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Catalytic α-hydroxylation of ketones under $CuBr_2$ or HBr/DMSO systems

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ABSTRACT

An efficient and facile α-hydroxylation of ketones catalyzed by $CuBr_2$ or HBr in DMSO is developed, providing secondary/tertiary α-hydroxy carbonyl compounds in moderate to good yields (up to 87%). A series of control experiments suggested that water and DMSO may work cooperatively in the hydrolysis step.

1. Introduction

α-Hydroxyketones are not only important constituents of many biologically active natural products but also served as intermediates in some important organic transformations.[1] Therefore, a number of methods have been developed for the preparation of α-hydroxy ketones moieties. Among them, the most frequently used methodologies are the oxidation of the enolates or silyl enol ethers compounds with metal oxidants[2] (i.e., thallium(III) acetate, oxone, osmium tetroxide), hypervalent iodine compounds,[3] peroxide,[4] oxaziridine.[5] With regard to ecological and economical concerns, the direct α-hydroxylation of carbonyl compounds with molecular oxygen catalyzed by metal salts is the ideal of choice.[6] Ritter and co-workers have developed an elegant site-specific α-hydroxylation reaction of carbonyl compounds using a dinuclear Pd(II) complex as a catalyst and molecular oxygen as an oxidant, affording tertiary α-hydroxycarbonyl compounds.[7] Of particular note is the elegant work of Jiao and co-workers, in which an efficient approach of α-hydroxylation of carbonyl compounds with $Cs_2CO_3/P(OEt)_3/O_2$ system was found to give tertiary α-hydroxycarbonyl compounds without any transition-metal catalysts.[8] However, this method is limited to tertiary Csp^3–H bond substrates and requires 2 equiv of $P(OEt)_3$ as reducing agent.[9] Moreover, it was reported that the direct oxidation of enolizable ketones using 2-alkylidene-4-oxothiazolidine vinyl bromide as a catalyst in DMSO allows the introduction of a secondary or tertiary hydroxy group via α-bromination and hydrolytic step.[10] Herein, we would like to describe full details of our elaborative experiments on a $CuBr_2$ or HBr/DMSO catalyzed facile α-hydroxylation of ketones, and water and DMSO was proposed to work jointly for the formation of α-hydroxycarbonyl compounds.

2. Results and discussion

Recently, MacMillan reported an efficient α-amination of ketones catalyzed by copper(II) bromide in DMSO.[11] On the other hand, α-halogenated ketones could be hydrolyzed to the corresponding α-hydroxyketones under strong polar aprotic solvent[12] or oxidized to the 1,2-diketone compounds in the DMSO system.[10,13,14] Inspired by these elegant works, we envisaged that a similar $CuBr_2$ catalytic system would be also applicable to a α-hydroxylation of ketones. We then began our investigation by using propiophenone (**1a**) as model substrate to perform the α-hydroxylation in the presence of $CuBr_2$ (10 mol %) in DMSO at room temperature under an air atmosphere, which is an optimal reaction condition from MacMillan's work. Unfortunately, no expected α-hydroxyketones was observed (Table 1, entry 1). To our delight, raising the reaction temperature to 90 °C, the desired α-hydroxylation product **2a** was obtained in 65% yield (Table 1, entry 2). Screening of various of copper salts turned out that $CuBr_2$ was the most suitable catalyst (Table 1, entries 2–5). Interestingly, adding 30 mol % lithium bromide to the $Cu(ClO_4)_2$ reaction system, the reaction proceeded to give corresponding product **2a** in 28% yield, presumably due to the in situ formation of $CuBr_2$ (Table 1, entries 5–6). Screening of

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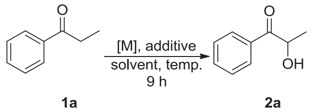
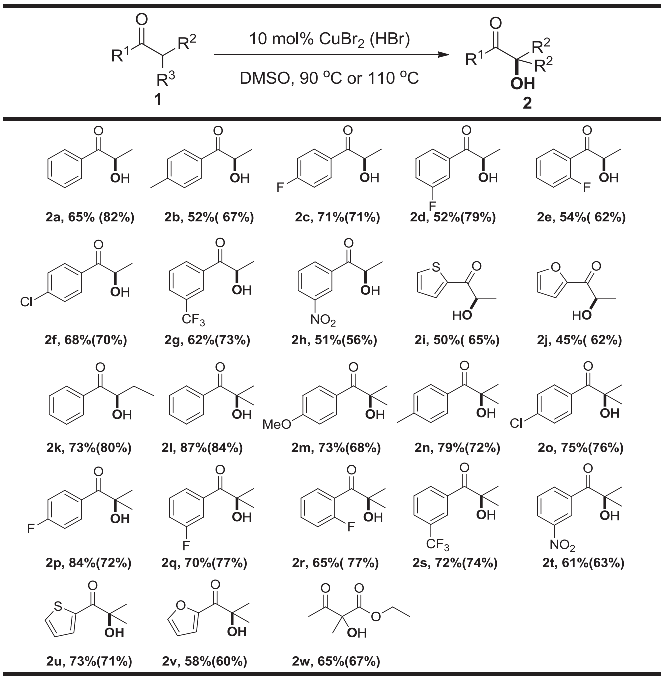
Table 1
Initial studies toward α-hydroxylation of ketones[a]



Entry	Metal	Solvent	Temp (°C)	Yield[b]
1	$CuBr_2$	DMSO	rt	0
2	**$CuBr_2$**	**DMSO**	**90**	**65**
3	$CuCl_2$	DMSO	90	5
4	CuBr	DMSO	90	0
5	$Cu(ClO_4)_2$	DMSO	90	0
6[c]	$Cu(ClO_4)_2$	DMSO	90	28
7	$CuBr_2$	DMF	90	Trace
8	$CuBr_2$	Toluene	90	0
9	$CuBr_2$	1,4-Dioxane	90	0
10	$CuBr_2$	CH_2ClCH_2Cl	90	0
11	$CuBr_2$	CH_3NO_2	90	0
12	$CuBr_2$	Butanol	90	0
13[d]	$CuBr_2$	DMSO	90	63
14	HBr	DMSO	90	69
15[e]	**HBr**	**DMSO**	**90**	**82**

Bold: optimized reaction conditions.
[a] Reaction conditions: **1a** (0.5 mmol), catalyst (10 mol %), solvent (2 mL), air atmosphere, 9 h.
[b] Isolated yield.
[c] With 30 mol % LiBr.
[d] With N_2 atmosphere.
[e] 4 mL DMSO.

Table 2
Scope of the α-hydroxylation of ketones[a]



[a] Reaction conditions: ketone 0.5 mmol, catalyst 10 mol%, solvent 2 mL, air atmosphere, 9 h, 90 °C .The value in brackets is the isolated yield of the reaction with HBr (10 mol%) in DMSO (4 mL) for 12 h; The reaction temperature for α-methine carbonyls is 110 °C .

solvents, such as DMF, CH_3NO_2, and toluene instead of DMSO, gave no desired product (Table 1, entries 7–12). Furthermore, this reaction also proceeded smoothly under nitrogen, which indicated aerobic oxygen is not involved in this reaction (Table 1, entry 13, 63% yield). On the other hand, according to the reported mechanisms,[10,12] $CuBr_2$ could be converted directly into Br_2 or hydrolyzed into HBr followed by DMSO-mediated oxidation to form Br_2. With the well known chemistry properties of $CuBr_2$ and HBr/DMSO system, we speculated that the key catalyst for the $CuBr_2$-catalyzed α-hydroxylation of ketones could be the 'HBr'. Therefore, 10 mol % of HBr aqueous solution (40 wt %) was employed instead of $CuBr_2$. Expectedly, a slightly better yield of **2a** was obtained (Table 1, entry 14, 69% yield). Further optimization by the use of 4 mL of DMSO gave an optimal result (Table 1, entry 15, 82% yield). Although, it is obvious that the HBr/DMSO system is more efficient than the $CuBr_2$/DMSO combination, it is still unclear if the copper itself involved in the α-hydroxylation process.

With optimized conditions in hand, we next investigated the scope and generality of this $CuBr_2$ or HBr/DMSO catalyzed α-hydroxylation of ketones as shown in Table 2. The scope of α-methylene carbonyls were first investigated. The various electron-rich (**2a**–**b**) and electron-poor (**2c**–**h**) aryl ketones all underwent a smooth transformation to form the corresponding α-hydroxyketones in moderate to good yields. The α-hydroxylation of heteroaromatic ketones can also proceeded smoothly, delivering α-hydroxyketones in moderate yields (**2i**–**j**). *n*-Butyrophenone showed very similar reactivity to **2a** under both $CuBr_2$ and HBr/DMSO conditions (**2k**). Interestingly, for the all tried α-methylene carbonyls, the HBr/DMSO system showed relatively higher catalytic activities than the $CuBr_2$/DMSO system. Next, the scope of α-methine carbonyls were investigated. The reaction of isobutyrophenone with 10 mol % $CuBr_2$ in DMSO at the temperature of 90 °C for 9 h yielded the tertiary α-hydroxyketone **2l** in 68% yield, but raising the temperature to 110 °C increased the yield to 87%, which could be ascribed to the steric effect of bulkier α-methine substrate. Therefore, the following α-hydroxylation of other α-methine substrates were carried out at 110 °C. To our delight, the substituted isobutyrophenones with electron-donating (**2m**–**n**) or electron-withdrawing (**2o**–**t**) substituent on the phenyl ring and heteroaromatic isobutyrophenones (**2u**–**v**) were all compatible in this $CuBr_2$ or HBr/DMSO catlyzed α-hydroxylation. The hydroxylation of dicarbonyl compounds (**2w**) could also proceed smoothly in moderate yields. Notably, unlike the cases of α-methylene substrates, the $CuBr_2$/DMSO system showed similar reactivities to the HBr/DMSO for the α-methine substrates, and even better yields were obtained in some cases (**2l**–**n**, **2p**).

It is noteworthy that some ketones were reacted to give not only the corresponding α-hydroxyketones but also the byproduct by further transformation as shown in Scheme 1. For example, the reaction of cyclopentyl phenyl ketone **3a** yielded α-hydroxyketone **4a** and dehydration product **4aa** ($CuBr_2$/DMSO: 50% and 42%, respectively; HBr/DMSO: 62% and 33%, respectively). Benzyl phenyl ketone **3b** was found to be transformed to α-hydroxyketone **4b** and α-diketone **4ba** ($CuBr_2$/DMSO in 2 h: 44% and 22%, respectively; HBr/DMSO in 3 h: 56% and 23%, respectively), but prolongation of the reaction time to 9 h resulted in α-diketone **4ba** in almost quantitative yields under both reaction conditions. Moreover, the reaction of 1,1-diphenylacetone **3c** generated α-hydroxyketone **4c** and deacetylation product **4ca** ($CuBr_2$/DMSO in 3 h: 35% and 60%, respectively; HBr/DMSO in 6 h: 44% and 47%, respectively)and the yield of **4ca** could be increased dramatically (92% and 97% for both conditions, respectively)when the reaction time was prolonged to 9 h. To our surprise, the reaction of dibenzoylmethane **3d** was found to produce 1,2-diketone **4ba** in a high yield presumably through a decarbonylation pathway. In order to understand the reactivity of α-methylene and α-methine, two 2-aryl cyclohexanones **3e** or **3f** were chosen to perform the control experiments under both conditions. To our surprise, the reaction underwent smoothly in the presence of $CuBr_2$, however generating ketoacid **4e** and **4f** instead of normal α-hydroxylation in good yields. Notably, the HBr/DMSO system gave no any desired product and the unexpected ketoacid. Therefore, we speculated that a direct copper-catalyzed oxidative C–C bond cleavage may occur. The further study on this unexpected reaction is underway in our laboratory.