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SHORT COMMUNICATION

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Synthesis of 1,2,4-Thiadiazoles by Oxidative Dimerization of Carbothioamides by Using Oxone

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Dedicated to the memory of Professor Alan R. Katritzky

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1,2,4-Thiadiazoles were efficiently synthesized in good yields through the oxidative dimerization of carbothioamides by using Oxone as a readily available, inexpensive, and environmentally safe oxidant. A similar reaction of phenylselenoamide led to the corresponding 1,2,4-phenylselenadiazole in high yield.

Introduction

1,2,4-Thiadiazoles are important heterocycles with numerous applications as pharmaceuticals, fungicides, herbicides, bacteriocides, dyes, lubricant additives, and vulcanization accelerators.[1] Particularly interesting are the medicinal properties of 1,2,4-thiadiazoles that serve as important pharmacophores in inhibitors targeting the cysteine residues of proteins.[2] The most common approach to the synthesis of medicinally important 1,2,4-thiadiazoles involves the oxidative dimerization of thioamides.[3] A particularly important class of oxidants for the synthesis of 1,2,4-thiadiazoles from thioamides is represented by organohypervalent iodine reagents,[4] for example, (diacetoxyiodo)benzene,[4d–4f] 2-iodoxybenzoic acid (IBX),[4g] and recyclable hypervalent iodanes.[4e,4h] Other reagents, such as polymer-supported diaryl selenoxide and telluroxide,[5a,5b] *tert*-butyl hypochlorite (*t*BuOCl),[5c] *N*-bromosuccinimide (NBS),[5d] and dimethyl sulfoxide derived electrophilic reagents[5e] have also been utilized as oxidants in this dimerization. However, these methods have only limited applicability for the synthesis of thioamides because they involve toxic reagents and harsh conditions and usually produce nitriles and isothiocyanates as byproducts.[1,6] Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) is known as an inexpensive and environmentally safe oxidant that is useful for numerous oxidation reactions.[7a,7b] Previously, the reaction of thioamides with Oxone under solvent-free conditions leading to the corresponding carbonyl compounds in good yields was reported.[8] However, to the best of our knowledge, the Oxone-promoted dimerization of thioamides to 1,2,4-thiadiazoles is still unknown.

In this communication, we describe the dimerization of thioamides and selenoamide by using Oxone as an inexpensive and environmentally safe terminal oxidant. Oxone is known to be a convenient oxidant, and it has been used for many important reactions such as C–H oxidation,[9a–9c] oxidative cleavage reactions,[9d,9e] and oxidative rearrangement reactions.[9f–9h] Several research groups have also reported the use of Oxone as a terminal oxidant for catalytic reactions induced by organohypervalent iodine species generated in situ from iodoarenes as precatalysts.[10] Very recently, our group also reported that Oxone is an excellent terminal oxidant for the hypervalent iodine catalyzed Hofmann rearrangement[11a] and for the hypoiodite-mediated catalytic oxidative cyclization of aldoximes and alkenes leading to isoxazolines and isoxazoles.[11b,11c]

Results and Discussion

We investigated the dimerization reaction of thiobenzamide (**1a**, 1 equiv.) by using various solvents and different terminal oxidants (Table 1). As the initial step, we attempted to perform hypervalent iodine catalyzed oxidative dimerization of thiobenzamide by analogy with the known hypervalent iodine mediated cyclizations.[4,11] In the presence of PhI as a precatalyst (10 mol-%) and Oxone as a terminal oxidant, the dimerization of **1a** afforded desired thiadiazole **2a** in 97% yield (Table 1, entry 1). However, in the absence of PhI under similar reaction conditions, desired thiadiazole **2a** was formed in a comparable 95% yield (Table 1, entry 2), which led us to the conclusion that

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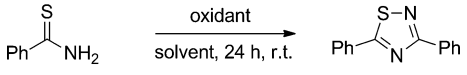
Oxone alone could be used as an efficient oxidant in this reaction. Out of several solvents tested, dichloromethane was found to be the best solvent for this reaction (Table 1, entries 3–8). We also tested several other oxidants under these conditions (Table 1, entries 9–14). The best yields of thiadiazole **2a** (95–100%) were obtained with Oxone, $NaIO_4$, and $KBrO_3$, whereas $NaIO_3$, *t*BuOOH, H_2O_2, and $K_2S_2O_8$ were inefficient oxidants in this reaction. We decided to use Oxone in our following studies because $NaIO_4$ and $KBrO_3$ are potentially dangerous compounds owing to their toxicity and their ability to form explosive mixtures with organic materials. Decreasing the amount of Oxone from 2.0 to 1.2 equiv. led to a reduced yield of the product (Table 1, entry 15). The addition of water for better solubility of Oxone also resulted in a reduced yield (Table 1, entry 16).

Table 1. Optimization of the oxidative dimerization of thiobenzamide.[a]



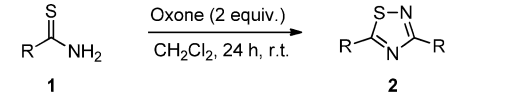
1a **2a**

Entry	Solvent	Oxidant (equiv.)	Yield [%][b]
1[c]	CH_2Cl_2	Oxone (2)	(97)
2	CH_2Cl_2	Oxone (2)	95 (95)
3	MeCN	Oxone (2)	(64)
4	$CHCl_3$	Oxone (2)	(82)
5	EtOAc	Oxone (2)	(76)
6	hexane	Oxone (2)	(62)
7	toluene	Oxone (2)	(73)
8	MeOH	Oxone (2)	(1)
9	CH_2Cl_2	$KBrO_3$ (2)	(100)
10	CH_2Cl_2	$NaIO_3$ (2)	(5)
11	CH_2Cl_2	$NaIO_4$ (2)	(100)
12	CH_2Cl_2	*t*BuOOH (2)	(0)
13	CH_2Cl_2	H_2O_2 (2)	(6)
14	CH_2Cl_2	$K_2S_2O_8$ (2)	(84)
15	CH_2Cl_2	Oxone (1.2)	(82)
16	CH_2Cl_2/H_2O (2:1)	Oxone (2)	(47)

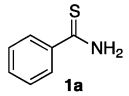
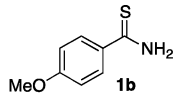
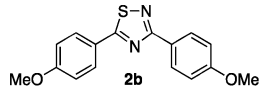
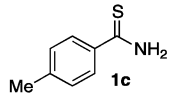
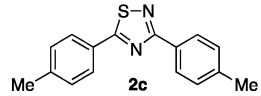
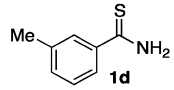
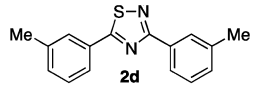
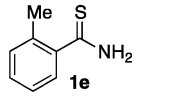
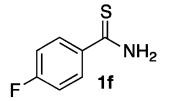
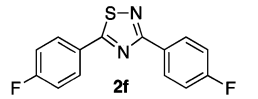
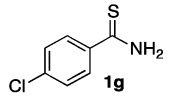
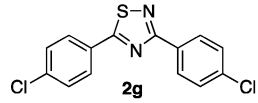
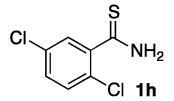
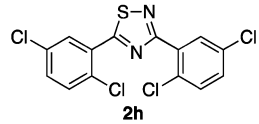
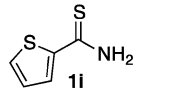
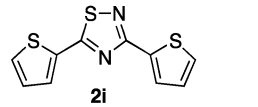
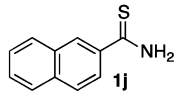
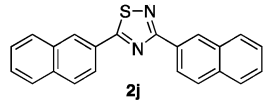
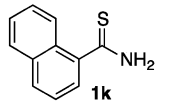
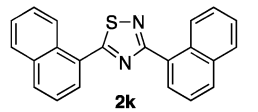
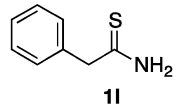
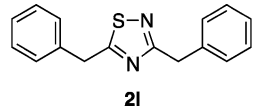
[a] The oxidative dimerization of thiobenzamide (**1a**) was performed at room temperature for 24 h (control by TLC) by using the oxidant (1.2–2.0 equiv.). [b] Yield of isolated product; the yield as determined by NMR spectroscopy is given in parentheses. [c] PhI (10 mol-%) was added.

By using the optimized reaction conditions, we investigated the conversion of various thioamides **1** to respective 1,2,4-thiadiazoles **2** (Table 2). In general, thiobenzamides with either electron-donating or electron-withdrawing substituents afforded corresponding 1,2,4-thiadiazoles **2** in good yields (Table 2, entries 1–8). This reaction also gave good yields for thiophene carbothiamide and naphthalene carbothioamides (Table 2, entries 9–11). However, the reaction of thiobenzamides with a bulky *ortho* and *meta* substituents in the phenyl ring and the reaction of benzyl thioamide required a longer time and heating to 40 °C (Table 2, entries 4, 5, 8, and 12). Unfortunately, the reaction of aliphatic thiocarboamides and dithiobenzamides did not afford the desired products.

Table 2. Oxidative dimerization of thioamides **1** with Oxone under the optimized reaction conditions.[a]



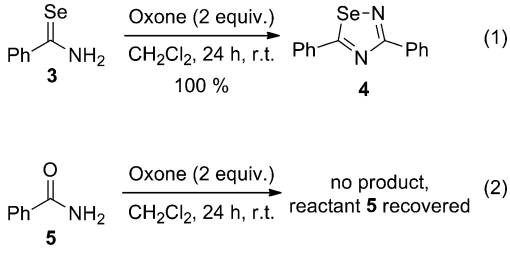
1 **2**

Entry	Thioamide **1**	Thiadiazole **2**	Yield [%][b]
1	 **1a**	 **2a**	95
2	 **1b**	 **2b**	86
3	 **1c**	 **2c**	98
4	 **1d**	 **2d**	81 (88)[c]
5[d]	 **1e**	 **2e**	83
6	 **1f**	 **2f**	92
7	 **1g**	 **2g**	96
8[e]	 **1h**	 **2h**	66
9	 **1i**	 **2i**	89
10	 **1j**	 **2j**	93
11	 **1k**	 **2k**	86
12[e]	 **1l**	 **2l**	71

[a] The dimerization of thioamide **1** with Oxone (2 equiv.) was performed in CH_2Cl_2 at room temperature for 24 h. [b] Yield of isolated product. [c] Reaction was performed for 48 h. [d] Reaction was performed for 72 h. [e] Reaction was performed for 72 h at 40 °C.

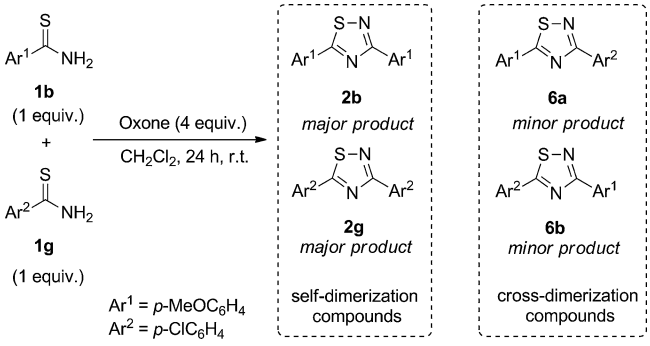
Compared to known methods for the oxidative dimerization reaction of thiobenzamide by using various oxidizing reagents,[4,5] our method affords 1,2,4-benzothiadiazoles **2** in similar or better yields. Next, we tried to prepare 1,2,4-

selenadiazole by replacing thiobenzamide with benzoselenoamide. Fortunately, our optimized reaction conditions worked for the efficient preparation of 1,2,4-selenadiazole **4** by dimerization of benzoselenoamide **3** in quantitative yield [Scheme 1, Equation (1)]. This reaction has also been performed by using hypervalent iodine reagents[12a] and other oxidants.[12b] As expected, the reaction of benzamide **5** under our conditions did not afford the corresponding dimerization product, and reactant **5** was recovered from the reaction mixture [Scheme 1, Equation (2)].



Scheme 1. Dimerization reactions of benzoselenoamide and benzamide.

Finally, we investigated the cross-dimerization reaction by using benzothioamides **1b** and **1g** (Scheme 2). Unfortunately, corresponding self-dimerization compounds **2b** and **2g** were obtained as major products and cross-dimerization compounds **6a** and **6b** were isolated as minor products.



Scheme 2. Cross-dimerization reaction with the use of **1b** and **1g**.

Conclusions

In conclusion, we developed an oxidative dimerization reaction for the synthesis of 1,2,4-thiadiazoles by using Oxone as a readily available, inexpensive, safe, and environmentally benign oxidant under mild conditions. This convenient procedure gives good results for the dimerization of substituted thiobenzamides, carbothiamidess and phenylselenamide.

Experimental Section

General Procedure for the Synthesis of Thiadiazoles: Oxone (1 mmol) was added to a solution of thioamide **1** (0.5 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature or 40 °C for 24 to 72 h (control by TLC). Upon completion of the reaction, the mixture was filtered, the inorganic solids on the filter were washed with CH_2Cl_2, and then the combined solution was evaporated in vacuo. The residue was separated by column chromatography (hexane/ethyl acetate = 1:3 or 1:5) to afford analytically pure thiadiazole **2**.

3,5-Diphenyl-1,2,4-thiadiazole (2a): Reaction of thiobenzamide **1a** (69 mg, 0.50 mmol) according to the general procedure afforded **2a** (57 mg, 95%) as a white microcrystalline solid. Colorless needles (recrystallized from dichloromethane/hexane), m.p. 89.8–90.2 °C (ref.[13] m.p. 89–90 °C). IR (KBr): $\tilde{\nu}$ = 3060, 3036, 1508, 1482, 1440, 1423, 1331, 1274, 1248 cm^{-1}. ^1H NMR (500 MHz, [D_6]acetone): δ = 8.44–8.37 (m, 2 H), 8.19–8.11 (m, 2 H), 7.69–7.52 (m, 6 H) ppm. ^{13}C NMR (125 MHz, [D_6]acetone): δ = 189.3, 174.4, 133.8, 133.1, 131.4, 131.4, 130.4, 129.7, 129.0, 128.3 ppm.

Supporting Information (see footnote on the first page of this article): General experimental remarks, experimental details, and spectra of the products.

Acknowledgments

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