

Copper-Catalyzed C-C(O)C Bond Cleavage of Monoalkylated β -Diketone: Synthesis of α,β -Unsaturated Ketones

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Abstract

A new and simple route for the synthesis of α,β -unsaturated ketones via cleavage of the C-C(O)C single bond of monoalkylated β -diketone has been described. The reaction was catalyzed by copper, a cheap transition metal in a weakly basic medium (K_3PO_4) at room temperature. To carry out this study, we first had to synthesize the monoalkylated β -diketones 1. Afterwards, α,β -unsaturated ketones 2 were obtained with high yields around 80%. Finally, all the products were characterized by ¹H NMR, ¹³C NMR, and HRMS spectra.

Keywords

Monoalkylated β -diketone, α,β -Unsaturated Ketones, Copper-Catalyzed, C-C(O)C Bond Cleavage

1. Introduction

Transition-metal-catalyzed C-C bond cleavage has long been a line of research capable of producing a new mode of reactivity in organic synthesis [1] [2] [3] [4]. This way of doing this involves three or four membered ring strain release [5] [6], aromatization, β -carbon-elimination [7] [8] and by using carbonyl group such as chelation assistance [9] have been reported to cleave C-C bond. However, the activation of the C-C(O)C bond using transition metals is less reported. Monoalkylated β -diketones have been successfully used in the literature as a

substrate in the case of the activation of the C-C(O)C bond [10], copper-catalyzed C-C(O)C Bond Cleavage has been a challenging research area due to the high reactivity problem of resulting monoalkylated β -diketonetoward the metal catalysts. Numerous research works carried out in recent years have shown that α,β -unsaturated carbonyl compounds such as α,β -unsaturated ketones **2** constitute an important class in organic synthesis [11] [12]. These molecules have the advantage of being intermediates in a chemical synthesis, of having several reactive sites. α,β -unsaturated ketones are known to be good Michael acceptors because of the electron-withdrawing groups offering the possibility of carrying out a -1,4 addition in the presence of a nucleophile. Thus, in 2013, yonghuang *et al.* [13] proposed the synthesis of α,β -unsaturated carbonyl compounds via a visible-light; this reaction was promoted by organocatalytic aerobic oxidation. In a recent publication, makotoyasuda *et al.* [14] described a method for the synthesis of α -Alkenyl α,β -Unsaturated ketones via dehydrogermylation of oxagermacycles; the reaction was carried in the presence of germanium(II) salts and aldehydes to afford two classes of α -alkenyl α,β -unsaturated ketones. Very recently, Sung you hongand co-worker [15] developed the hydroacylation reactions of alkynes using aldehydes for the synthesis of α,β -unsaturated ketones through nickel-catalysed. However, the procedures used for these reactions lead to a series of shortcomings such as: i) the reaction is carried out in the presence of visible-light, ii) the reaction requires the presence of germanium (II) salt which is not really accessible, iii) the reaction involves the stabilization of an acyl-nickel I complex assisted by heteroatom chelation. The literature report clearly that the synthesis of α,β -unsaturated ketones is less and less studied, but this field still remains an area of action for organic chemists. Herein, we report copper-catalyzed C-C(O)C Bond cleavage of monoalkylated β -diketone **1** to provide the α,β -unsaturated ketones **2**. We began our study by synthesizing the monoalkylated β -diketone compounds **1** using the method proposed by using an alkyl halide which can be condensed on a β -diketone in a basic medium. The monoalkylated β -diketones **1** are then used for the synthesis of α,β -unsaturated ketones **2** in the presence of copper as catalyst and formaldehyde in a weakly basic medium (Figure 1).

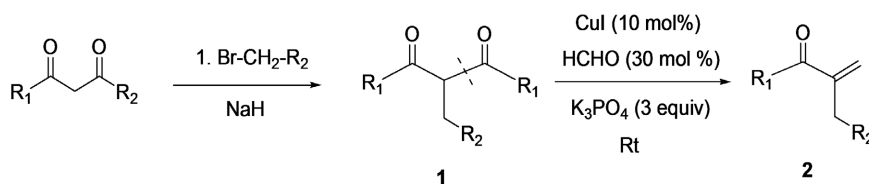


Figure 1. Synthesis of α,β -unsaturated ketones **2**.

2. Experimental Procedures

2.1. Materials

All reagents were purchased from commercial sources and used without further

treatment, unless otherwise indicated. Analytical thin-layer chromatography (TLC) was performed on Quindao Haiyang plastic silica gel plates and new products were purified by column chromatography over ZCX-II 300 - 400 mesh silica gel. Petroleum ether (PE) refers to the fraction boiling in the 30 - 60°C range. Melting points were obtained using a Yuhua X-4 apparatus. ¹H NMR (500 MHz) and ¹³C NMR (125 MHz) spectra were recorded at 25°C using a Varian Unity 500 spectrometer, with TMS as internal standard. Mass spectra were recorded on an AutoflexIII Smart beam MS-spectrometer. High resolution mass spectra (HRMS) were recorded on a Bruker micro Tof using ESI method. Chemical shifts were reported in parts per million on the scale relative to an internal standard (tetramethylsilane, or appropriate solvent peaks) with coupling constants given in hertz. HNMR multiplicity data are denoted by s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet).

2.2. General Procedure for the Synthesis of Compounds

2.2.1. General Procedure for the Synthesis of Monoalkylated β -Diketones **1**

NaH (100 mmol) and anhydrous THF (4 mL) are introduced at 0°C into a round-bottomed 250 mL flask, then acetylacetone (100 mmol) is added in 20 mL of anhydrous THF with stirring. After 1 hour of stirring, methyl bromoacetate (100 mmol) is added. The mixture is refluxed for 20 hours. After cooling the mixture, the solution is hydrolyzed with cold water. The organic phase is extracted with ether (3 × 25 mL) then dried over MgSO₄. The solvent is evaporated by a rotary evaporator to isolate methyl 3-acetyl-4-oxopentanoate **1a** (15.493 g, 90 % yield).

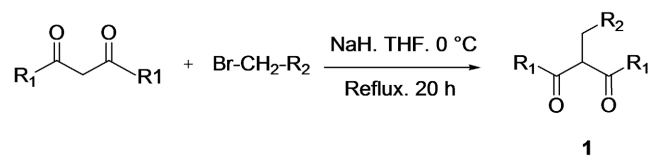
2.2.2. General Procedure for the Synthesis of α,β -Unsaturated Ketones **2**

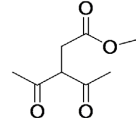
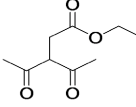
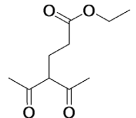
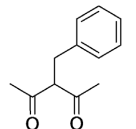
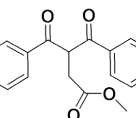
The solution of monoalkylated β -diketone **1a** (20 mmol), CuI (10 mol%), formaldehyde (4 mL) and K₃PO₄ (3 equiv) were placed in a round-bottomed flask containing a magnetic stirrer under air atmosphere. The mixture was then stirred at room temperature for 2 hours. The resulting solution was extracted with ether (10 mL × 3), and the combined organic layer was washed with brine solution (10 mL) and concentrated in vacuo. The crude residue was purified using silica gel column chromatography with petroleum ether/ethyl acetate (20:1) as the eluent to afford the corresponding product **2a** (2.274 g, 80 % yield).

3. Results and Discussion

The results of the reaction between β -diketone and methyl bromoacetate to form the monoalkylated β -diketone **1** have been presented in **Table 1**. In general, the yields obtained are between 61% and 90%. Compounds **1c** and **1d** have a fairly low yield (entries 3 and 4), this is explained by the complexity of the fairly large alkyl group.

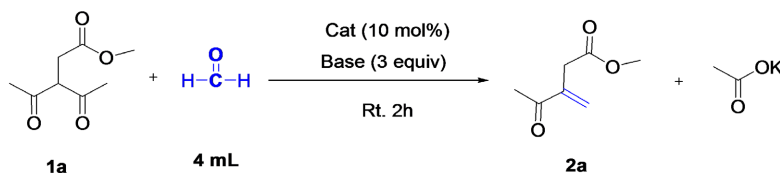
The optimization condition of copper-catalyzed C-C(O)C bond cleavage of monoalkylated β -diketone was investigated by using different conditions (**Table 2**).

Table 1. Synthesis of monoalkylated β -diketone **1**.

Entry	R ₁	R ₂	monoalkylated β -diketone 1	Yield (%)
1	Me	COOMe	 1a	90
2	Me	COOEt	 1b	88
3	Me	CH ₂ -COOEt	 1c	73
4	Me	Ph	 1d	61
5	Ph	COOMe	 1e	89

We started our investigation to use monoalkylated β -diketone **1a** (20 mmol), CuCl (10 mol%), formaldehyde (4 mL) and K₂CO₃ (3 equiv). We found that the product was observed at 42% of yield (**Table 2**, entry 1). The use of copper Cu-Brand CuI led us to obtain α,β -unsaturated ketone product **2a** respectively in 48% and 61% yield (**Table 2**, entries 2-3). However, the experience with Cu(OAc)₂ as catalyst in the same conditions, revealed **2a** in 23% yield (**Table 2**, entry 4). Base was major element for this reaction. Thus, when we used for the first time K₃PO₄ as base in the same conditions, the product **2a** was clearly isolated in 80% yield (**Table 2**, entry 5). Various bases such as 4-dimethylaminopyridine (DMAP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and calcium carbonate (CaCO₃) were also tried, only CaCO₃, gave an appreciable result in 33% (**Table 2**, entry 8). When we use Pyridine as a base, no desired product was obtained (**Table 2**, entry 9).

Based on the optimization of this reaction in (**Table 2**, entry 5), the scope of Copper-Catalyzed C-C(O)C Bond Cleavage of monoalkylated β -diketone **1** for the synthesis of α,β -unsaturated ketones **2** (**Table 3**) was investigated. We found that all the monoalkylated β -diketone **1** were efficiently transformed to the

Table 2. Optimization condition of Copper-Catalyzed C-C(O)C Bond Cleavage of monoalkylated β -diketone.

Entry	Cat	Base	2a Yield (%)
1	CuCl	K ₂ CO ₃	42
2	CuBr	K ₂ CO ₃	48
3	CuI	K ₂ CO ₃	61
4	Cu(OAc) ₂	K ₂ CO ₃	23
5	CuI	K ₃ PO ₄	80
6	CuI	DMAP	21
7	CuI	DBU	18
8	CuI	Ca ₂ CO ₃	33
9	CuI	Pyridine	0

corresponding α,β -unsaturated ketones **2a-2e** in good yields. However, the nature of the alkylating group and also the α group of ketones have a great influence on this transformation. Thus, we found a decrease in yield during the synthesis of compounds **2d** and **2e** (Table 3, entries 4-5).

3.1. Characterization Data of Monoalkylated β -Diketone 1

Methyl 3-acetyl-4-oxopentanoate 1a

¹H-NMR (500 MHz, CDCl₃) δ = 2.33 (s, 6H, 2 CH₃), 2.89 (d, J = 7 Hz, 2H, CH₂), 3.71 (s, 3H, CH₃O), 4.17 (t, J = 7 Hz, 1H, CH). ¹³C NMR (125 MHz; CDCl₃): δ = 29.7, 32.3, 52.1, 63.3, 171.6, 202.5. HRMS (ESI-TOF) calcd for C₈H₁₂NaO₄, [M + Na]⁺ 195.0633 Found 195.0631.

Ethyl 3-acetyl-4-oxopentanoate 1b

¹H-NMR (500 MHz, CDCl₃) δ = 2.31 (s, 6H, 2CH₃), 2.89 (d, J = 7 Hz, 3H, CH₃), 2.90 (d, J = 7 Hz, 2H, CH₂CO), 3.95 - 4.32 (m, 3H, CH₂, CH). ¹³C NMR (125 MHz; CDCl₃): δ = 14.2, 29.6, 32.5, 61.2, 63.3, 171.2, 202.4. HRMS (ESI-TOF) calcd for C₉H₁₄NaO₄, [M + Na]⁺ 209.0790 Found 209.0787.

(3-ethoxybut-3-en-1yl)pentane-2,4-dione 1c

¹H-NMR (500 MHz, CDCl₃) δ = 1.21 (t, J = 7 Hz, 3H), 2.14 - 2.32 (m, 4H, CH₂-CH₂), 2.22 (s, 6H, 2CH₃), 4.10 - 4.20 (m, 3H, CH-CH₂). ¹³C NMR (125 MHz; CDCl₃): δ = 13.9, 28.9, 31.2, 34.5, 60.3, 65.9, 172.3, 203.4. HRMS (ESI-TOF) calcd for C₁₀H₁₆NaO₄, [M + Na]⁺ 223.0946 Found 223.0941.

3-benzylpentane-2,4-dione 1d

¹H-NMR (500 MHz, CDCl₃) δ = 2.05 (s, 6H, 2CH₃), 3.13 (d, J = 7 Hz, 2H, CH₂), 4.01 (t, J = 7 Hz, 1H, CH), 7.20 (s, 5H, Ar). ¹³C NMR (125 MHz; CDCl₃):

Table 3. Copper-catalyzed C-C(O)C bond cleavage of monoalkylated β -diketone.

Reaction scheme: Monoalkylated β -diketone **1** (20 mmol) reacts with $\text{H}-\text{C}(\text{O})-\text{H}$ in the presence of CuI (10 mol%) and K_3PO_4 (3 equiv) at room temperature for 2 hours to yield β -unsaturated ketone **2** and a potassium enolate salt $\text{R}_1\text{C}(\text{O})\text{OK}$.

Entry	monoalkylated β -diketone 1	Product 2	Yield (%)
1	1a	2a	80
2	1b	2b	79
3	1c	2c	88
4	1d	2d	64
	1e	2e	61

$\delta = 29.7, 32.9, 69.9, 128.7, 128.6, 127.0, 127.3, 126.3, 203.5$. HRMS (ESI-TOF) calcd for $\text{C}_{12}\text{H}_{14}\text{NaO}_2$, $[\text{M} + \text{Na}]^+$ 213.0891 Found 213.0901

Methyl 3,3-dibenzoylpropanoate 1e

$^1\text{H-NMR}$ (500 MHz, CDCl_3) $\delta = 3.05$ (d, $J = 7\text{Hz}$, 2H, CH_2), 3.64 (s, 3H, CH_3O), 5.75 (t, $J = 7\text{ Hz}$, 1H, CH), 7.17 - 8.05 (2m, 10H, 2Ar). $^{13}\text{C NMR}$ (125 MHz; CDCl_3): $\delta = 33.2, 52.3, 52.4, 128.8, 129.0, 133.9, 135.5, 171.8, 195.1$. HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{16}\text{NaO}_4$, $[\text{M} + \text{Na}]^+$ 319.0946 Found 319.0949.

3.2. Characterization Data of α,β -Unsaturated Ketones 2

Methyl 3-methylidene-4-oxopentanoate 2a

$^1\text{H-NMR}$ (500 MHz, CDCl_3) $\delta = 2.31$ (s, 3H, CH_3), 3.25 (s, 2H, CH_2), 3.67 (s, 3H, CH_3O), 5.94 (s, 1H, $\text{CH}_2=$), 6.16 (s, 1H, $\text{CH}_2=$). $^{13}\text{C NMR}$ (125 MHz; CDCl_3): $\delta = 25.1, 36.4, 52.0, 128.5, 142.4, 171.5, 198.3$. HRMS (ESI-TOF) calcd for $\text{C}_7\text{H}_{10}\text{NaO}_3$, $[\text{M} + \text{Na}]^+$ 165.0528 Found 165.0530.

Ethyl 3-methylidene-4-oxopentanoate 2b

elimination of **Cu^{II}-species II** gives **Cu^I** and the intermediate **III**. Then, the intermediate **III** affords the complex **IV**. Finally, The rearrangement of complex **IV** leads to C-C bond cleavage, affording desired α,β -unsaturated ketones product **2**. Indeed, the byproduct, such as potassium methanoate, could be isolated in some cases.

4. Conclusion

Transition-metal catalyzed C-C bonds activation has become an invaluable tool for the synthesis chemistry. These methods, in particular copper-catalyzed, have been used for the synthesis of a variety of compounds. In this article, we have developed a new type of copper-catalyzed C-C(O)C bond cleavage of common monoalkylated β -diketone for the synthesis of α,β -unsaturated ketones which could be used for their properties in organic chemistry. The usage of inexpensive copper catalyst under open air conditions makes this protocol very green and practical. A variety of α,β -unsaturated ketones derivatives having different substituted groups was obtained in moderate to high yields. The details of the mechanism of this transformation are still under study by our research team.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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