

Expedient Synthesis of 1,2,4-Thiadiazoles from Primary Thioamides Using Calcium Hypochlorite in Dichloromethane

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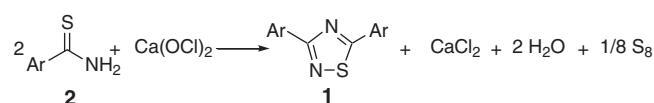
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Recently, 1,2,4-thiadiazoles have drawn a considerable research interest from synthetic and medicinal chemists since many natural and synthetic compounds incorporating these structural units have shown a wide range of biological activities.¹ For example, 1,2,4-thiadiazoles are found as the core structural units in such molecules as cefozopran,^{2a} a commercial antibiotic, acetylcholinesterase inhibitors.^{2b}

Therefore, various new synthetic approaches to 1,2,4-thiadiazole derivatives have been explored in the last decade. Among them, the oxidative dimerization of thioamides using a variety of oxidizing reagents, *e.g.*, IBX/TEAB, CAN, Cu(OTf)₂, *t*-BuOCl, oxone, *t*-butyl nitrite, is the most typical approach to these compounds.³ Many synthetic methods, however, have limitations such as strict reaction conditions, use of expensive oxidants, and the formation of toxic byproducts. Therefore, it is highly desired to develop simple and eco-friendly synthetic routes for 1,2,4-thiadiazoles using inexpensive oxidants under mild conditions.

Calcium hypochlorite (Ca(OCl)₂), a stable solid alternative to NaOCl, has been used as a useful oxidant in organic reactions.⁴ We herein wish to report an expedient synthesis of thiadiazoles **1** from primary thioamides **2** using Ca(OCl)₂ in CH₂Cl₂ under mild conditions (Scheme 1).

To obtain the basic information regarding the optimal reaction conditions, thiobenzamide **2a** was tested as a model compound. When **2a** was reacted with Ca(OCl)₂ (65% purity, 1.0 equiv) in CH₂Cl₂ at rt. for 24 h, the reaction was incomplete (Entry 1). With an excess of Ca(OCl)₂ (1.7 equiv), **2a** was completely converted to thiadiazole **1a** in 83% yield (Entry 2). CH₃CN was also attempted as a reaction solvent, however, the result was poor (Entry 3). Thus, the reaction conditions of Entry 2 were adopted as

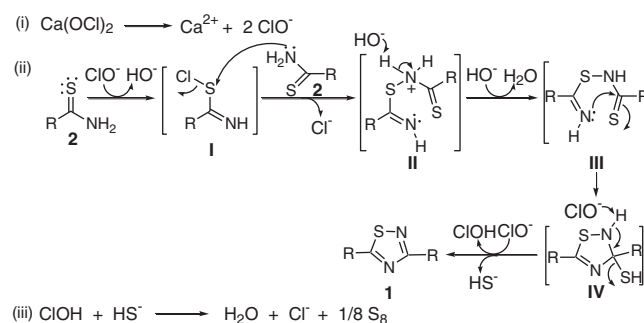


Scheme 1. A novel approach to thiadiazoles **1** from primary thioamides **2** utilizing Ca(OCl)₂.

the standard conditions, and various thioamides were reacted with Ca(OCl)₂ and the results are summarized in Table 1.

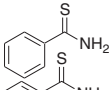
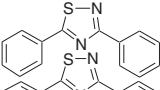
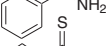
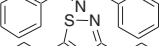
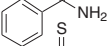
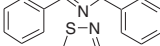
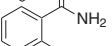
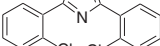
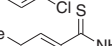
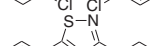
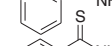
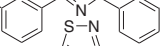
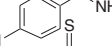
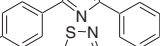
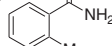
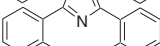
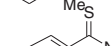
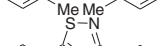
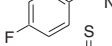
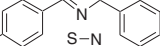
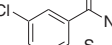
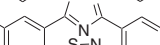
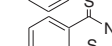
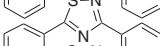
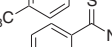
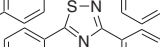
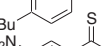
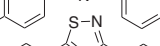
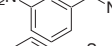
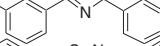
As shown in Table 1, the reactions of thiobenzamides with Ca(OCl)₂ generally proceeded smoothly in all cases regardless of the nature (EWG or EDG) and the positions of substituents on the aromatic rings (Entries 4–12). No significant electronic effect of the substituent on the aromatic ring was observed, whereas minor steric effect appeared to be working since thioamides bearing substituent at *o*-position gave lower yields than those bearing substituent at *p*-position. In general, the desired thiadiazoles **1** were obtained in good to excellent yields ranging from 78% to 88%. Delighted with the successful results, we then attempted reaction of thioamides with naphthyl, benzyl, and thiophene. Thioamide **2k** was reacted smoothly to give the desired thiadiazole **1k** in 79% yield, whereas thioamide **2l** required more oxidant and a longer reaction time to complete the reaction. In the case of thioamide **2m**, a less amount of Ca(OCl)₂ was used to obtain **1m** in 67% yield.

A plausible reaction mechanism is proposed in Scheme 2. Hypochlorite anion, dissociated from Ca(OCl)₂, converts thioamide **2** into *S*-chloro thioimine **I**.^{3d} This intermediate **I** is then nucleophilic attacked by another thioamide **2** through amino group to form **II**, which is then proton-abstracted by OH[−] to furnish **III**. Intramolecular



Scheme 2. Plausible reaction mechanism for Ca(OCl)₂-mediated synthesis of thiadiazoles **1** from primary thioamides **2**.

Table 1. Oxidative dimerization of thioamides **2** to thiadiazoles **1** with $\text{Ca}(\text{OCl})_2$.^a

Entry	Thioamide 2		Equiv	Time (h)	Thiadiazole 1	(Yields, %) ^b
1		2a	1.0	24		1a 55
2		2a	1.7	24		1a 83
3		2a	1.7	24		1a 69 ^c
4		2b	1.7	24		1b 81
5		2c	1.7	24		1c 79
6		2d	1.7	20		1d 88
7		2e	1.7	24		1e 78
8		2f	1.7	24		1f 87
9		2g	1.7	24		1g 83
10		2h	1.7	24		1h 87
11		2i	1.7	18		1i 85
12		2j	1.7	24		1j 84
13		2k	1.7	24		1k 79
14		2l	2.0	30		1l 80
15		2m	1.5	24		1m 67

^a Thioamide **2** (1.0 mmol), $\text{Ca}(\text{OCl})_2$ (\times equiv), CH_2Cl_2 (5.0 mL), rt (25–28°C), Ar.^b Isolated yields by flash column chromatography on silica gel.^c CH_3CN was used as reaction solvent.

nucleophilic attack of thiocarbonyl group by imino group in **III** affords the cyclized intermediate **IV**. Amino-proton abstraction by ClO^- and following migration of electron-pair in **IV** would release HS^- and furnish 1,2,4-thiadiazoles **1**.

In conclusion, a novel approach to 1,2,4-thiadiazoles from primary thioamides using $\text{Ca}(\text{OCl})_2$ has been developed (Appendix S1, Supporting Information). Considering such advantages as utilization of inexpensive and safe oxidant $\text{Ca}(\text{OCl})_2$, simple and eco-friendly procedures, mild reaction conditions, wide substrate scope, and good to high yields, this new synthetic protocol could be a method of choice in the synthesis of 1,2,4-thiadiazoles from primary thioamides.

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