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IBX/TEAB-mediated oxidative dimerization of thioamides: synthesis of 3,5-disubstituted 1,2,4-thiadiazoles

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ABSTRACT

Thioamides undergo oxidative dimerization on treatment with hypervalent iodine(V)-containing reagents, particularly *o*-iodoxybenzoic acid (IBX), in the presence of tetraethylammonium bromide (TEAB) to generate 3,5-disubstituted 1,2,4-thiadiazoles in excellent yield.

1. Introduction

Thiadiazoles are important precursors for the synthesis of many bioactive molecules belonging to various therapeutic categories, such as *anti*-microbial agents,[1] fungicides,[2] herbicides,[3] and *anti*-biotics.[4,5] The methods used for the preparation of 3,5-disubstituted 1,2,4-thiadiazoles may be divided into three categories, which include intramolecular cyclization,[6–8] intermolecular cyclization,[9,10] and oxidative dimerization.[11–17] The latter has been carried out by using different oxidizing agents, such as nitrous acid,[11] polymer-supported diaryl selenoxide and telluroxide,[12] organotellurium,[13] *p*-toluenesulfinic acid,[14] phenyliodine (III) diacetate,[15] *t*-butyl hypochlorite,[16] and dimethylsulfoxide-electrophilic reagents.[17] Some of these methods suffer from drawbacks such as the formation of nitriles and isothiocyanates as by-products.

In continuation of our ongoing studies[18] exploring the use of hypervalent iodine (V) in organic synthesis, we report herein *o*-iodoxybenzoic acid (IBX) as an effective promoter of oxidative dimerization of thiomides **1** to yield 3,5-disubstituted 1,2,4-thiadiazoles **2** as shown in Scheme 1.

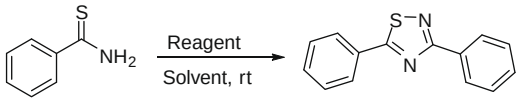
1 **2**

Scheme 1. Oxidative dimerization of thioamides.

2. Result and discussion

Treatment of phenylthioamide **1a** with IBX in acetonitrile for 60 min generated **2a** in 95% yield. When tetraethylammonium bromide (TEAB) was used in combination with IBX, as expected, the reaction was greatly accelerated and proceeded to completion within just 5 min with an equimolar ratio of IBX and TEAB without decreasing the yield. Various investigations toward optimization of

Table 1
Optimization of reagents and reaction conditions[a]



1a **2a**

Entry	Reagent (mol equiv)	Solvent	Time (min)	Yield[b] (%)
1	IBX (1.5)	MeCN	60	95
2	IBX/TEAB (1.1/0.2)	MeCN	50	95
3	**IBX/TEAB (1.1/1.1)**	**MeCN**	**5**	**95**
4	IBX/TEAB (1.1/1.1)	CH_2Cl_2	10	94
5	IBX/TEAB (1.1/1.1)	Toluene	60	85
6	DMP[c]/TEAB (1.1/1.1)	MeCN	10	94

Bold entries indicates best reaction conditions.
[a] Reactions were carried out on a 5-mmol scale at rt.
[b] Yields obtained after column chromatography.
[c] Dess–Martin periodinane.

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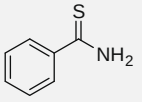
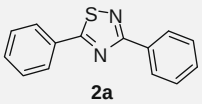
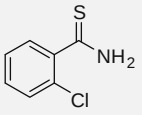
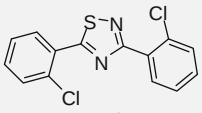
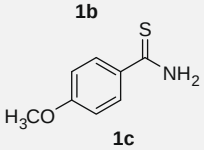
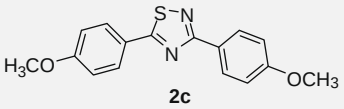
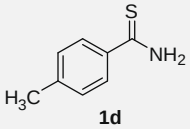
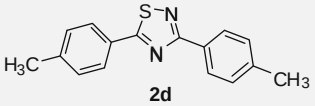
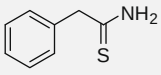
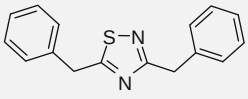
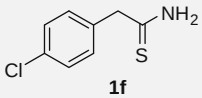
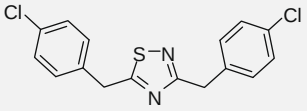
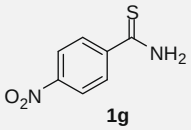
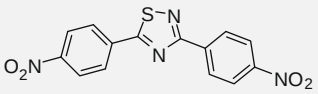
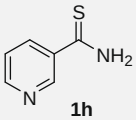
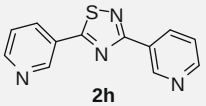
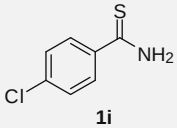
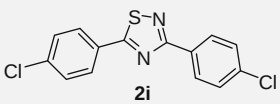
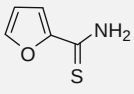
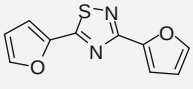
the reaction conditions with respect to hypervalent iodine-containing reagents, appropriate solvents, and the molar ratio (Table 1) were carried out. In the studies on solvents, acetonitrile was found to be the best solvent.

As observed from Table 1, the reaction proceeded well in acetonitrile and chlorinated solvents, such as CH_2Cl_2, and was slow and incomplete in toluene; this could be attributed to the very low solubility of the reagent.

To establish the generality of the reaction, various types of thioamides have been prepared by established methods[19] and subjected to the reaction under optimized conditions; the results are summarized in Table 2.

As reported in Table 2, a variety of substrates—aromatic, heteroaromatic and benzylic thioamides—underwent oxidative dimerization to form the corresponding 3,5-disubstituted 1,2,4-thiadiazoles. All the reactions were clean, smooth, and achieved completion within 5–15 min, providing high yield. A noteworthy feature of the reaction was that the benzylic position and the pyridine moiety remained unaffected (Table 2, entries 5, 6, and 8). In conclusion, it has been established that hypervalent iodine (V)-

Table 2
Oxidative dimerization of thioamides to 3,5-disubstituted 1,2,4-thiadiazoles[a]

Entry	Substrate (**1**)	Product (**2**)	Time (min)	Yield[b] (%)
1	 **1a**	 **2a**	5	95
2	 **1b**	 **2b**	10	93
3	 **1c**	 **2c**	5	96
4	 **1d**	 **2d**	5	96
5	 **1e**	 **2e**	10	90
6	 **1f**	 **2f**	10	90
7	 **1g**	 **2g**	15	91
8	 **1h**	 **2h**	15	90
9	 **1i**	 **2i**	10	92
10	 **1j**	 **2j**	15	88

[a] Reactions were carried out on a 5-mmol scale in acetonitrile at room temperature with IBX (1.1 equiv) and TEAB (1.1 equiv).
[b] Yields obtained after column chromatography.

containing reagent is suitable for the oxidative dimerization of thioamides. A reagent system consisting of a combination of IBX/TEAB has been developed for the clean, efficient, rapid, and chemoselective synthesis of 3, 5-disubstituted 1,2,4-thiadiazoles under mild conditions.

3. General experimental procedure for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles

To a stirred suspension of IBX (1.54 g, 5.5 mmol) in MeCN (20 mL) was added TEAB (1.16 g, 5.5 mmol). A yellow suspension was observed to which substrate (5 mmol) was added in one portion after 5 min at room temperature. Consumption of starting material was observed by TLC. After completion of reaction, acetonitrile was removed under reduced pressure and the resultant residue was washed with ethyl acetate (25 mL) followed by 10% sodium bisulfite solution (25 mL), saturated sodium carbonate (25 mL), and brine (25 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude product. Pure product was isolated after column chromatography (silica gel mesh size 60–120, eluent ethyl acetate/*n*-hexane (5:95).

4. Spectral data for 3,5-disubstituted-1,2,4-thiadiazoles

4.1. 3,5-Diphenyl-1,2,4-thiadiazole (2a)

Solid, mp = 90–92 °C, [lit[17] 91–91.5 °C]. IR (KBr) ν_{max} (cm^{-1}): 3050, 1590, 1472. ^1H NMR (60 MHz, $CDCl_3$): δ 8.37–8.28 (m, 2H), 7.92–8.03 (m, 2H), 7.41–7.79 (m, 6H) ppm. ^{13}C NMR (60 MHz, $CDCl_3$): δ 188.07, 173.72, 140.86, 132.78, 131.88, 130.59, 130.31, 129.21, 128.64, 128.28, 127.80, 127.4 ppm.

4.2. 3,5-Bis(2-chlorophenyl)-1,2,4-thiadiazole (2b)

Solid, mp = 92–95 °C, [lit[20] 93–96 °C]. IR (KBr) ν_{max} (cm^{-1}): 3055, 1570, 1478. ^1H NMR (60 MHz, $CDCl_3$): δ 8.71–8.57 (m, 1H), 8.07–7.98 (m, 1H), 7.54–7.31 (m, 6H) ppm. ^{13}C NMR (60 MHz, $CDCl_3$): δ 183.05, 173.98, 133.90, 133.50, 132.50, 132.18, 132.00, 130.91, 130.82, 130.63, 130.44, 129.7, 127.51, 126.7 ppm.

4.3. 3,5-Bis(4-methoxylphenyl)-1,2,4-thiadiazole (2c)

Solid, mp = 139–140 °C, [lit[17] 139–139.5 °C]. IR (KBr) ν_{max} (cm^{-1}): 3035, 1602, 1489. ^1H NMR (60 MHz, $CDCl_3$): δ 8.30–7. 93 (m, 4H), 7.18–7.06 (m, 4H), 3.85 (s, 6H) ppm. ^{13}C NMR (60 MHz, $CDCl_3$): δ 187.39, 173.34, 162.46, 161.25, 135.66, 133.99, 131.12, 129.88, 129.15, 127.79, 125.99, 123.64, 114.53, 113.96 ppm.

4.4. 3,5-Bis(4-methylphenyl)-1,2,4-thiadiazole (2d)

Solid, mp = 130–131 °C, [lit[17] 130.5–131 °C]. IR (KBr) ν_{max} (cm^{-1}): 3042, 1599, 1485. ^1H NMR (60 MHz, $CDCl_3$): δ 8.24–7.96 (m, 4H), 7.56–7.30 (m, 4H), 2.40 (s, 6H) ppm.

4.5. 3,5-Dibenzyl-1,2,4-thiadiazole (2e)

Oil, (lit[17] = oil). IR (neat) ν_{max} (cm^{-1}): 3029, 1598, 1488. ^1H NMR (60 MHz, $CDCl_3$): δ 7.35 (s, 10H), 4.32 (s, 2H), 4.27 (s, 2H) ppm.

4.6. 3,5-bis(4-chlorobenzyl)-1,2,4-thiadiazole (2f)

Solid, mp = 61–63 °C, [lit[17] 60–62 °C]. IR (KBr) ν_{max} (cm^{-1}): 3030, 1602, 1492. ^1H NMR (60 MHz, $CDCl_3$): δ 7.75–7.48 (m, 8H), 4.26 (s, 2H), 4.17 (s, 2H) ppm.

4.7. 3,5-Bis(4-nitrophenyl)-1,2,4-thiadiazole (2g)

Solid, mp = 200–202 °C, [lit[16] 198–199 °C]. IR (KBr) ν_{max} (cm^{-1}): 1602, 1535, 1408, 1345, 1322, 850. ^1H NMR (60 MHz, $CDCl_3$): δ 7.68–7.61 (m, 4H), 7.88 (d, 2H), 8.19 (d, 2H) ppm.

4.8. 3,5-Bis(3-pyridinyl)-1,2,4-thiadiazole (2h)

Solid, mp = 133–135 °C, [lit[16] 136–137 °C]. IR (KBr) ν_{max} (cm^{-1}): 1588, 1482, 1405, 1345, 1300, 1035, 723. ^1H NMR (60 MHz, $CDCl_3$): δ 9.60–9.56 (m, 1H), 9.30–9.25 (m, 1H), 8.81–8.76 (m, 2H), 8.74–8.33 (m, 2H), 7.53–7.45 (m, 2H) ppm.

4.9. 3,5-Bis(4-chlorophenyl)-1,2,4-thiadiazole (2i)

Solid, mp = 161–162 °C, [lit[17] 161.5–162 °C]. IR (KBr) ν_{max} (cm^{-1}): 3035, 1595, 1492. ^1H NMR (60 MHz, $CDCl_3$): δ 8.26–7.99 (m, 4H), 7.72–7.42 (m, 4H) ppm.

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