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Short communication

Calcium catalyzed Mukaiyama–Mannich addition of silyl enol ethers to nitrones

Elizabeth A. Congdon, Kristine A. Nolin *

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ABSTRACT

A method for synthesizing β-(silyloxy)amino carbonyls through the addition of ketone-derived silyl enol ethers to N-phenyl nitrones has been developed. The transformation is catalyzed by a commercially available calcium(II) complex affording β-(silyloxy)amino carbonyls in good to excellent yield.

1. Introduction

The use of nitrones as coupling partners in 1,3-dipolar cycloaddition reactions has been well documented [1]. This includes the reaction of nitrones with ketone-derived silyl enol ethers, which has been shown to lead to the formation of isoxazolidines (Fig. 1, pathway 1) [2]. However, if the ketone-derived silyl enol ether reacts with the nitrone via a Mukaiyama–Mannich-type addition (pathway 2), the synthesis of β-amino carbonyl compounds can be achieved [3]. This is the favored pathway when nitrones are reacted with silyl ketene acetals in the presence of Lewis acids [4,5]. This variation on the traditional Mukaiyama–Mannich reaction, utilizing nitrones as the electrophilic reagent, is rare due to the competing cyclization reaction [6,7]. Catalytic methods for the addition of ketone-derived silyl enol ethers to other imine equivalents have been reported. Many of these methods include the use transition metal complexes such as those of Au(I) [8], Ag (I) [9], Ir(I) [10], Zn(II) [11] and polyoxotungstates [12].

Previous studies reported from our laboratory have demonstrated the ability of calcium(II) complexes to catalyze addition reactions. The abundance and benign nature of Ca(II) makes complexes of this metal attractive for use as catalysts in organic methodology [13,14]. We recently reported the use of $Ca(OAc)_2$ as a robust catalyst for the addition of unactivated thiols to donor-acceptor cyclopropanes [15]. In addition, commercially available $Ca(OTf)_2$ readily facilitated the 1,3-dipolar cycloaddition of donor-acceptor cyclopropanes and nitrones providing tetrahydro-1,2-oxazines [16]. Having demonstrated the compatibility of calcium(II) complexes with nitrones, we speculated these Lewis acidic complexes could facilitate the cycloaddition reaction of nitrones and silyl enol ethers. However, we were excited to find that the reaction favored the pathway that led to the formation of β-(silyloxy)amino carbonyls. Herein, we report successful development of a practical and general catalytic method for the Mukaiyama–Mannich-type addition of ketone-derived silyl enol ethers to nitrones.

2. Experimental

2.1. Material and methods

Calcium triflate, N,α-diphenyl nitrone, and 1-phenyl-1-trimethylsiloxyethylene, 1-(trimethylsiloxy)cyclopentene, 1-(trimethylsiloxy)cyclohexene, and (1-tert-butylvinyloxy)trimethylsilane were obtained from commercial sources and used without further purification. Nitrones were synthesized according to literature procedures. [17].

2.2. General procedure

In an inert glovebox, calcium triflate (6.8 mg, 0.02 mmol, 0.02 eq) was added to a 3 mL conical glass vial with a stir bar. After the vial was removed from the glove box, nitrone (1.0 eq, 1.0 mmol), silyl enol ether (1.5 mmol, 1.5 eq), and dry MeCN (1.0 mL, 1.0 M) were added under an atmosphere of nitrogen. The reaction solution was stirred and heated to 50–70 °C, and the progress of the reaction was monitored by TLC. Upon completion, the vial was removed from the heat and cooled to room temperature while stirring. The reaction mixture was

* Corresponding author.
E-mail address: knolin@richmond.edu (K.A. Nolin).

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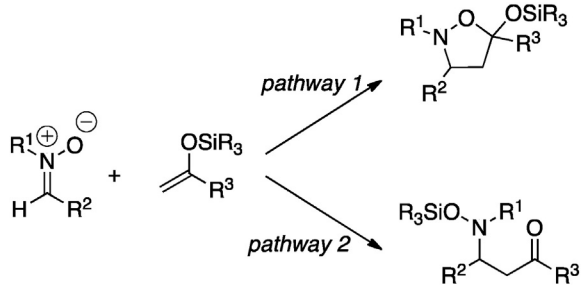


Fig. 1. Possible reaction pathways.

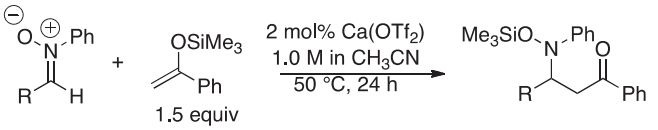
loaded directly onto a silica gel column and purified by flash chromatography (10–20% EtOAc or ether in hexanes).

3. Results and discussion

A brief survey of commercially available calcium(II) complexes revealed that CaI_2 could facilitate the addition of nitrone **1** and silyl enol ether **2** leading to the formation of siloxy amine **3** in 62% conversion at room temperature in dichloromethane after 21 h (Table 1, entry 1). The reaction was plagued by significant hydrolysis of the silyl enol ether. The hydrolysis was minimized by switching to acetonitrile as the solvent, albeit with slightly lower conversion. In this solvent, the siloxy amine was formed in 58% conversion of the nitrone in 21 h (entry 2). The reaction temperature was increased to 50 °C and an additional catalyst screen was performed over a period of 17 h. Under these conditions, $Ca(NTf_2)_2$ and $Ca(OTf)_2$ were identified as the most robust catalysts leading to the formation of **3** in 71% and 79% conversion respectively (entries 6 & 7). The catalyst loading of $Ca(OTf)_2$ could be decreased to 2 mol% and full conversion by extending the reaction time to 24 h (entry 8).

Using the optimized reaction conditions of 1.5 eq of silyl enol ether **2** and 2 mol% $Ca(OTf)_2$ in dry acetonitrile (1 M) at 50 °C, we proceeded to explore the scope of the reaction by adding acetophenone derived silyl enol ether **2** to N-phenyl nitrones bearing varying aryl substitutions. The reaction of **1** with **2** provided **3** in 95% isolated yield after purification (Table 2 entry 1). Electron-rich and electron-deficient nitrones formed the corresponding β-hydroxylamino carbonyls in excellent yields (93–96%, entries 2–5). The more sterically encumbered nitrones **4e** and **4f** were also reactive. Nitrone **4e**, derived from 1-naphthaldehyde, produced **5e** in 93% yield after reacting with **2** (entry 6). However, 2-methylphenyl nitrone **5f** produced the corresponding product in slightly lower yield, 84% (entry 7). Nitrones bearing heteroaromatic substitutions were also reactive under the standard conditions. Nitrone **4 g**, derived from 2-methylfurfural, afforded **5g** in high yield, 94% (entry 8). The lower yield associated with reaction of the 2-thiophenyl substituted nitrone **4h** (76%, entry 9) are attributed to difficulty in separating the β-(silyloxy)amino carbonyl compound **5h** from trace amounts of starting material. Gratifyingly, the bulky 3-(N-tosyl)indolyl nitrone **4i** was reactive under the standard conditions and provided **5i** in 72% yield (entry 10). Attempts to expand the scope to include N-methyl and alkyl nitrones were unsuccessful under the reaction conditions.

Table 2
Examining the scope of the nitrones.



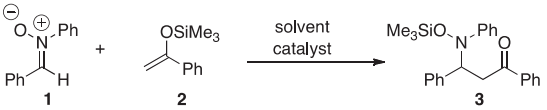
1, 4a-i **2** **3, 5a-i**

Entry	R		Isolated yield (%)	
1	Ph	**1**	95	**3**
2	4-methoxyphenyl	**4a**	93	**5a**
3	4-methylphenyl	**4b**	95	**5b**
4	4-bromophenyl	**4c**	94	**5c**
5	4-chlorophenyl	**4d**	96	**5d**
6	1-naphthyl	**4e**	93	**5e**
7	2-methylphenyl	**4f**	84	**5f**
8	5-(2-methylfuranyl)	**4g**	94	**5g**
9	2-thiophenyl	**4h**	76	**5h**
10	3-(N-Ts)-indolyl	**4i**	72	**5i**

Having demonstrated the generality of the reaction toward differentially substituted N-phenyl nitrones, we next turned our attention to structure of the silyl enol ether. As described above, the acetophenone derived silyl enol ether **2** was a highly reactive coupling partner with a range of N-phenyl nitrones. Now, bulky and cyclic silyl enol ethers were examined for their ability to add to benzaldehyde-derived N-phenyl nitrone **1**. For these reactions, the temperature was increased to 70 °C. Gratifyingly, the bulky pinacolone-derived silyl enol ether **6a** readily reacted with **1** to produce the corresponding β-(silyloxy)amino carbonyl **7a** in 95% yield (Table 3, entry 1). Cyclic enol ethers **6b** and **6c** are typically more challenging coupling partners than their acyclic counter parts. Gratifyingly, under the reaction conditions, the cyclic ketones **7b** and **7c** were furnished in good yield, 88 and 58% respectively. The reactions proceeded with moderate diastereoselectivity in favor of the anti addition product [18a,b] for the cyclopentanone-derived silyl enol ether **6b** (3:1 entry 2) and 2:1 in favor of the syn addition product [18b–d] for the cyclohexanone-derived silyl enol ether **6c** (entry 3). [19].

The following catalytic cycle is proposed for the reaction. The Lewis acidic metal center coordinates with the nitrone, likely via exchange with one of the triflate ligands, generating complex **8** (Scheme 1). The silyl enol ether then adds to the activated nitrone to generate putative intermediate **9**. From **9**, we envisioned two pathways for release of the final product and regeneration of the catalyst. First, silyl transfer, likely

Table 1
Reaction optimization.



1 **2** **3**

Entry	Catalyst	Solvent (1 M)	Cat. loading (mol%)	Temp. (°C)	Time (h)	Conversion (%)
1	CaI_2	CH_2Cl_2	5	rt	21	62
2	CaI_2	CH_3CN	5	rt	21	58
3	CaI_2	CH_3CN	5	50	17	46
4	$Ca(CO_2C_2H_5)_2$	CH_3CN	5	50	17	0
5	$Ca(acac)_2$	CH_3CN	5	50	17	0
6	$Ca(NTf_2)_2$	CH_3CN	5	50	17	71
7	$Ca(OTf)_2$	CH_3CN	5	50	17	79
8	$Ca(OTf)_2$	CH_3CN	2	50	24	100

Reactions run with 1.5 eq of **2** at 1.0 M. Conversion determined by ^1H NMR.