FULL PAPER

Novel and Efficient One Pot Condensation Reactions between Ketones and Aromatic Alcohols in the Presence of CrO₃ Producing α,β-Unsaturated Carbonyl Compounds

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We report a new, effective and simple method for preparing α,β-unsaturated carbonyl compounds by reacting ketones and aromatic alcohols at 56 ℃ in the presence of CrO₃ (CrO₃ acts as an oxidant and also a catalyst) for around 10 h. The condensation reactions occurred effectively among a wide combination of ketones and alcohols. The procedure is simple and the yields can be high up to 98%. And a probable mechanism is proposed.

Keywords   one pot condensation reaction, ketone, alcohol, CrO₃, α,β-unsaturated carbonyl compound

Introduction

α,β-Unsaturated carbonyl compounds such as benzalacetones and chalcones are important chemical compounds and have numerous applications in various areas.[1] For examples, benzalacetone is a brightening agent in electroplating industry, a mordant in the dyeing industry, a raw material for flavors, and a stabilizer for pesticides.[1a] Chalcones are also widely applied in industries for their antineoplastic, spasmolytic, antibiotic, bacteriostatic and bactericidal properties.[1b,1c]

Usually, α,β-unsaturated carbonyl compounds are products of Claisen-Schmidt condensation reactions between aldehydes and ketones under basic or acidic conditions.[2] Using alcohols and ketones directly, *i.e.*, using alcohols to replace corresponding aldehydes to produce the same α,β-unsaturated carbonyl compounds is significant because many aldehydes are synthesized by selective oxidation of alcohols,[3,4] will reduce the reaction steps and the cost. It is also noted that in other cases of aldehyde/ketone condensation reaction, the aldehydes used are produced from other sources rather than alcohols; it is uncertain which is cheaper between an aldehyde and its corresponding alcohol. On these occasions, using alcohol/ketone condensation reactions can provide a new pathway for preparing α,β-unsaturated carbonyl compounds. Recently, Park *et al*.[5] used palladium or gold nanoparticles entrapped in aluminum hydroxide to successfully catalyze benzyl alcohol/ketone reactions to produce corresponding α,β-unsaturated ketones in toluene in the presence of 3 equiv. base and under 1 atm (1 atm＝1.01×10⁵ Pa) O₂. It is remarkable that the yields and the selectivities of the alcohol/ketone condensation reactions are very high.

Besides, to the best of our knowledge, this is the only example of alcohol/ketone condensation reaction reported so far. However, the tedious and costly processes for preparing the noble metal catalyst may limit the practical application. Here we report that, by simply reacting ketones and aromatic alcohols at 56 ℃ in the presence of CrO₃ (CrO₃ acts as an oxidant and also a catalyst) for around 10 h, α,β-unsaturated ketones can be produced in the yields being high up to 98%. The final products can be easily separated from the reaction system. Based on the results of our control experiments, it is suggested that during the alcohol/ketone condensation reactions ketones reacted with the intermediates (rather than the products) of the CrO₃/aromatic alcohols oxidation reactions, leading to α,β-unsaturated ketones.

Experimental

General procedures for the formation of α,β-unsaturated carbonyl compounds: Small sheet-like particles of CrO₃ (2.4 g, 0.024 mol) were gradually added to the selected ketone (0 ℃, 0.3 mol). Before the reaction, most of the added CrO₃ was dissolved by the ketone. The remaining small portion of the CrO₃ was suspended in the reaction system before the reaction and then dissolved gradually with the progress of the reaction. Then the selected alcohol (0.02 mol) was added gradually. The mixture was stirred (or refluxed when acetone was used as the ketone) at 56 ℃ for 10 h. After reaction, the mixture was poured into 100 mL of water and extracted ether (50 mL×3). Last traces of Cr species in the reaction system can easily be removed by filtering the ethereal solution through small amount of silica gel. Samples were analyzed by GC-MS using in-

ternal standard.

Results

The present study on alcohol/ketone condensation reactions started from the system of benzyl alcohol and acetone, since the corresponding condensation products (benzalacetone and dibenzalacetone) are among the most useful α,β-unsaturated carbonyl compounds. The results demonstrate that benzyl alcohol can react with acetone in the presence of CrO_3 under certain conditions, producing both benzalacetone and dibenzalacetone (Scheme 1). It is noted that benzaldehyde was also produced. However, the yields are very small (less than 3%). The reaction conditions were optimized through variation of reaction time, ratio of CrO_3/benzyl alcohol and reaction temperature. The reaction conditions were optimized for maximum total yield of the condensation products and the highest selectivity for benzalacetone (Table 1). The conditions listed in Entry 1 lead to the maximum total yield of the two condensation products of 86% (including 14% dibenzalacetone), and those in Entry 2 result in the highest selectivity for benzalacetone (including only 3% dibenzalacetone) and a relatively high total products yield of 83%. In the reaction system, acetone acted as both the solvent and the reactant, and CrO_3 as the oxidant as well as the catalyst (as explained below).

Scheme 1 One pot condensation of benzyl alcohol and acetone in the presence of CrO_3
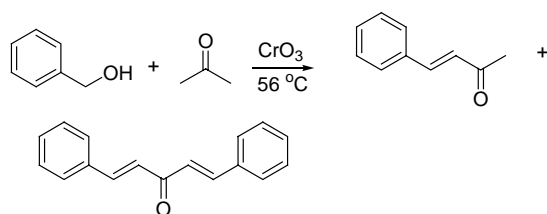
Furthermore, the reaction was extended to other alcohol/ketone systems. As mentioned above, both dibenzalacetone and benzalacetone are very useful.[1a,d] Beside, they can be separated conveniently based on the large difference between their boiling points, and the total products yield is significant. For the similar reasons, aldehyde/ketone condensation reactions reported

in literature aimed at the highest total yields. Accordingly, also for the sake of simplicity, we carried out other alcohol/ketone condensation reactions under the same conditions as those for maximum total products yield in the benzyl alcohol/acetone reaction (Entry 1, Table 1), except for the reaction system of which the reaction temperature had to be increased to 90 ℃ (Entry 3, Table 2). The data in Table 2 indicate that under such reaction conditions, the condensation reactions occurred effectively among a wide combination of ketones and alcohols, producing corresponding α,β-unsaturated carbonyl products. No competitive side reactions such as product decomposition, self condensation, etc., were observed based on GC-MS measurements. Benzyl alcohol reacted successfully with aliphatic ketones (Table 2, Entries 1, 3, 5) as well as aromatic ketones (Table 2, Entries 2 and 4). Furthermore, other aromatic alcohols such as 4-methoxybenzyl alcohol and furfuryl alcohol also reacted effectively with acetone to produce the corresponding α,β-unsaturated carbonyl compounds (Table 2, Entries 6—8). The yields of the condensation products can be high up to 98% (Table 2, Entry 6). The condensation of butanone and benzyl alcohol yielded two products, the internal enone and the terminal enone[6] in a total yield of 73% (Table 2, Entry 5). Neither electron-donating nor electron-withdrawing substituent groups on the ketones or the alcohols have a remarkable effect on the yields. However, the reactions of ketones with aliphatic primary alcohols did not afford the corresponding α,β-unsaturated products in a significant yield (as indicated by Entry 9).
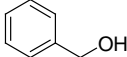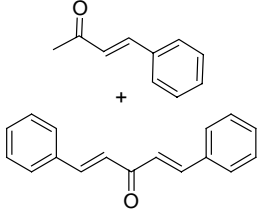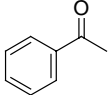
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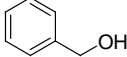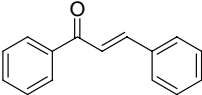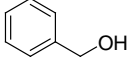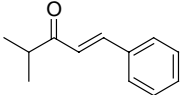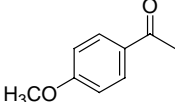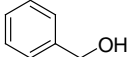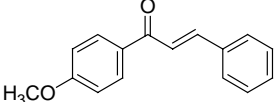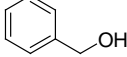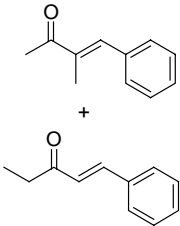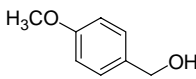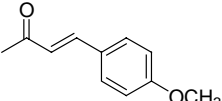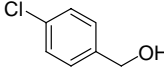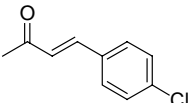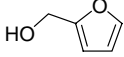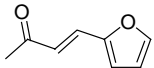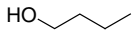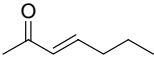
As mentioned above, except for the alcohol/ketone condensation reactions reported by Park et al.[5] where nanoparticles of noble metals were used as the catalyst, all the aldol condensation reactions reported took place between aldehydes and ketones. Although there are some other catalytic systems (without CrO_3) for the α-alkylation of ketones by alcohols or other compounds,[7] the products are saturated ketone and the reaction mechanism is different from that of alcohol/ketone condensation reactions reported in the present study. Therefore, to the best of our knowledge, the present

Table 1 Reaction conditions optimized for maximum total condensation products yield (Entry 1) and the highest selectivity for benzalacetone (Entry 2)[a]

Entry	Moar ratio of CrO$_3$/ benzyl alcohol	Molar ratio of acetone/ benzyl alcohol	Conversion of benzyl alcohol[b]/%	Yield of benzalacetone[b]/%	Yield of dibenzalacetone[b]/%
1	1.2 ∶ 1	15 ∶ 1	90	72	14
2	1.2 ∶ 1	27 ∶ 1	91	80	3

[a] Reaction conditions: Mixtures of acetone (0.3 mol for Entry 1 and 0.54 mol for Entry 2) and benzyl alcohol (0.02 mol) was heated in the presence of CrO_3 (0.024 mol) at 56 ℃ for 10 h. [b] Results obtained by GC-MS tests.

Table 2 Condensation of ketones and alcohols to produce the corresponding α,β-unsaturated ketones[a]

Entry	Ketone	Alcohol	Time/h	Product	Yield[b]/%
1			10		86
2			10		91
3			6		83[c]
4			10		65
5			10		73
6			10		98
7			10		97
8			10		80
9			10		Trace

[a] Reaction conditions: Mixtures of the selected ketone (0.3 mol) and the selected alcohol (0.02 mol) was heated in the presence of CrO₃ (0.024 mol) at 56 ℃ for 10 h. [b] Results obtained by GC-MS. [c] Reacted at 90 ℃.

study represents the second method for successful alcohol/ketone condensation reactions. Compared with the alcohol/ketone condensation reactions reported by Park *et al.*,[5] the method of the present study is simple, low cost and easy to operate, and the yields in some reaction systems of the present study (Entries 2, 6 and 7 in Table 2) are as high as those obtained in Park's reaction systems. Even compared with some of Claisen-Schmidt aldehyde/ketone condensation reactions, besides the above mentioned advantage of reducing the reaction steps and/or providing a new pathway for producing α,β-unsaturated carbonyl compounds, the yields ob-

tained in the present study are similar to or considerably higher than the respective values obtained via Claisen-Schmidt condensation reactions. For examples, it was reported that microwave irradiation enhanced benzaldehyde/acetone condensation, and produced 80% benzalacetone using aqueous NaOH as a catalyst.[8] The yield of the same condensation reaction catalyzed by ionic liquids 2-HEAP is 86%.[9] In these two cases, the yields are similar to that obtained in the present study for benzalacetone via the benzyl alcohol/acetone condensation (which is 86%, Entry 2 in Table 1). Claisen-Schmidt condensation of benzaldehyde with

acetophenone afforded a 81% yield of chalcone after 18 h at 80 ℃ in DMF in the presence of Zn(bpy)(OAc)$_2$[10] and a 75% yield after 24 h at 120 ℃ using bamboo char sulfonic acid as catalyst,[11] whereas the present study afforded a much higher yield of 91% (Entry 2, Table 2) for chalcone from the benzyl alcohol/acetophenone condensation reaction at 56 ℃ for 10 h.

We noted that in literature,[3] CrO$_3$ was used for oxidizing hydroxyl groups to carbonyl compounds in relatively high yields. In most of the oxidation reactions, CrO$_3$ pyridine complex [such as PDC (pyridium dichromate) or PCC (pyridium chlorochromate) regents which are thought as the most reliable oxidation reagents for alcohols[4]], rather than CrO$_3$ alone, was used. The reaction temperature is 20 ℃ or below, rarely using ketones as the solvents.[12] Briefly speaking, we have not found a single example in the literature in which all the conditions and requirements for the alcohol/ketone condensations were met. Therefore, only the oxidation products were obtained from the reported systems of oxidizing alcohols by CrO$_3$.

It is known that CrO$_3$ can oxidize primary alcohols into aldehydes. Is it possible that the aldehydes produced from the oxidation reaction of the alcohols reacted with ketone to produce corresponding α,β-unsaturated carbonyl compounds? This possibility is excluded by the results of our control experiments. In the control experiments, we heated benzaldehyde with acetone in the presence of 1.2 equiv. of CrO$_3$ with or without small amount of water (See Supporting Information, S1) at 56 ℃ for 10 h. However, the total products yields of benzalacetone/dibenzalacetone obtained in the repeated control experiments were less than 10%. As mentioned above, in the present study, when reacting benzyl alcohol instead of benzaldehyde with acetone at 56 ℃ in the presence of CrO$_3$ for 10 h, condensation products were produced in the yield of 86%. The large difference in the yields suggests that there is a synergy between the oxidation reaction and the condensation reaction in the benzyl alcohol/acetone reaction. Ketones react with the intermediate of the alcohol/CrO$_3$ oxidation reaction rather than with the aldehydes under the reaction conditions. Therefore, a probable mechanism is proposed in Scheme 2. According to the well accepted mechanism for CrO$_3$/alcohol oxidation reactions,[13] the intermediate of the CrO$_3$/alcohol reaction is the ester of chromic acid (**1**, Scheme 2); $HCrO_4^-$ is produced in the system by the reaction between CrO$_3$ firstly with trace water in the environment and subsequently with the water either from the environment or from the oxidation reaction and the condensation reaction. Then $HCrO_4^-$ reacts with alcohol, forming the ester.[13] The intermediate **1** is attacked by the enol form of acetone because the CrO$_3$H group, a strong electron deficient Lewis acid, increased the electrophilicity of and thus activated the carbon atom C*, forming cation **2**. In this way, the intermediate **1** reacted with acetone directly rather than was transferred to aldehydes. The cation **2**, which is also the intermediate of aldehyde/ketone condensation reaction to produce α,β-unsaturated carbonyl compounds, was prompt to eliminate H$_2$O to produce benzalacetone **3**, according to the largely reported mechanism for the aldehyde/ketone condensation reactions.[14] In the proposed mechanism, CrO$_3$ acts as a catalyst and an oxidant.

Conclusions

In summary, we reported a new, effective and simple method for the preparation of α,β-unsaturated carbonyl compounds directly from ketones and aromatic alcohols in the presence of CrO$_3$. The procedure is simple and the yields can be high up to 98%. A probable mechanism is proposed. The process represents a step towards wider range of available substrates and reduced cost of production, and has the potential to be adapted to industrial production of benzalacetones and chalcones.

Scheme 2 Probable mechanism for the benzyl alcohol/acetone condensation reaction
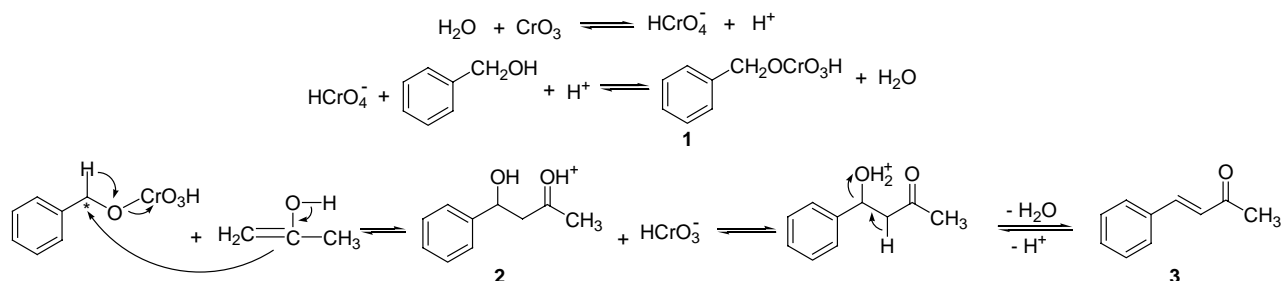
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(E1104281　Zhao, C.)