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Silver-catalyzed decarboxylative cross-coupling of α -keto acids with alkenes giving approach to chalcones

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ARTICLE INFO

ABSTRACT

A silver-catalyzed decarboxylative cross-coupling of α -keto acids with alkenes is reported. The method, with a wide range of substrate tolerance and mild operational conditions, can produce various chalcone derivatives in moderate to high yields from easily available starting materials.

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1. Introduction

Catalytic C-C bond formations, for the great values of applications in synthetic chemistry, have been well-studied for decades. Apart from transition metal catalyzed cross-coupling reactions, C-C bonds building through radical process and C-H bond activation, owe to the strength of atom economy and other virtues, have attracted great attention in recent years.¹ Among them, with the easily availability from natural products as well as the industrial suppliers, great advances have been taken from the carboxylic acids and their derivatives to investigations in the radical decarboxylative coupling reactions.²

Chalcone derivatives are widely found in natural products, and were extensively applied in medical science and other technologies³. For the reactivity and important scaffold in organic chemistry, chalcones are also used as significant building blocks and intermediates in organic synthesis⁴.

Plenty of efforts have already been made for the synthetic strategies of chalcones derivatives in the past decades⁵. But in most cases of these transformations, strong base, noble metal catalysts, ligands and hash operations were always required. In comparison, decarboxylative coupling reactions, which were endowed with high transformation efficiency, nontoxic byproduct, cheap and widely available materials, and other advantages, were so far underdeveloped. In 2014, a catalytic decarboxylative acylfluorination of styrenes with α -keto acids and Selectfluor is reported by Duan and coworkers.^{2m} In this precedent work, chalcone was observed as a byproduct in the

reaction when NaHCO₃ was used as an additive. In 2015, Wang^{6a} and Guo^{6b} group have respectively reported doubledecarboxylative coupling reactions of α -keto acids with cinnamic acids for the preparation of chalcone derivatives (Scheme 1, a and b). Based on these studies, we consider that to develop a decarboxylative coupling of α -keto acids with alkenes to produce chalcones can be a more atom economical approach.

In this paper, a silver catalyzed decarboxylative coupling of α keto acids with alkenes is reported. This base free methodology, providing a convenient route to chalcone derivatives, was enclosed with advantages of atom economy, mild operation conditions and wide substrate tolerance, giving the corresponding products in moderate to good yields. The operation is easy for handling and the starting materials as well as the additives are easily prepared or commercially available.

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Scheme 1. Decarboxylative cross-coupling of α -keto acids.

2. Results and discussion

2.1. Optimizations

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Table 1. Optimizations of the conditions^a



entry	catalyst	oxidant	solvent	yield ^b
1	AgNO ₃	$K_2S_2O_8$	MeCN	12%
2	AgNO ₃	$K_2S_2O_8$	H ₂ O	trace
3	Ag ₂ CO ₃	$K_2S_2O_8$	H_2O	trace
4	Ag ₂ CO ₃	$K_2S_2O_8$	MeCN	72%
5	Ag ₂ CO ₃	$K_2S_2O_8$	MeCN/H ₂ O (1:1)	43%
6	Ag ₂ CO ₃	$K_2S_2O_8$	МеОН	21%
7	Ag ₂ CO ₃	$Na_2S_2O_8$	MeCN	11%
8	Ag ₂ CO ₃	$(NH_4)_2S_2O_8$	MeCN	18%
9	Ag ₂ O	$K_2S_2O_8$	MeCN	27%
10	AgOAc	$K_2S_2O_8$	MeCN	14%
11	١	$K_2S_2O_8$	MeCN	n. r.
12 ^c	Ag ₂ CO ₃	$K_2S_2O_8$	MeCN	65%
13 ^d	Ag ₂ CO ₃	$K_2S_2O_8$	MeCN	62%

^a Conditions: **1a** (0.2 mmol), **2a** (1.0 mmol), catalyst (10 mol%), oxidant (0.6 mmol), solvent (2 mL), 100 °C, 24 h.

^b Isolated yields.

^c Temperature at 120 °C;

^d Reaction for 36 h.

At the beginning of our studies upon this decarboxylative cross-coupling process, reactions of 2-oxo-2-phenylacetic acid (**1a**) with 1-methyl-4-vinylbenzene (**2a**) were investigated as our model reaction under different conditions (table 1). We are glad to see that when the starting materials **1a** and **2a** were treated with $K_2S_2O_8$ and $AgNO_3$ in MeCN as solvent under 100 °C for 24 h, desired product **3a** was obtained from the reaction mixture (entry 1). Therefore, different oxidants, silver salts and solvents were screened to achieve a more effective reaction condition. It

was found that Ag₂CO₃ can perform a better catalyst compared with AgNO₃, AgO and AgOAc (entry 4 compared with entry 1, 9, 10). Further investigations indicated the essential ingredient of silver salts in this oxidative coupling, since no reaction took place without this catalyst (entry 11). We also examined different oxidants, and it came out that the reactions with $K_2S_2O_8$ as oxidant could give a higher yield, whereas with Na2S2O8 or $(NH_4)_2S_2O_8$ gave poor performance in the tests (entry 4 compared with entry 7, 8). MeCN can be used as a good solvent in this process, since water does not support reaction as solvent (entry 2, 3). Mixture of MeCN and water as solvent also gave a lower yield of 3a compared with MeCN only (entry 5 compared with entry 4). To raise the temperature or prolong the reaction time didn't enhance the transformation yields (entry 12 and 13). Different ratio of starting materials or the additives in the reactions were also tested (see the Supporting information), and finally with these experimental results, the optimized reaction conditions were generalized as 10 mol% of Ag₂CO₃ as catalyst, 3 equiv. K₂S₂O₈ as oxidant in MeCN as solvent under 100 °C (entry 4).





Scheme 2. Scope of the substrates

With the optimized conditions, a series of alkenes were reacted with the 2-oxo-2-phenylacetic acid (1a) under the optimized conditions, respectively (Scheme 2). The corresponding products (3a-3g) were obtained in moderate to good yields. Alkyl or halogen substituted styrenes can be tolerated well. Different α -keto acids were also tested (3h-3u) with various alkenes, and they were all well sustained. Methoxyl group on aryl rings of the α -keto acids may slightly affect the transformation, giving product 3k and 3l in comparatively low yields. But it is glad to see that alkene with fused-ring like 2vinylnaphthalene was also sustained in this transformation, giving the desired product 3t in moderate yield. And α -keto acid of heterocyclic derivative as the 2-oxo-2-(thiophen-2-yl)acetic acid can give the coupling product 3u, either. These results reflected a wide tolerability of this catalytic process.

2.3. Mechanism studies

In order to have an insight of the mechanism of this decarboxylative cross-coupling process, the reactions were operated with radical inhibitors (see the Supporting information). When 3 equiv. of TEMPO (2,2,6,6-tetramethylpiperidinooxy) or BHT (2,6-di-tert-butyl-4-methylphenol) were added into the reactions of **1a** with **2a** under the standard condition, it was observed that the reactions were totally inhibited (Scheme 3). And when BHT was used, an adduct of BHT with acyl radical was isolated and determined by NMR and MS. These results suggest that a radical process may be involved. And with the previous literatures^{5e, 6}, a proposed mechanism of this reaction is illustrated in scheme 4.



Since no product **3a** was observed without silver catalyst (table 1, entry 11), we speculate that silver plays a significant role in this decarboxylative cross-coupling process. Firstly, a low valent silver species donates an electron to the $K_2S_2O_8$ and was oxidized into a higher valent silver species. Then an acyl radical **A** is produced from a silver induced decarboxylation of the α -keto acid **1a** with a reduction of silver. And subsequently a radical addition process of **A** to **2a** gives a radical intermediate **B**. Eventually, with immediate oxidation by the high valent silver species and coordinated with a deprotonation process, the final product **3a** is produced from **B**, and the low valent silver species is again oxidized by $K_2S_2O_8$ into the high valent silver species.



Scheme 4. Proposed Mechanism

3. Conclusion

In summary, a decarboxylative cross-coupling process of α keto acids with alkenes is reported. The approach, with the easily available starting materials, using silver carbonate as a catalyst and K₂S₂O₈ as an oxidant, provides a novel methodology to get the chalcone derivatives in moderate to high yields. Preliminary results of mechanism experiments indicated that a free-radical process may be involved in this transformation. Further investigations upon the mechanism studies as well as the expansion of the substrate scope are currently undergoing in our group.

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Acceleration The approach provides a novel methodology to get the chalcone derivatives in good yields.