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Highly efficient synthesis of 3,5-disubstituted 1,2,4-thiadiazoles using pentylpyridinium tribromide as a solvent/reagent ionic liquid

Hassan Zali-Boeini[a], Arash Shokrolahi[b], Abbas Zali[b]* and Kamal Ghani[b]

[a]*Department of Chemistry, University of Isfahan, PO Box 81746-73441, Isfahan, Islamic Republic of Iran;* [b]*Department of Chemistry, Malek-Ashtar University of Technology, PO Box 83145-115, Shahin shahr, Islamic Republic of Iran*

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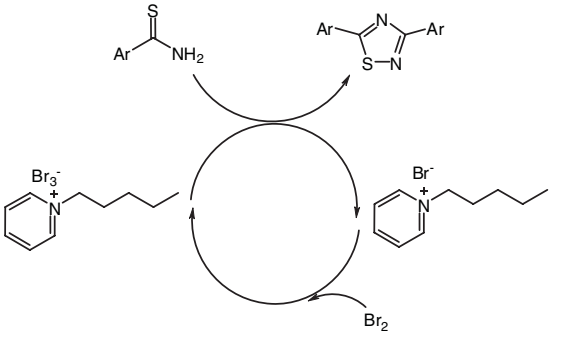
In this paper, a facile and highly efficient synthesis of 3,5-disubstituted 1,2,4-thiadiazoles by oxidative dimerization of thioamides using pentylpyridinium tribromide is reported.



Keywords: 3,5-disubstituted 1,2,4-thiadiazoles; thiobenzamide; pentylpyridinium tribromide; oxidative cyclization; ionic liquid

1. Introduction

1,2,4-Thiadazoles are important heterocycles, which have been the subject of great interest because of their biological activities (*1*). Very interesting therapeutic applications have been found in

*Corresponding author. Email: abbasazali@gmail.com

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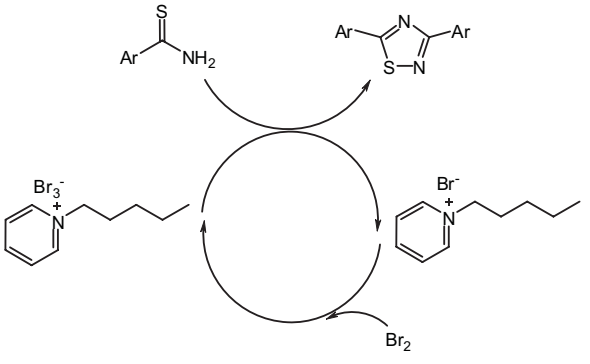
the 1,2,4-thiadiazole system and its usefulness as a pharmacophore in medicinal chemistry has prompted the advances in thechemistry of this system (*2*). A large number of 1,2,4-thiadiazoles have been used and patented in the agricultural (*3*, *4*) and medicinal industries (*5–7*). Also, thiadiazole derivatives have shown good corrosion inhibitor effects in aggressive media (*8–10*).

The main synthetic route to obtain symmetrical 3,5-dialkyl/diaryl-1,2,4-thiadiazole derivatives generally comprises an oxidation step of the thioamides followed by the cyclization to the corresponding thiadiazole. Various oxidizing agents such as nitrous acid (*11*), hydrogen peroxide (*12*), thionyl chloride (*13*), a mixture of HCl–DMSO (*14*), pyridinium salt–DMSO (*15*), polymer-supported diaryl selenoxide and telluroxide (*16*), organotellurium (*17*), *p*-toluenesulfinic acid (*18*), phenyliodine (III) diacetate (*19*, *20*), *t*-butyl hypochlorite (*21*), *N*-bromosuccinimide (*22*), and *o*-iodoxybenzoic acid in the presence of tetraethylammonium bromide (*23*) have been employed for this transformation. Although the above reagents provide efficient access to 1,2,4-thiadiazoles, several drawbacks are associated with their utilization and many of these reagents are poisonous or corrosive and can be difficult to manipulate on small scales. The formation of nitrile and isothiocyanate by-products and tedious workup are also disadvantages of these protocols.

Room temperature ionic liquids (RTILs) are currently attracting considerable attention as potentially benign solvents/reagents for organic transformations, and a large number of reactions have been successfully performed using these solvents. They are non-volatile, have excellent chemical and thermal solubility, and can solubilize a wide variety of substrates (*24*). Pentylpyridinium tribromide is a non-volatile ionic liquid analog of bromine, which plays a dual role as a solvent and a reagent and can be easily prepared from commercially available starting materials (*25*).

Herein, we report a rapid, mild, facile, and efficient method for the synthesis of symmetrical 3,5-diaryl-1,2,4-thiadiazoles by oxidative dimerization of the corresponding thiobenzamides using pentylpyridinium tribromide (Scheme 1).



Scheme 1. Oxidative dimerization of thioamides.

2. Results and discussion

As reported in Table 1, a variety of thiobenzamides successfully underwent oxidative dimerization to form the corresponding 3,5-disubstituted 1,2,4-thiadiazoles using pentylpyridinium tribromide as a non-volatile RTIL and as an alternative reagent to liquid bromine. All the reactions were clean and smooth and proceeded without the formation of any tarry materials and were completed within 3–7 min, providing a high yield. The other advantage of the presented methodology lies in the fact that the reagent can be readily recovered and reused several times. The recovery and regeneration of pentylpyridinium tribromide involved the extraction of the aqueous layer from the reaction mixture with ether followed by treatment with bromine. Then, the precipitated pentylpyridinium tribromide

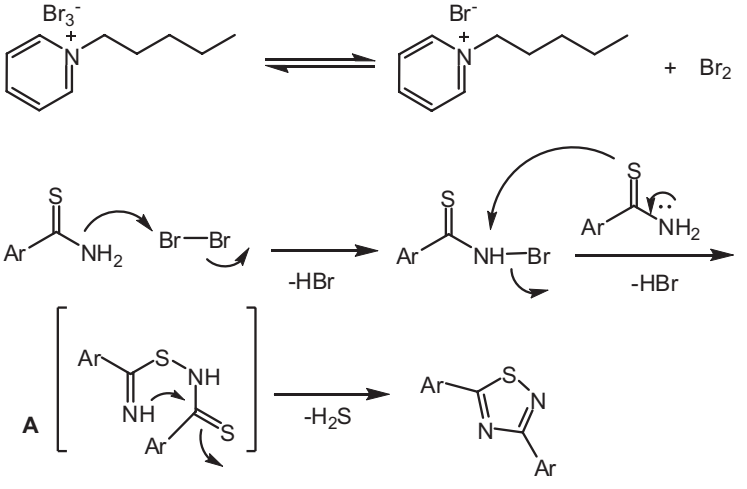
Table 1. Rapid and efficient conversion of thioamides to 1,2,4-thiadiazole derivatives.

Entry	Ar	Time (min)	Yield[a] (%)	Reference
1	Ph	4	97	15
2	4-Me-C_6H_4	3	95	15
3	4-NO_2-C_6H_4	7	89	23
4	3-Br-C_6H_4	4	93	26
5	4-Br-C_6H_4	4	95	20
6	2-Cl-C_6H_4	6	90	23
7	3-Cl-C_6H_4	5	92	20
8	4-Cl-C_6H_4	4	94	15
9	4-F-C_6H_4	6	88	26
10	4-MeO-C_6H_4	3	91	15
11	2,4-Cl_2-C_6H_3	5	90	26
12	2-Furanyl	4	92	20

Note: [a]All yields refer to isolated products.

was separated 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 during the reaction.

We propose a plausible reaction pathway, as shown in Scheme 2. Probably, this reaction proceeds via the formation of *N*-bromothioamide and subsequent dimerization to give intermediate A, which undergoes intermolecular cyclization to the corresponding 1,2,4-thiadiazole.



Scheme 2. Proposed mechanism for the formation of 3,5-disubstituted 1,2,4-thiadiazoles.

3. Experimental

3.1. *General experimental information*

All the solvents were used as purchased from commercial sources. Thin-layer chromatography (TLC) was performed using silica gel 60 F_{254} pre-coated plates (0.25 mm). All the products were purified by crystallization to homogeneity by TLC analysis (single spot), using a UV lamp and/or iodine and/or CAN or basic $KMnO_4$ for detection purposes. NMR spectra were recorded on 500 MHz spectrometers. ^1H and ^{13}C NMR chemical shifts are reported as δ using residual solvent as an internal standard.

3.2. *General procedure for the preparation of pentylpyridinium tribromide*

Bromine (64.48 g, 404.7 mmol) was added over 30 min to solid crushed pentylpyridinium bromide (93.07 g, 404.4 mmol) under mechanical stirring and cooling in a water bath affording a deep red liquid. After stirring for 2 h, the liquid was left in vacuo overnight (yield, 156 g (99%); melting point, 0°C).

3.3. *General procedure for the preparation of thiobenzamides*

Method A. In a round-bottomed flask, the benzamide derivative (5 mmol) was dissolved in dry THF (20 ml) and then P_2S_5 (1.12 g, 5 mmol) was added and the mixture was heated at 65°C for 3 h. Thereafter, the reaction mixture was cooled, poured in $NaHCO_3$ (10%, 50 ml), and stirred for 30 min. Then, the resulting yellow solid was filtered, dried, and recrystallized from EtOAc to give thiobenzamide as light yellow prisms.

Method B. In a round-bottomed flask, a mixture of the benzonitrile derivative (5 mmol), $(NH_4)_2S$ (20%, 5 ml), and an ammonia solution (32%, 2 ml) was dissolved (or suspended) in EtOH (5 ml) and stirred at room temperature for 16 h. Thereafter, water (10 ml) was added to the mixture and the precipitated compound was filtered. Then, the resulting crude thiobenzamide derivative was recrystallized from EtOAc–hexane to obtain pure compounds as yellow prisms.

3.4. *General procedure for the preparation of 3,5-diaryl-1,2,4-thiadiazole*

Finely pulverized thiobenzamide (10 mmol) and pentylpyridinium tribromide (10 mmol, 3.90 g) were mixed and the resulting orange syrup was stirred for the times given in Table 1. At the start of the reaction, the reaction mixture was yellow and it turned to a pale yellow after completion of the reaction. Thereafter, 20 ml water was added to the reaction mixture. Then, the precipitated compound was filtered and crystallized in ethanol (or ethanol–chloroform) to obtain pure target compounds as white to light yellow needles and in good to excellent yields.

It is worthwhile to note that the ionic liquid pentylpyridinium bromide was recycled from the reaction mixture and the reagent was regenerated by the direct action of bromine. The effectiveness of this recycling and regenerating process was tested and found effective for up to six cycles.

3.5. *Spectroscopic data for compounds*

3.5.1. *3,5-Diphenyl-1,2,4-thiadiazole* (*Entry 1*)

White needles (EtOH), m.p. 91–93°C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.43 (d, $J = 8.0$ Hz, 2H), 8.10 (d, $J = 7.5$ Hz, 2H), 7.52–7.60 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): 185.8, 174.1, 132.6, 130.7, 130.3, 129.2, 128.7, 128.5, 127.5.

3.5.2. *3,5-Di-p-tolyl-1,2,4-thiadiazole* (*Entry 2*)

White crystals (EtOH), m.p. 129–131°C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.31 (d, $J = 8.1$ Hz, 2H), 7.98 (d, $J = 8.1$ Hz, 2H), 7.34–7.37 (m, 4H), 2.51 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 180.2, 171.3, 140.6, 138.3, 137.8, 131.3, 129.4, 128.3, 127.5, 21.8, 21.6.

3.5.3. *3,5-Bis(4-nitrophenyl)-1,2,4-thiadiazole* (*Entry 3*)

Light yellow needles (EtOH–$CHCl_3$), m.p. 201–202°C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.63 (d, $J = 8.2$ Hz, 2H), 8.45 (d, $J = 8.2$ Hz, 2H), 8.43 (d, $J = 8.2$ Hz, 2H), 8.30 (d, $J = 8.2$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 187.4, 173.3, 148.2, 139.8, 128.9, 126.8, 126.4, 125.8, 123.5, 121.5.

3.5.4. *3,5-Bis(3-bromophenyl)-1,2,4-thiadiazole* (*Entry 4*)

White crystals (EtOH–$CHCl_3$), m.p. 138–140°C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.51 (s, 1H), 8.32 (d, $J = 8.7$ Hz, 1H), 8.21 (s, 1H), 7.93 (dd, $J = 8.7$, 1.5 Hz, 1H), 7.60–7.68 (m, 2H), 7.35–7.42 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 186.8, 172.4, 134.9, 134.5, 133.4, 130.8, 130.3, 126.9, 126.1, 123.4, 122.9. Anal. calcd for $C_{14}H_8Br_2N_2S$: C, 42.45; H, 2.04; N, 7.07; S, 8.10. Found: C, 42.28; H, 1.99; N, 7.15; S, 8.31.

3.5.5. *3,5-Bis(4-bromophenyl)-1,2,4-thiadiazole* (*Entry 5*)

White crystals (EtOH–$CHCl_3$), m.p. 167–169°C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.24 (d, $J = 8.5$ Hz, 2H), 790 (d, $J = 8.5$ Hz, 2H), 7.66 (d, $J = 6.9$ Hz, 2H), 6.64 (d, $J = 6.9$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 187.2, 172.9, 132.8, 132.3, 131.6, 129.8, 129.5, 128.8, 126.6, 125.1. Anal. calcd for $C_{14}H_8Br_2N_2S$: C, 42.45; H, 2.04; N, 7.07; S, 8.10. Found: C, 42.30; H, 2.01; N, 7.10; S, 8.25.

3.5.6. *3,5-Bis(2-chlorophenyl)-1,2,4-thiadiazole* (*Entry 6*)

White crystals (EtOH), m.p. 93–95°C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.65 (td, $J = 7.2$, 2.1 Hz, 1H), 8.05 (td, $J = 7.2$, 2.2 Hz, 1H), 7.55–7.60 (m, 2H), 7.46–7.48 (m, 2H), 7.40–7.42 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 183.1, 173.2, 133.8, 133.3, 132.3, 132.1, 130.9, 130.8, 130.7, 129.6, 127.5, 126.8. 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, 2.45; N, 9.05; S, 10.55.

3.5.7. *3,5-Bis(3-chlorophenyl)-1,2,4-thiadiazole* (*Entry 7*)

White crystals (EtOH–$CHCl_3$), m.p. 128–129°C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.39 (s, 1H), 8.27 (d, $J = 7.0$ Hz, 1H), 8.07 (s, 1H), 7.90 (d, $J = 7.6$ Hz, 1H), 7.52–7.54 (m, 1H), 7.43–7.49 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 186.9, 172.5, 135.5, 134.8, 134.3, 132.1, 132.0, 130.6, 130.0, 128.5, 127.3, 126.4, 125.7. Anal. calcd for $C_{14}H_8Cl_2N_2S$: C, 54.74; H, 2.62; N, 9.12; S, 10.44. Found: C, 54.60; H, 2.51; N, 9.10; S, 10.61.

3.5.8. *3,5-Bis(4-chlorophenyl)-1,2,4-thiadiazole* (*Entry 8*)

White crystals (EtOH–$CHCl_3$), m.p. 162–164°C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.32 (d, $J = 8.6$ Hz, 2H), 8.99 (d, $J = 8.5$ Hz, 2H), 7.51 (d, $J = 8.5$ Hz, 2H), 7.48 (d, $J = 8.6$ Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 187.0, 172.9, 135.7, 134.8, 131.3, 129.7, 129.4, 128.9, 127.7, 126.8.

3.5.9. *3,5-Bis(4-fluorophenyl)-1,2,4-thiadiazole* (*Entry 9*)

White crystals (EtOH), m.p. 186–188°C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.38 (ddd, $J = 12.2$, 6.7, 3.3 Hz, 2H), 8.05 (ddd, $J = 11.9$, 5.2, 2.8 Hz, 2H), 7.16–7.24 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): 187.0, 172.8, 166.0, 165.2, 163.9, 163.2, 130.4, 129.6, 116.5, 115.7. Anal. calcd for $C_{14}H_8F_2N_2S$: C, 61.30; H, 2.94; N, 10.21; S, 11.69. Found: C, 61.21; H, 2.80; N, 10.02; S, 11.80.

3.5.10. *3,5-Bis(4-methoxyphenyl)-1,2,4-thiadiazole* (*Entry 10*)

Pale yellow needles (EtOH–$CHCl_3$), m.p. 138–139°C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.33 (dd, $J = 6.9$, 2.0 Hz, 2H), 7.99 (dd, $J = 6.8$, 2.0 Hz, 2H), 7.00–7.03 (m, 4H), 3.90 (s, 3H), 3.89 (s,

3H); ^{13}C NMR (125 MHz, $CDCl_3$): 180.4, 171.6, 162.9, 136.7, 134.5, 133.5, 132.6, 126.9, 114.5, 113.1, 113.0, 57.7, 57.5.

3.5.11. *3,5-Bis(2,4-dichlorophenyl)-1,2,4-thiadiazole* (*Entry 11*)

White needles (EtOH–$CHCl_3$), m.p. 133–134°C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.57 (d, J = 8.7 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H), (d, J = 2.1 Hz, 1H), (d, J = 2.1 Hz, 1H), (dd, J = 8.7, 2.1 Hz, 1H), (dd, J = 8.4, 2.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 182.3, 173.2, 138.0, 136.4, 136.3, 134.4, 134.2, 133.1, 131.4, 130.8, 130.3, 120.7, 128.1, 127.2. Anal. calcd for $C_{14}H_6Cl_4N_2S$: C, 44.71; H, 1.61; Cl, 37.71; N, 7.45; S, 8.53. Found: C, 44.60; H, 1.54; N, 7.37; S, 8.74.

3.5.12. *3,5-Di(furan-2-yl)-1,2,4-thiadiazole* (*Entry 12*)

White needles (EtOH), m.p. 104–106°C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.94 (d, J = 3.6 Hz, 1H), 7.70 (d, J = 3.7 Hz, 1H), 7.59 (d, J = 5.1 Hz, 1H), 7.46 (d, J = 5.0 Hz, 1H), 7.13–7.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 185.4, 171.1, 158.9, 151.4, 151.0, 147.6, 116.9, 116.7, 112.3.

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