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Green Protocol for Synthesis of the 3,5-Disubstituted 1,2,4-Thiadiazoles Using N-Benzyl-DABCO-Tribromide in Aqueous Media

H. Zali Boeini
Department of Chemistry, University of Isfahan, Isfahan, 81764-73441, Iran

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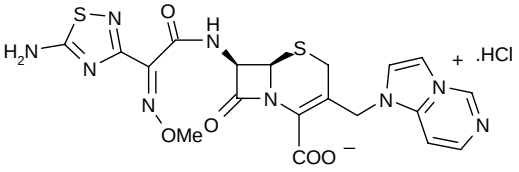
A novel and simple method for rapid conversion of thioamides to the corresponding 1,2,4-thiadiazole derivatives was developed. It was shown that, thioamides undergo clean and efficient oxidation and cyclization in their conversion to 1,2,4-thiadiazoles using N-benzyl-DABCO-tribromide in wet solid-solid conditions.

Keywords: Synthesis, 3,5-Disubstituted 1,2,4-thiadiazoles, N-Benzyl-DABCO-tribromide, Aqueous media

INTRODUCTION

The synthesis of 1,2,4-thiadiazoles has attracted a great deal of interest through the years due to their biological activities. 1,2,4-Thiadiazole derivatives are widely found in bioorganic and medicinal chemistry with applications in drug discovery and development for treatment of human leukemia cell [1], such as Cathepsin B inhibitors [2], allosteric modulators [3], factor XIIIa inhibitors [4], non-ATP competitive glycogen synthase kinase 3β inhibitors [5], and dual 5-lipoxygenase and cyclooxygenase inhibitors [6]. Some of these show intense muscarinic [7] and cardiprotective activities [8]. Monocyclic 1,2,4-thiadiazoles have been widely claimed to be useful insecticidal, herbicidal and fungicidal agents [9]. Recently the thiol-traping properties of 1,2,4-thiadiazole systems have been surveyed [10]. Although there are numerous 1,2,4-thiadiazole derivatives with interesting biological and therapeutic activities, the only commercialized 1,2,4-thiadiazole drug is the antibiotic Cefozopran [11].



Cefozopran

The usefulness of 1,2,4-thiadiazole as pharmacophore in medicinal chemistry has attracted interest in the synthesis of this system. The main synthetic route to obtain symmetrical 3,5-dialkyl/diaryl-1,2,4-thiadiazole derivatives generally comprises an oxidation step of the thioamides following the cyclization to the corresponding thiadiazoles. Various oxidizing agents such as halogens [12], nitrous acid [13], hydrogen peroxide [14], thionyl chloride [15], a mixture of HCl-DMSO [16], and pyridinium salt-DMSO [17] have been employed for this procedure. Meanwhile the reaction of 1-monosubstituted thioureas with bis (acyloxyiodo) arenes has been reported as a synthetic procedure to obtain 3,5-bis-(phenylamino)-1,2,4-thiadiazoles [18]. Although all of the above reagents successfully perform the desired reaction in moderate to good yields, several drawbacks are associated with their utilization in the reaction course, which are poisonous or corrosive and difficult to manipulate in small

*Corresponding author. E-mail: h.zali@chem.ui.ac.ir

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-Bezyl-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 filterd, 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-bezyl-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-bezyl-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 ºC; IR (KBr) υ_{max} (cm^{-1}) 3083, 2743, 1454, 1263, 1095, 785. ^1H NMR ($CDCl_3$): δ (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^+). Anal. Calcd. For $C_{14}H_8N_4O_4S$: 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 ºC; IR (KBr) υ_{max} (cm^{-1}) 3097, 2751, 1461, 1257, 1089, 777. ^1H NMR ($CDCl_3$): δ (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^+). Anal. Calcd. For $C_{12}H_8N_4S$: C, 59.98, H, 3.36; N, 23.32. Found: C, 60.15; H, 3.33; N, 23.13.

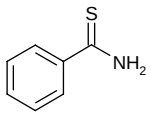
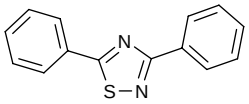
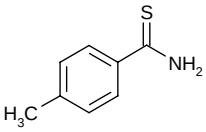
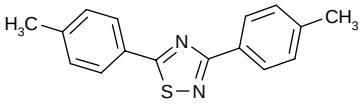
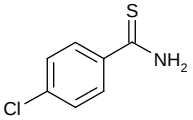
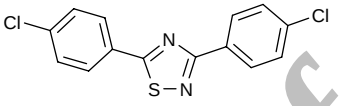
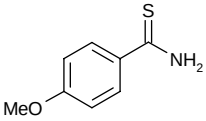
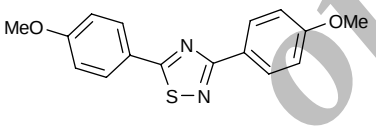
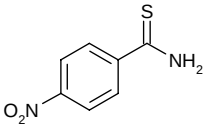
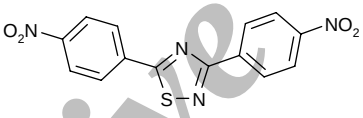
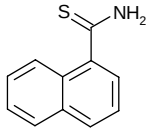
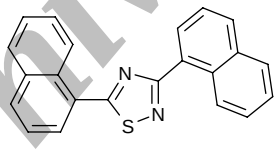
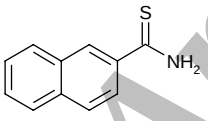
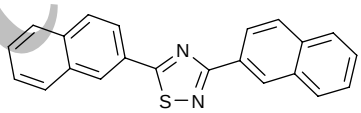
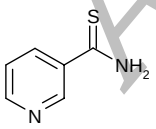
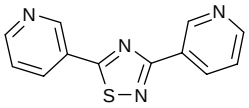
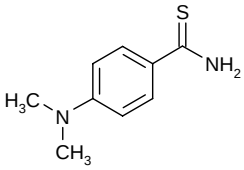
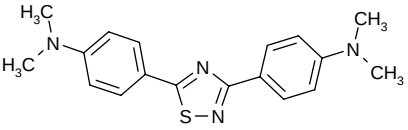
RESULTS AND DISSCUTION

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].

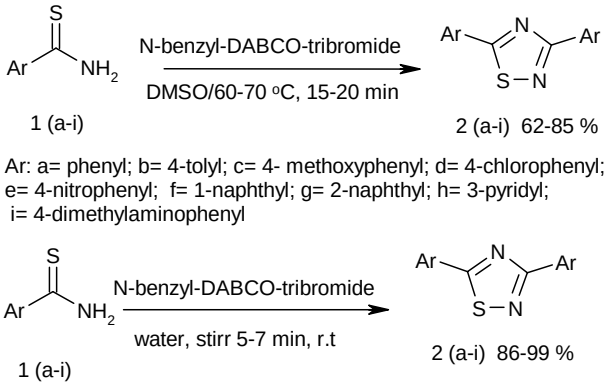
We introduced for the first time N-benzyl-DABCO-tribromide as a new OATB reagent. We found that N-benzyl-DABCO-tribromide is an effective reagent for the oxidative cyclization of thiobenzanilides to benzothiazoles [20], and for the deprotection of dithioacetals to the corresponding carbonyl compounds [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 ºC. 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

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

Entry	Thioamide	Product[a]	Time (min)[b]	Temp. (ºC)	M.P. (lit.)	Yield[c] 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

[a]All products were characterized by melting points, IR, ^{1}H NMR and their spectroscopic data, which were the same as those reported in the literature. [b]The reaction times were optimized after several experiments. [c]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-thiobenzamide **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 thiobenzamides 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.

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