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High yielding protocol for oxidative dimerization of primary thioamides: a strategy toward 3,5-disubstituted 1,2,4-thiadiazoles

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ABSTRACT

Ceric ammonium nitrate (CAN), a highly versatile reagent, was found to efficiently mediate the oxidative dimerization of primary thioamides in acetonitrile at room temperature leading to the rapid and expeditious synthesis of symmetrically 3,5-disubstituted 1,2,4-thiadiazoles in high yields.

In recent years, synthesis of 1,2,4-thiadiazole core unit has been the subject of considerable attention as several derivatives of this heterocyclic motif are found in several natural products and biologically active compounds.[1] Although, currently, the only commercial antibiotic cefozopran[2] contains the 1,2,4-thiadiazole scaffold, a number of derivatives related to this system are often endowed with a wide range of biological activities, e.g., treatment of human leukemmia,[3] Alzheimer's disease,[4] G-protein coupled receptors,[5] and acetylcholinesterase inhibitors.[6] In addition to their use as pharmacophores, thiadiazoles are useful as thiol trapping agents,[7] pesticides,[8] and corrosion inhibitors.[9] Recently, new alkaloid polycarpathiamines A[10] exhibited cytotoxic activity against L5178Y murine lymphoma cells (IC_{50} 0.41 μM) (Fig. 1).

The classical methods utilized for the synthesis of 3,5-diaryl-1,2,4-thiadiazoles may be divided into three categories, which include (i) intramolecular cyclization, (ii) intermolecular cyclization, and (iii) oxidative dimerization of thioamides. 3,5 unsymmetrically disubstituted 1,2,4-thiadiazoles have been synthesized by intramolecular oxidative cyclization of amidinithioureas[8a] and 1,3-dipolar cycloaddition of nitrile sulfides to nitriles.[11] Undoubtedly, thioamides are widely used as versatile building blocks in preparative organic synthesis and especially in the construction of heterocyclic compounds.[12] The most common synthetic route to the synthesis of 1,2,4-thiadiazoles involves the oxidative dimerization of primary thioamides by using metal and organic-based oxidizing reagents, such as nitrous acid,[13] *t*-BuOCl,[14] pentylpyridinium tribromide,[15] NBS,[16] DMSO-electrophilic reagents,[17] DDQ,[18] organohypervalent iodine reagents,[19] Oxone,[20] polymer-supported diaryl selenoxide and telluroxide.[21] Nonetheless, many of these protocols suffer from limitations such as long reaction times, large excess of reagents, tedious work-up, harsh reaction conditions, and the formation of nitriles and isothiocyanates as by-products.[22] Consequently, there is a need to develop a practical method that minimized or eliminated the disadvantages enumerated above, while maintaining the ease of work-up and purification that are hallmarks of the traditional methods.

Over the past few years, cerium(IV) compounds represent the most notable oxidants among lanthanide reagents. In particular, cerium(IV) ammonium nitrate $(NH_4)_2[Ce(NO_3)_6]$, has emerged as a well-known one-electron oxidant and has been extensively used for a plethora of organic transformations[23] such as carbon–carbon bond formation, protection/deprotection sequences, or by Lewis acid catalysis. CAN has the additional advantages of having a low toxicity besides being air-stable, of low cost, easily handled and reasonably soluble in many organic media, allowing for a considerable degree of experimental simplicity. The versatility of CAN encouraged us to carry out the oxidative dimerization of primary thioamides **1** to the corresponding 3,5-disubstituted 1,2,4-thiadiazoles **2** under benign conditions. In this communication, we wish to report a practical, and efficient strategy for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles by employing ceric ammonium nitrate at ambient temperature in the absence of ligands or additives as shown in Scheme 1. The protocol affords a potential

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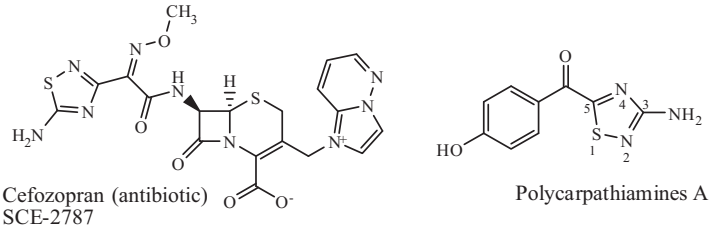
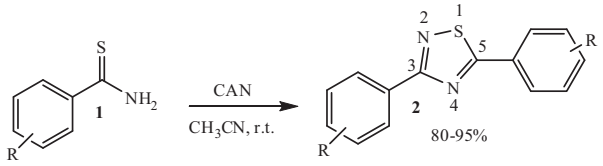


Figure 1. Bioactive molecules containing thiadiazole moiety.



Scheme 1. Synthesis of 3,5-disubstituted 1,2,4-dithiadiazoles via oxidative dimerization of primary thioamides.

route for the access of the target products with wide substrate scope. To the best of our knowledge, CAN has not yet been exploited for the synthesis of symmetrically 1,2,4-thiadiazoles.

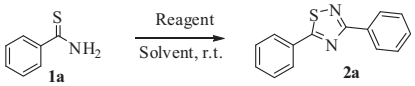
Therefore, we first investigated the optimization of the reaction conditions using thiobenzamide as a model substrate, and the role of various conditions on the reaction system was studied with respect to potential catalysts, temperature, and appropriate solvents. The results are illustrated in Table 1. The reaction was feasible in all the reagents and solvents tested. However, the optimum reaction conditions are CAN in acetonitrile at rt producing the high yield of **2a** in a few minutes (Table 1, entry 10). Low yields were obtained in the case of EtOAc or THF was employed as the solvent. The experiments were run from 0 °C to 25 °C. We observed that those conducted at room temperature (23–25 °C) were obtained in high yields, whereas at 0 °C led to a lower yield of product and requires longer reaction times (Table 1, entry 11).

With the optimized reaction conditions in hand, we then examined the scope and limitations of the current protocol by using diverse primary thioamides, including aromatic, heterocyclic, and aliphatic ones that could be converted into the corresponding 1,2,4-thiadiazoles (**2a**–**l**) and the results are summarized in Table 2. In general, aromatic primary thioamides bearing electron-donating as well as electron-withdrawing substituents on the aromatic rings at different positions, efficiently proceeded to afford the corresponding 3,5-disubstituted 1,2,4-thiadiazoles in high yields without the formation of nitriles and isothiocyanates as byproducts. The results established that no significant electronic effects of the substituent on the phenyl ring (Ar) were observed. It is noteworthy to mention here that, by reacting a mixture of equivalent molar quantities of thioamides **1b** (*p*-OCH_3) and **1e** (*p*-CH_3) with ceric ammonium nitrate in acetonitrile at room temperature we hoped to get asymmetrical 3,5-disubstituted thiadiazoles. To our surprise, however, the anticipated asymmetrical thiadiazole formation did not occur; instead, symmetrically 3,5-disubstituted thiadiazoles **2b** and **2e** were obtained in 96% and 93% isolated yields.

On the basis of our observations and the literature precedents, a tentative mechanistic pathway for the oxidative self-dimerization of primary thioamide **1a** is delineated in Scheme 2. Initially, nucleophilic attack by sulfur of another molecule of thioamide gives the intermediate (**A**) which on further oxidation affords 3,5-disubstituted-1,2,4-thiadiazole **2**. In order to further validate the reaction mechanism, we performed oxidative dimerization of **1a** that was suppressed by the presence of a free radical scavenger 2,6-di-*tert*-butyl-4-methyl phenol (1.0 equiv of each) and found that a significant reduction in yield but only a trace amount of product **2** was isolated, indicating that radical intermediates are involved in the present reaction.

In conclusion, we have described an efficient and straightforward synthesis of symmetrically 3,5-disubstituted-1,2,4-thiadiazoles by the oxidative dimerization of thiobenzamides using CAN as a benign oxidant. The present protocol has salient features such as utilization of inexpensive, readily available, and easy to handle oxidant CAN, short reaction times, mild reaction conditions, excellent yields, and large substrate scope which make this methodology superior to the existing ones. Application of this novel synthetic strategy to access biologically important heterocyclics is currently underway in our laboratory and will be reported in due course.

Table 1
Optimization of the reagents and solvent effects on the dimerization of primary thioamides[a]



Entry	Reagent	Solvent	Time (min)	Yield[b] (%)
1	$Co(NO)_3{\cdot}6H_2O$	EtOAc	4	20
2	$Co(NO)_3{\cdot}6H_2O$	CH_3CN	6	25
3	$(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$	EtOAc	5	27
4	$(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$	Isopropanol	8	35
5	$(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$	CH_3CN	4	39
6	$(NH_4)_2Ce(NO_3)_6$	EtOAc	8	57
7	$(NH_4)_2Ce(NO_3)_6$	THF	4	79
8	$(NH_4)_2Ce(NO_3)_6$	CH_3NO_2	6	84
9	$(NH_4)_2Ce(NO_3)_6$	CH_3OH	4	93
10	$(NH_4)_2Ce(NO_3)_6$	CH_3CN	3	95[c]
11	$(NH_4)_2Ce(NO_3)_6$	CH_3CN	15	80[d]

[a] Reactions were carried out on a 5 mmol scale in a suitable solvent (2 mL) at room temperature with reagent (5 mmol).
[b] Isolated yields after purification.
[c] Optimum reaction conditions.
[d] Reaction carried out at 0 °C.

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

To a stirred solution of arylthioamide (0.685 g, 5.0 mmol) in acetonitrile (2 mL) at room temperature was added ceric ammonium nitrate (2.74 g, 5.0 mmol) in one portion. The color of the reaction solution changed to bright orange yellow at the beginning of the reaction and gradually changed to pale yellow. The reaction mixture was stirred magnetically at room temperature for the specified time (see Table 1) until starting material could no longer be detected by TLC (petroleum ether/EtOAc, 95:5). After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3 × 5 ml) followed by brine (5 ml). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced