



Lewis acid-promoted cascade reaction for the synthesis of Michael acceptors and its application in a dimerization reaction



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ARTICLE INFO

Article history:

Received 17 March 2017

Received in revised form

25 April 2017

Accepted 4 May 2017

Available online 6 May 2017

Keywords:

Dimethyl sulfoxide

Michael acceptors

Lewis acid

Pummerer

Dimerization

ABSTRACT

An efficient Lewis acid-promoted cascade reaction with dimethyl sulfoxide as a methylene source for the synthesis of Michael acceptors is reported. The key to developing this procedure is the selection of a mild base to modulate the equilibrium of various intermediates in order to drive the reaction forward to the formation of Michael acceptor and dimeric compound products. Extensive studies were performed to gain insight into a possible reaction mechanism.

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1. Introduction

Molecules containing various Michael acceptor scaffolds are common in pharmaceuticals, agrochemicals and natural products and have attracted considerable attention from organic chemists and medicinal chemists.¹ Michael acceptors have been found to have various different biological activities, such as antibacterial, anticancer and antiviral activities.² For example, the crystal structure of HCoV-NL63 M^{Pro} complexed with a Michael acceptor inhibitor was obtained, providing insight into the rational development of wide spectrum antiviral therapeutics to treat infections caused by human coronaviruses.³ Two Michael acceptors used as cysteine protease inhibitors, K-777 (CRA-3316) and rupintrivir (AG7088), and developed to treat Chagas disease and as an antirhinoviral agent, respectively, are already in clinical trials.⁴ On the other hand, as basic building blocks Michael acceptors have

been extensively employed in the area of organic chemistry, such as in multicomponent cascade or Domino reactions,⁵ transition-metal catalyzed reactions,⁶ enantioselective organocatalysis⁷ and complex natural product synthesis.⁸

In the textbook of graduate students, dimethyl sulfoxide (DMSO) is described as a high-boiling, protic and low-toxicity solvent, and a widely used oxidant⁹ in several named reactions, such as the Swern oxidation¹⁰ and Pfitzner-Moffatt oxidation.¹¹ In the past few decades, the nature of DMSO has been further exploited as a reagent that can act as an oxygen source, a carbon source and a sulfur source.¹² However, the reaction scope of DMSO is still limited and needs to be expanded. To date, a cascade reaction with DMSO as both a solvent and one-carbon source for the preparation of Michael acceptors has not been reported.

Herein, we report a Lewis acid-promoted cascade reaction for the synthesis of α,β -unsaturated amides. The proper choice of base in the reaction results in the production of dimeric compounds. The Pummerer rearrangement with DMSO as a methylene source is believed to be an initial step for the reaction based on mechanistic studies.

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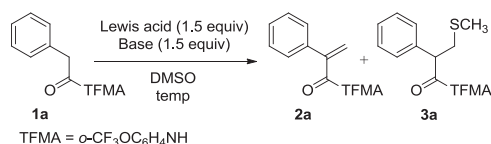
2. Results and discussion

We are focused on C(sp³)-H bond functionalization reactions.¹³ In this project, the C(sp³)-H bond functionalization in amide substrate **1a** was tested under the following reaction conditions: CoCl₂ (1.5 equiv), KOAc (2.0 equiv) and AgOAc (2.0 equiv) dissolved in DMSO (2.0 mL) in a microwave and heated at 150 °C for 2 h. To our delight, functionalization at the benzylic position occurred as expected, affording α , β -unsaturated carboxylamide **2a** in a 23% yield (Table 1, entry 1). Control experiments showed that this reaction proceeded with similar results in the absence of AgOAc, while the reaction did not occur without KOAc (Table 1, entries 2–4). Then, various Lewis acids were screened in this reaction (Table 1, entries 5–9). When one equivalent of PbCl₂ was used as the Lewis acid, the yield of product **2a** increased to 55% along with some amount of sulfide product **3a** (Table 1, entry 9). The effect of the base on the reaction was screened with various bases. The results of this screening indicated that potassium acetate and sodium acetate are the most favorable bases for this reaction (Table 1, entries 9–11 and details in supporting information). When the reaction was carried out in air or under O₂ atmosphere, the yield of product decreased (Table 1, entries 12–13). In contrast, under N₂, the reaction afforded product **2a** in a 65% yield (Table 1, entries 14). This indicated that the oxidizing reagents hindered the reaction from proceeding. The effect of temperature on the reaction was subsequently investigated, which showed that temperatures either above 160 °C or below 150 °C were not suitable for this reaction (Table 1, entries 14–17). Finally, optimized reaction conditions of PbCl₂ (1.5 equiv) and KOAc (1.5 equiv) in DMSO at 156 °C in a sealed tube under N₂ for 13 h gave the product **2a** in 77% yield and **3a** in 12% yields, respectively (Table 1, entry 17). Interestingly, when Ac₂O

was used instead of PbCl₂, sulfide product **3a** was obtained in 50% yield (Table 1, entry 18). The combination of Ac₂O/AcOH, or Ac₂O/TsOH, or TFAA/TFA in DMSO, commonly used in the Pummerer rearrangement reaction, did not afford any product.

The coexistence of products **2a** and **3a** throughout the process of optimizing the reaction conditions stimulated us to investigate the mechanism of this reaction. Several experiments concerning the study of the mechanism were conducted (eqs. (1)–(4)). Isolated sulfide **3a** was subjected to the standard reaction conditions, affording product **2a** in 75% yield with 22% recovery of **3a** (eq. (1)). When purified **2a** was put back under the standard conditions, it gave 17% yield of **3a** with 74% recovery of **2a**. These results indicated that there is an equilibrium between **2a** and **3a** in the reaction mixture. When the reaction was carried out in DMSO-d₆, it provided the corresponding deuterated products (**d**₂-**2a** and **d**₅-**3a**) in 73% and 9% yields, respectively, which provided precise evidence for the methylene group originating from the solvent dimethylsulfoxide (eq. (3)). When six equivalents of TMPO was added to a reaction run under the reaction conditions, 53% of **2a** and 5% of **3a** were still obtained, which suggested that this reaction probably did not involve any radical species (eq. (4)). Moreover, two control experiments showed that both Lewis acid PbCl₂ and KOAc are necessary for the reaction to occur (see the supporting information).

Table 1
Optimization of reaction conditions.^{a,b}



Entry	Lewis acid	Base	Additive (equiv)	Temp (°C)	Product (%)	
					2a	3a
1	CoCl ₂	KOAc	AgOAc/2	150	23	—
2	—	KOAc	AgOAc/2	150	12	8
3	CoCl ₂	—	AgOAc/2	150	trace	—
4	CoCl ₂	KOAc	—	150	24	—
5	CoF ₂	KOAc	—	150	26	6
6	CoBr ₂	KOAc	—	150	20	6
7	ZnCl ₂	KOAc	—	150	30	9
8	MnCl ₂	KOAc	—	150	23	7
9	PbCl ₂	KOAc	—	150	55	18
10	PbCl ₂	NaOAc	—	150	55	14
11	PbCl ₂	KHCO ₃	—	150	10	—
12 ^c	PbCl ₂	KOAc	—	150	33	21
13 ^d	PbCl ₂	KOAc	—	150	trace	—
14 ^e	PbCl ₂	KOAc	—	150	65	18
15 ^e	PbCl ₂	KOAc	—	160	48	26
16 ^e	PbCl ₂	KOAc	—	156	66	14
17 ^e	PbCl ₂	KOAc	—	156	77	12
18	Ac ₂ O	KOAc	—	156	—	50

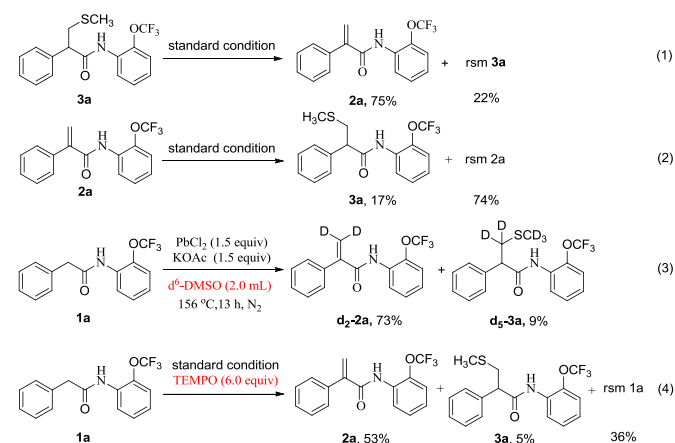
^a Entry 1–11 was conducted in microwave for 2 h, entry 12–18 was conducted in sealed tube for 13 h. Isolated yields.

^b Lewis acid (1.0 equiv) was used in entry 9–16.

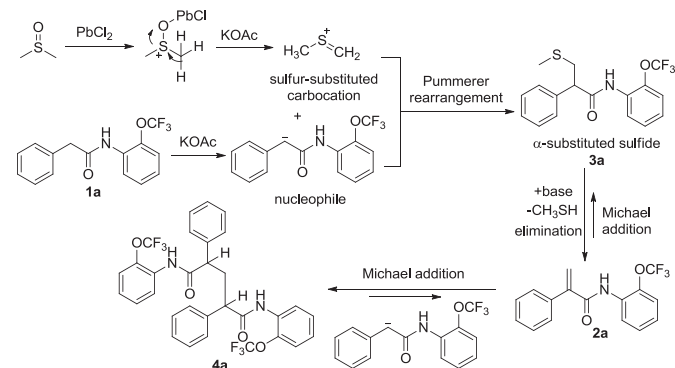
^c The reaction was carried out in air.

^d The reaction was carried out under O₂.

^e The reaction was carried out under N₂.



Based on these preliminary results and some leading references on the Pummerer rearrangement¹⁴ reaction, a rational mechanism for this reaction is proposed in Scheme 1. A sulfur-substituted carbocation is obtained through promotion by both the Lewis acid (PbCl₂) and base (KOAc), and it then reacts with a carbon nucleophile to afford α -substituted sulfide **3a**. There is an equilibrium between **3a** and **2a** in the reaction mixture. Michael acceptor



Scheme 1. Possible mechanism.

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