Tetrahedron Letters 58 (2017) 3262–3266

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Simultaneous Ring-Opened THF and insertion of diazoketone derived carbene into carbonyl O-H: Synthesis for β-keto enol ethers

Wenwen Chen *, Hongbo Wang, Yanxia Zhang, Tianjun Hu, Jianfeng Jia, Haishun Wu *

Key Laboratory of Magnetic Molecules & Magnetic Information Materials Ministry of Education, School of Chemistry and Material Science, Shanxi Normal University, Linfen 041004, China

ARTICLE INFO

Article history:
Received 2 May 2017
Revised 30 June 2017
Accepted 4 July 2017
Available online 5 July 2017

Keywords:
β-keto enol ethers
Diazoketones
Carbene
Ring-opening

ABSTRACT

A novel tandem synthesis of β-keto enol ethers was developed *via* the reaction of α-diazoketones, 1,3-diketones and THF catalyzed by cheap and available CuI under extremely simple conditions. During the course of the reaction, the ring-opened THF and diazocarbonyl derived carbene simultaneously inserted into O-H of 1,3-diketones.

Introduction

β-keto enol ethers as important building block have attracted much attention.[1] Meanwhile, many of them not only have novel medicinal properties,[2] but also are versatile intermediates in organic synthesis for the construction of various biologically active compounds (Fig. 1).[3–9] Numerous methods have been developed for the formation of β-keto enol ethers in literatures. Most traditional methods are summarized into two strategies: (a) β-diketones by treatment with alcohols;[10] (b) the acylation of the acetal.[11] However, those approaches often suffer from major or minor limitations, such as drastic reaction conditions, low yields, tedious work-up procedures and co-occurrence of several side reactions. Therefore, the development of more efficient routes which used more suitable materials is still desirable.

α-diazoketones have been extensively used as key intermediates in organic synthesis.[12–14] It is well known that O-H insertion reactions of diazoketones with aliphatic/aromatic alcohols catalyzed by transition-metal complexes can be smoothly finished to form the new ether linkages (Scheme 1, path a).[15,16] When the insertion reactions are performed in THF, the results are unexpected, in which carbene derived from diazocarbonyl inserted into O-H of alcohols, simultaneously ring-opened THF (Scheme 1, path b).[17] 1,3-Diketonesas, the precursor of enols are always used in organic synthesis.[18] Herein, we would like to report a novel synthesis of enol ethers *via* the tandem reaction of diazoketones, 1,3-diketones in THF catalyzed by cheap and available CuI under extremely simple conditions.

Results and discussion

Initially, 2-diazoacetophenone was used as starting materials to react with 1,3-diketones for getting the corresponding cycloaddition product. However, when the reaction was carried out in THF, it did not proceed in an expected manner and an unpredicted product, β-keto enol ether was obtained. Thus, a new process of three component tandem synthesis of enol ethers was disclosed and these structurally novel products could increase the diversity of structures and properties.

Our research commenced with the reaction of 2-diazoacetophenone (**1a**) (0.5 mmol) as the model substrate with dibenzoyl methane (1.0 mmol) in THF in the presence of CuI as a catalyst at room temperature. Gratifyingly, β-keto enol ether (**3a**) was obtained with the yield of 71%. As shown in Table 1, the yield of **3a** was decreased when the reaction was catalyzed by 1-copper (I) alkyne (Table 1, entry 2). In sharp contrast, $Cu(OTf)_2$ gave almost no product (Table 1, entry 3). This result also strongly indicated that Cu(I) was more suitable for this transformation than Cu(II). This may be caused by too fast formation of the corresponding carbene intermediate in the presence of $Cu(OTf)_2$ to be controlled. The extremely high reactivity of carbene leads to a dimer which can't react with **2a** and THF because of their low reactivity. For the same reason, $Co(OAc)_2$ and $FeCl_3$ also didn't afford the product (Table 1,

---

* Corresponding authors.

E-mail address: chenwenwen12@126.com (W. Chen).

http://dx.doi.org/10.1016/j.tetlet.2017.07.021
0040-4039/

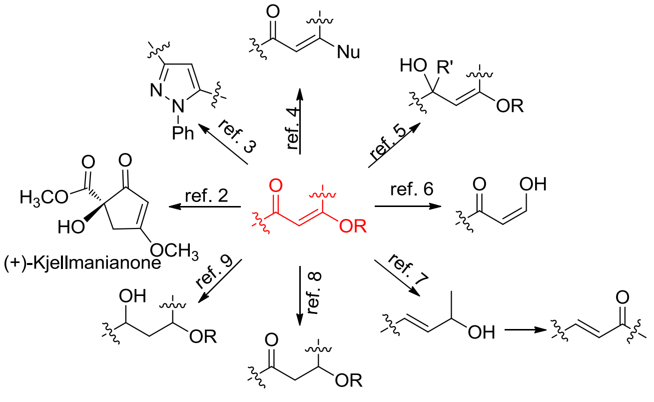
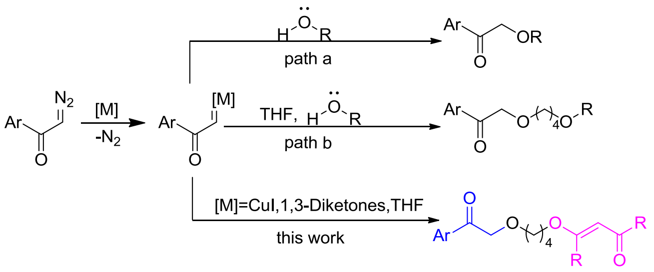


Fig. 1. Applications of β-keto enol ethers.



Scheme 1. Insertion reactions and this work.

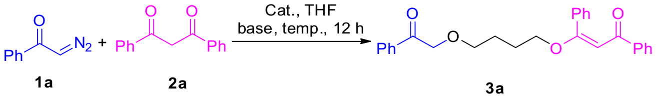
entries 4–5). AgOAc and $ZnCl_2$ were inactive to this reaction because they can't transform 2-diazoacetophenone to carbene and it still existed even after 24 h (Table 1, entries 6–7). It got the product with the yield of 82% in the presence of rhodium octanoate as a catalyst (Table 1, entry 8). Considering that it is cheaper and more available, CuI was chosen as the catalyst for this reaction.

To the best of our knowledge, bases can promote 1,3-diketones to enols. Subsequently, the effect of bases on this reaction was tested. Unfortunately, no better results were observed by using different bases. As a result, the yield of **3a** was decreased sharply by the increase of the basicity (Table 1, entries 9–13). Maybe the deprotonation of bases is unfavorable for this transformation. However, when AcOH was used in this system 4-(2-oxo-2-phenylethoxy)butyl acetate rather than **1a** was produced. Thus, as a reactant not an additive, the reactivity of AcOH is better than that of **2a** (Table 1, entry 14). The gas is released vigorously when H_2SO_4 was used and only dimers of carbene were obtained (Table 1, entry 15). In addition, the reaction yield was influenced obviously by temperature, and the suitable temperature was observed to be 40 °C (Table 1, entry 1). Decreasing or elevating the reaction temperature failed to increase the yield and an unwanted by-product was formed at higher temperature (Table 1, entries 16–17).

Further experiments proved that the yield of **3a** was influenced significantly by the reactant ratios. As shown in Table 1, the yield of **3a** was increased by the increase of the ratio of **1a** and **2a** as the decomposition of diazoketone to dimers (Table 1, entries 18–22). It was preferable to use 2.5 equiv. of 2-diazoacetophenone with the yield of 90% (Table 1, entry 21). In summary, extensive screening showed that the optimized reaction conditions were 0.5 mmol dibenzoylmethane, 2.5 equivalents of 2-diazoacetophenone, and CuI as a catalyst in 1 mL of THF at 40 °C for 12 h (Table 1, entry 21).

With the optimized reaction conditions in hand, we set out to explore the substrate scope of this catalyst system for the simultaneous insertion reaction and ring-opening reaction. As shown in Scheme 2, all tested 1,3-diketones **2a–2m** gave the desired products **3a–3m** in modest to excellent yields. The reactions of 1,3-diketones bearing electron-donating groups were mainly

Table 1
Reactions by Using **1a** as a Substrate.[a]



Entry	Catalyst	Base	**1a:2a** (mole ratio)	T (°C)	Yield[b] (%)
1	CuI	–	1:2	40	71
2	Copper(I) phenylacetylide	–	1:2	40	61
3	$Cu(OTf)_2$	–	1:2	40	Trace
4	$Co(OAc)_2$	–	1:2	40	Trace
5	$FeCl_3$	–	1:2	40	Trace
6	AgOAc	–	1:2	40	NR
7	$ZnCl_2$	–	1:2	40	NR
8	Rhodium octanoate	–	1:2	40	82
9	CuI	Et_3N	1:2	40	43
10	CuI	$NaHCO_3$	1:2	40	65
11	CuI	Na_2CO_3	1:2	40	68
12	CuI	K_2CO_3	1:2	40	52
13	CuI	NaOH	1:2	40	5
14	CuI	AcOH	1:2	40	Trace
15	CuI	H_2SO_4	1:2	40	0
16	CuI	–	1:2	25	50
17	CuI	–	1:2	60	53
18	CuI	–	1.2:1	40	64
19	CuI	–	1.5:1	40	70
20	CuI	–	2.0:1	40	81
21	**CuI**	–	**2.5:1**	**40**	**90**
22	CuI	–	3.0:1	40	84

[a] The mixture of **1a**, **2a**, catalyst (0.1 mmol) and base (1 mmol, 2 eq.) in THF (1 mL) was stirred in a stoppered glass tube.
[b] The isolated yields.