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Original article

Green synthesis of 1,2,4-thiadizoles from thioamides in water using molecular oxygen as an oxidant

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ABSTRACT

We present here an efficient green process for the synthesis of 1,2,4-thiadiazoles *via* iodine-catalyzed, oxidative dimerization of thioamides in water using molecular oxygen as a terminal oxidant. Under the optimized reaction conditions, aryl thioamides produced 3,5-diaryl-1,2,4-thiadiazoles in good to excellent yields. Alkyl thioamides and substituted thioureas could also provide corresponding 1,2,4-thiadiazole products.

1. Introduction

It is generally acknowledged that there is an increasing demand for more environmentally acceptable processes, which would feature the elimination of waste at the source and the avoidance of using toxic and/or hazardous substances [1]. Without question, using water as a reaction medium and/or molecular oxygen as an oxidant is consistent with the principles of green chemistry, because water is considered a safe and environmentally benign solvent on account of its massive abundance, non-toxicity and non-inflammability [2]. On the other hand, molecular oxygen is reputed to be an ideal oxidant due to its natural, inexpensive, and eco-friendly characters, with water as the sole byproduct [3].

1,2,4-Thiadazoles are recognized as an important class of heterocyclic molecules, which exhibit remarkable biological activities and are broadly found in bioorganic and medicinal chemistry with applications in drug discovery and development [4]. For example, 3,5-bis(indolyl)-1,2,4-thiadiazole derivative **A** (Fig. 1) showed potent cytotoxicity against human cancer line and 3,5-bis(pyridin-3-yl)-1,2,4-thiadiazole **B** (Fig. 1) is identified as an inhibitor of aromatase for cancer treatment [5,6]. Thiadiazole compound **C** (Fig. 1) was developed as an agonists of sphingosine 1-phosphate receptor subtype 1 for the treatment of autoimmune diseases, such as multiple sclerosis and rheumatoid arthritis [7].

In view of the importance of 1,2,4-thiadiazoles, a number of processes have been developed to prepare this class of heterocyclic compound [4,8]. Among them, the oxidative dimerization of thioamides is the main strategy, which can be carried out by using different oxidizing agents, such as hypervalent iodine [9], alpha-bromo nitriles [10], and DMSO with the help of an electrophilic reagent [11], and so on [12]. Although able to provide high yields of

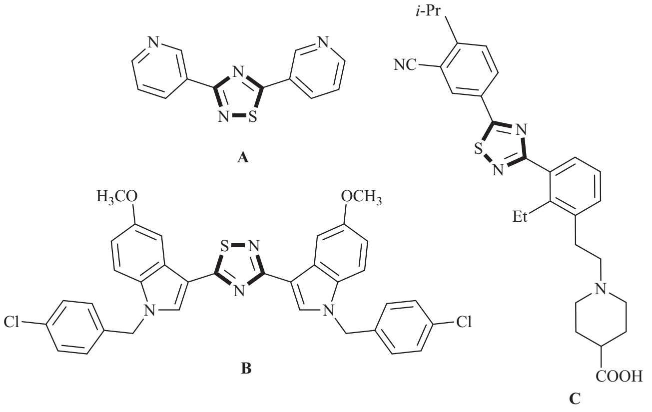

Fig. 1. Examples of bioactive 1,2,4-thiadiazoles.

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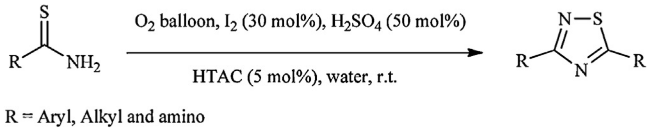


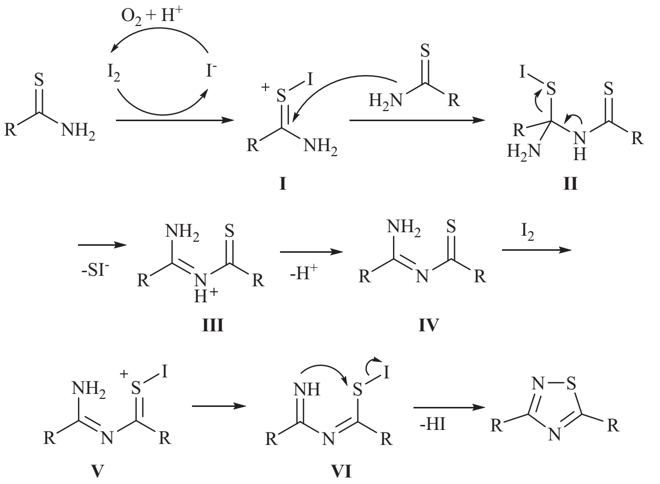
Scheme 1. Green process for the synthesis of 1,2,4-thiadiazoles.

1,2,4-thiadiazoles, these reported protocols suffer from drawbacks, such as toxic oxidants and/or hazardous, organic solvents. Herein, we present a green method for the synthesis of 1,2,4-thiadiazole heterocycles through iodine-catalyzed oxidative dimerization of thioamides in water using molecular oxygen as an oxidant (Scheme 1).

2. Experimental

All reagents were of analytical grade and obtained from commercial suppliers and used without further purification. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer, using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Mass spectra were obtained with a SHIMADZU model GCMS-QP5000 spectrometer. High-resolution mass spectra were performed on Finnigan MAT 95 spectrometer. TLC was performed by using commercially prepared 100–400 mesh silica gel plates (GF_{254}) and visualization was effected at 254 nm.

Synthesis of 1,2,4-thiadiazoles: Thioamide (1 mmol), I_2 (30 mol%), H_2SO_4 (50 mol%), hexadecyltrimethylammonium chloride (HTAC) (5 mol%) and water (2 mL) were added to a test tube attached to an oxygen balloon (1 atm). The system was stirred magnetically at r.t. for 12 h. The precipitate was collected by filtration. In the cases of **2a**, **2b**, **2d**, **2g**, **2h**, **2k**, **2l**, **2r**, the pure products were obtained as precipitates and were washed with methanol/water and dried. In other cases, the precipitates were purified by TLC to give pure 1,2,4-thiadiazole products. The characterization data and NMR spectra of the products can be found in Supporting information.



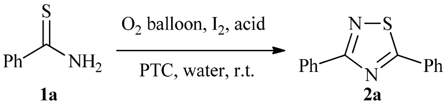
Scheme 2. Possible mechanism of iodine-catalyzed oxidative dimerization of thioamides.

3. Results and discussion

In order to explore the optimum reaction conditions, benzothioamide was selected as a model substrate. The experimental data are collected in Table 1. When benzothioamide reacted in water at room temperature for 12 h, using 20 mol% molecular iodine as the catalyst, in the presence of 1.0 equiv. of aqueous HCl, under 1 atm of pressure of dioxygen, the desired 1,2,4-thiadiazole was not detected by GC (Table 1, entry 1). Usually, the phase transfer catalyst can result in faster organic reactions in water, higher conversions or yields, and fewer byproducts. Based on this consideration, sodium dodecylbenzenesulfonate (SDS) was intro-

Table 1

Optimization of reaction conditions for the synthesis of 1,2,4-thiadiazoles from thioamides in water using oxygen as an oxidant.[a]



Entry	Catalyst	PTC	Acid	Time (h)	Yield (%)[b]
1	I_2 (30)	–	HCl	8	N. R.[c]
2	I_2 (30)	SDS	HCl	8	Trace
3	I_2 (30)	TEAC[e]	HCl	8	38
4	I_2 (30)	TBAC[f]	HCl	8	50
5	I_2 (30)	HTAC	HCl	8	72
6	I_2 (30)	BDHC[g]	HCl	8	69
7	I_2 (30)	HTAC	H_2SO_4[d]	8	85
8	I_2 (30)	HTAC	TsOH	8	74
9	I_2 (30)	HTAC	MsOH	8	70
10	I_2 (30)	HTAC	AcOH	8	51
11	I_2 (20)	HTAC	H_2SO_4	8	54
12	I_2 (50)	HTAC	H_2SO_4	8	83
13	I_2 (30)	HTAC	H_2SO_4	12	96
14	I_2 (30)	HTAC	H_2SO_4	16	96
15[h]	I_2 (30)	HTAC	H_2SO_4	12	60

[a] Reaction conditions: unless otherwise noted, all reactions were performed with benzothioamide (1 mmol), I_2 (indicated amount), Brønsted acid (1 equiv.), in water (2 mL) under O_2 (1 atm) at room temperature for selected reaction time.

[b] Isolated yield.

[c] N. R. = no reaction.

[d] 0.5 equiv.

[e] TEAC: tetraethylammonium chloride.

[f] TBAC: tetrabutylammonium chloride.

[g] BDHC: benzyldimethylhexadecylammonium chloride.

[h] The reaction was carried out in air.