination takes place at the aromatic rings. Several cases have been investigated and the results

are summarized in Table 1.

In summary, a very mild, efficient, and rapid conversion of thio benzamides to the corresponding thiadiazoles is reported. The reaction proceeds in wet solid-solid (solvent-free) reaction conditions with high yields. To the best of my knowledge, no such reagent system and reaction media for the preparation of 1,2,4-thiadiazoles has so far been reported in the literature. The reaction occurs cleanly in aqueous media without the formation of any tarry materials. Another advantage of this methodology lies in its applicability to large-scale synthesis of thiadiazoles. The work-up and isolation of the product is very simple and the reagent is recoverable. The starting materials are readily available and inexpensive.

## ACKNOWLEDGEMENTS

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