Tetrahedron 65 (2009) 9797–9800

Contents lists available at ScienceDirect

Tetrahedron

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

One-pot efficient synthesis of aryl α-keto esters from aryl-ketones

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ARTICLE INFO

Article history:
Received 10 July 2009
Received in revised form 12 September 2009
Accepted 18 September 2009
Available online 22 September 2009

Keywords:
One-pot
Aryl α-keto esters
Selenium dioxide
Ketalization

ABSTRACT

A novel one-pot synthesis of aryl α-keto esters was developed through oxidation of aryl-ketones using selenium dioxide, esterification accompanied by ketalization, and hydrolysis. Both aromatics and heteroaromatics gave good yields by this one-pot method.

1. Introduction

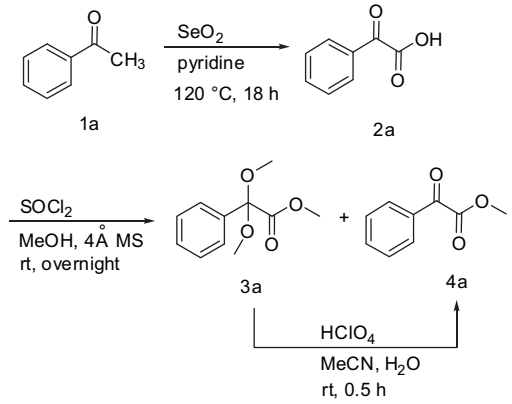
α-Keto esters play an essential role in biological processes. They serve as the backbones in some natural products, such as the 3-deoxy-2-ulosonic acids and their derivatives.[1] In addition, aryl α-keto esters are also used as key intermediates for the synthesis of bioactive compounds such as potent inhibitors of proteolytic enzymes,[2] inhibitors of leukotriene A4 hydrolase,[3] photopolymerization initiators,[4] and precursors in the asymmetric synthesis of α-hydroxy carboxylic acids.[5] α-Keto esters also show antisunburn effects.[6]

In the past several decades, there was much attention fixed on the synthesis of α-keto esters. Several routes were reported including oxidation of α-hydroxy esters with either PCC or Dess–Martin periodinane,[7] Friedel–Crafts acylation,[8] oxidative cleavage of cyano keto phosphoranes,[9] hydrolysis and esterification of acyl cyanides,[4] the reaction of organometallic species with oxalic ester derivatives,[10] and acylation or alkylation of mono-substituted 1,3-dithianes.[11] The most common route for synthesis of α-keto esters is the reaction of Grignard reagents with oxalyl chloride.[12] However all these methods involved either strict conditions, or complicated procedures, or in some cases the low yield and all of these drawbacks extremely limited its application. Herein we report a convenient route to synthesize α-keto esters from aryl-ketones via the one-pot method.

2. Results and discussion

There are many routes for synthesis of aryl α-keto esters as have been noted above, but there is no convenient one for their drawbacks. It is therefore of interest to develop new general synthetic methods for the preparation of α-keto esters.

First, a new route for synthesis of phenyl-α-keto ester from acetophenone **1a** was developed. As shown in Scheme 1, α-keto acid **2a** was obtained through oxidation of acetophenone **1a** by selenium dioxide in pyridine at 120 °C.[13] The following reaction of **2a** with thionyl chloride in methanol with molecular sieve afforded not only α-keto ester **4a** but corresponding ketal **3a** as well. To



Scheme 1. Three-step sequential procedure to synthesize α-keto ester **4a**.

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doi:10.1016/j.tet.2009.09.076

obtain ester product, hydrolysis of **3a** occurred using strong acid. Phenyl-α-keto ester **4a** was synthesized by three steps with a total yield of 74% in mild conditions using cheap reagents.

To further optimize the synthetic route in a more economic and simple manner, the possibility of using a one-pot approach was investigated. A mixture of acetophenone **1a** and 2.0 equiv selenium dioxide in dry pyridine was stirred at 120 °C under nitrogen. After consumption of acetophenone as monitored by TLC for 18 h, the reaction mixture was cooled to 0 °C, molecular sieve 4 Å (50% of acetophenone in weight) and excess methanol were added and the mixture was stirred for 10 min. Then 5.0 equiv thionyl chloride was added dropwise within 1 h, and the mixture was stirred at room temperature overnight. When the complete consumption of **2a** as determined by TLC, 5.0 equiv perchloric acid in acetonitrile and deionized water were poured into the mixture and stirred for another 0.5 h. After general work-up procedure, the residue was purified by chromatography. Fortunately, the phenyl-α-keto ester **4a** was obtained by one-pot method with same level of yield (76%) compared with the three-step method.

The reaction conditions for one-pot method were further optimized. The results are summarized in Table 1. The reaction yield was not changed obviously whether a one-pot approach was used or not (Table 1, entry 1 vs 2). The reaction was found to complete within 15 h when 2.0 equiv selenium dioxide was used (Table 1, entry 2 vs 3). Reaction temperature had less effect on the reaction yield during 100–120 °C (Table 1, entry 3 vs 4).

Table 1
Optimization of the reaction for synthesis of aryl α-keto ester from acetophenone **1a** by one-pot method[a]

Entry	Temp/°C	Time/h	SeO_2/equiv	Yield[c]/%
1[b]	120	18	2.0	74
2	120	18	2.0	76
3	120	15	2.0	76
4	100	15	2.0	77
5[d]	80	24	2.0	52
6	100	15	1.5	77
7[e]	100	24	1.2	41

[a] The reaction was carried out using one-pot procedure.
[b] The reaction was performed via three steps.
[c] Isolated yield.
[d] Under 80 °C with 1.5 equiv selenium dioxide, residual acetophenone retained after 24 h.
[e] Under 100 °C with 1.2 equiv selenium dioxide, residual acetophenone retained after 24 h.

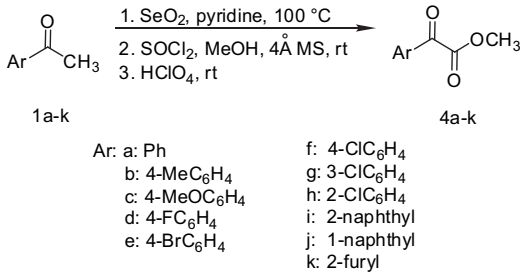
When reaction temperature was dropped to 80 °C, residual acetophenone was still retained after 24 h, and the yield was declined obviously (Table 1, entry 5). The suitable temperature for the reaction was found to be 100 °C (Table 1, entry 3–5). It was also found that yield of α-keto ester was not declined with the decreasing of selenium dioxide from 2.0 equiv to 1.5 equiv (Table 1, entries 4 vs 6). When 1.2 equiv of selenium dioxide was used under 100 °C, the reaction was not completed after 24 h and the yield was decreased dramatically (Table 1, entry 7).

Acid was necessary for hydrolysis of ketal generated in esterification in methanol. The effect of the acid on reaction yield by one-pot method was also investigated. Details are summarized in Table 2. It was crucial to choose proper acid for the hydrolysis of ketal and perchloric acid was found to be the most effective one (Table 2, entry 3).

Table 2
The effect of acid on the hydrolysis of ketal in one-pot method[a]

Entry	Acid	Concn/M	Yield/%
1	HCl	0.5	27
2	H_2SO_4	0.5	21
3	$HClO_4$	0.5	77

[a] The reaction was carried out from oxidation of acetophenone using 1.5 equiv selenium dioxide under 100 °C.



Scheme 2. Synthesis of aryl α-keto esters from aryl-ketones by one-pot.

The success of the one-pot method for synthesis of phenyl α-keto ester from acetophenone encouraged us to expand the scope of the reaction with carbonyl derived aryl-ketone and hetero-ketone (Scheme 2). The results are summarized in Table 3.

As shown in Table 3, all the reactions offered good yield though phenyl groups with either electric withdrawing or donating substituents (Table 3, entries 1–6). Furthermore, the yield was not affected by stereo effect at all (Table 3, entries 6–10). Moreover, 2-furyl group also affords corresponding α-keto ester in good yields (Table 3, entry 11). It was obvious that this one-pot procedure provided an efficient and general method for the synthesis of both aromatics and heteroaromatics α-keto esters.

3. Conclusion

In summary, a convenient one-pot method for synthesis of aryl α-keto esters was developed from cheap commercial available reagents under mild reaction conditions in high yields. This method was found to be a general route for both aromatic and heterocyclic compounds to afford corresponding α-keto esters in good yields.

4. Experimental section

4.1. General comments

All reactions stated were carried out in air atmosphere except otherwise. Pyridine was distilled from CaH_2. All commercial available reagents and solvents were purchased from Guoyao, Fisher and used without further purification. Column chromatography was run on silica gel (200–300 mesh). All ^1H NMR (400 MHz) spectra were recorded on a Varian MECURY plus-400 spectrometer.

4.2. Preparation of phenyl-α-keto ester by three-step method

*4.2.1. Preparation of phenyl-α-keto acid **2a**.* A mixture of acetophenone (0.48 g, 4.0 mmol) and selenium dioxide (0.89 g, 8.0 mmol) in dry pyridine (2.0 mL, 25 mmol) was stirred at 120 °C under nitrogen for 18 h. After the disappearance of acetophenone **1a** detected by TLC, the mixture was filtrated and removing the organic solvent by evaporation. Then 2 M sodium hydroxide solution was added to the residue and some ethyl acetate followed. Subsequently 36–38% concentrated hydrochloric acid was put into the mixture dropwise and α-keto acid **2a**[14] was separated out as a pale yellow oil (0.52 g, 3.5 mmol) in 87% yield. ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, J=7.6 Hz, 2H, ArH), 7.72 (d, J=7.6 Hz, 1H, ArH), 7.55 (t, J=7.8 Hz, 2H, ArH).

*4.2.2. Preparation of phenyl-α-ketal **3a** and phenyl-α-keto ester **4a**.* Keto acid **2a** (0.52 g, 3.5 mmol) was cooled in an ice bath and dissolved in methanol (2.9 mL, 72 mmol). Molecular sieve 4 Å (0.24 g) was then added and stirred for additional 10 min. After

Table 3
One-pot method of aryl α-keto esters from aryl-ketones

Entry	Substrate Ar–	Product	Yield/%
1	Ph	**4a**	77
2	4-MeC_6H_4	**4b**	76
3	4-$MeOC_6H_4$	**4c**	78
4	4-FC_6H_4	**4d**	80
5	4-BrC_6H_4	**4e**	75
6	4-ClC_6H_4	**4f**	76
7	3-ClC_6H_4	**4g**	79
8	2-ClC_6H_4	**4h**	75
9	2-Naphthyl	**4i**	74
10	1-Naphthyl	**4j**	71
11	2-Furyl	**4k**	73

thionyl chloride (1.5 mL, 20 mmol) was added dropwise over 1 h, the ice bath was removed and the mixture was stirred at room temperature overnight. The mixture was filtrated and the organic solvent was removed by evaporation. The residue can be purified, respectively, by silica gel column chromatography with petrol ether–ethyl acetate (30:1) to afford corresponding ketal **3a**[15] and keto ester **4a**.[16] It was found that the mole ratio of phenyl-α-ketal and phenyl-α-keto ester was 2:1. The residue after evaporation can be used directly in the following step without further purification.

*4.2.3. Preparation of phenyl-α-keto ester **4a**.* Perchloric acid (1.6 mL, 20 mmol) with acetonitrile (32 mL) and deionized water (3.2 mL) (0.5:10:1 in volume ratio) were poured into the above residue after evaporation. The mixture was stirred for 0.5 h. Excess acid was neutralized by saturated sodium bicarbonate. The organic solvent was removed by evaporation. Aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with petrol ether–ethyl acetate (10:1) to afford **4a** as a pale yellow oil (0.49 g, 3.0 mmol) in 85% overall yield from **2a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04–8.01 (m, 2H, ArH), 7.69–7.65 (m, 1H, ArH), 7.54–7.50 (m, 2H, ArH), 3.98 (s, 3H, OCH_3).

4.3. General procedures for aryl α-keto ester in one-pot

*4.3.1. Methyl 2-oxo-2-phenylacetate (**4a**).* A mixture of acetophenone (0.48 g, 4.0 mmol) and selenium dioxide (0.67 g, 6.0 mmol) in dry pyridine (2.0 mL, 25 mmol) was stirred at 100 °C under nitrogen for 15 h. The reaction was monitored by TLC. The mixture was cooled in an ice bath. Molecular sieve 4 Å (0.24 g) and methanol (2.9 mL, 72 mmol) were then added, and stirred for additional 10 min. After thionyl chloride (1.5 mL, 20 mmol) was added dropwise over 1 h, the ice bath was removed and the mixture was stirred at room temperature overnight. Perchloric acid (1.6 mL, 20 mmol) with acetonitrile (32 mL) and deionized water (3.2 mL) (0.5:10:1 in volume ratio) were poured into the flask, stirred for 0.5 h. Excess acid was neutralized by saturated sodium bicarbonate. The mixture was filtrated and the organic solvent was removed by evaporation. Aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with petrol ether–ethyl acetate (10:1) to afford **4a** as a pale yellow oil (0.51 g, 3.1 mmol) with 77% overall yield.

*4.3.2. Methyl 2-oxo-2-p-tolylacetate (**4b**).*[17] Yield 76%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J*=8 Hz, 2H, ArH), 7.31 (d, *J*=8 Hz, 2H, ArH), 3.97(s, 3H, OCH_3), 2.44 (s, 3H, $ArCH_3$).

*4.3.3. Methyl 2-(4-methoxyphenyl)-2-oxoacetate (**4c**).*[17] Yield 78%, white solid. Mp=44–45 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01–7.98 (m, 2H, ArH), 6.93–6.89 (m, 2H, ArH), 3.88 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3).

*4.3.4. Methyl 2-(4-fluorophenyl)-2-oxoacetate (**4d**).*[17] Yield 80%, white solid. Mp=46–48 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09–8.06 (m, 2H, ArH), 7.26–7.15 (m, 2H, ArH), 3.97 (s, 3H, OCH_3).

*4.3.5. Methyl 2-(4-bromophenyl)-2-oxoacetate (**4e**).*[18] Yield 75%, pale yellow solid. Mp=49–51 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92–7.90 (m, 2H, ArH), 7.66 (q, *J*=2.4 Hz, 2H, ArH), 3.96 (s, 3H, OCH_3).

*4.3.6. Methyl 2-(4-chlorophenyl)-2-oxoacetate (**4f**).*[18] Yield 76%, white solid. Mp=58–59 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (q, *J*=1.8 Hz, 2H, ArH), 7.49 (q, *J*=2.0 Hz, 2H, ArH), 3.96 (s, 3H, OCH_3).

*4.3.7. Methyl 2-(3-chlorophenyl)-2-oxoacetate (**4g**).*[18] Yield 79%, white solid. Mp=44–45 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (t, *J*=1.8 Hz, 1H, ArH), 7.94–7.91 (m, 1H, ArH), 7.65–7.62 (m, 1H, ArH), 7.47 (t, *J*=7.8 Hz, 1H, ArH), 3.99 (s, 3H, OCH_3).

*4.3.8. Methyl 2-(2-chlorophenyl)-2-oxoacetate (**4h**).*[18] Yield 75%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (q, *J*=1.8 Hz, 1H, ArH), 7.56–7.52 (m, 1H, ArH), 7.46–7.40 (m, 2H, ArH), 3.97 (s, 3H, OCH_3).

*4.3.9. Methyl 2-(naphthalen-2-yl)-2-oxoacetate (**4i**).*[19] Yield 74%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 (s, 1H, ArH), 8.07–7.89 (m, 4H, ArH), 7.68–7.57 (m, 2H, ArH), 4.04 (s, 3H, OCH_3).

*4.3.10. Methyl 2-(naphthalen-1-yl)-2-oxoacetate (**4j**).* Yield 71%, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43–8.41 (m, 1H, ArH), 8.09–8.07 (m, 1H, ArH), 7.88–7.85 (m, 2H, ArH), 7.53–7.46 (m, 3H, ArH), 3.65 (s, 3H, OCH_3).

*4.3.11. Methyl 2-(furan-2-yl)-2-oxoacetate (**4k**).*[20] Yield 73%, pale yellow solid. Mp=39–40 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77–7.75 (m, 2H, ArH), 6.64 (q, *J*=1.4 Hz, 1H, ArH), 3.96 (s, 3H, OCH_3).

Acknowledgements

This work was partially supported by the National Natural Science Foundation of China, Nippon Chemical Industrial Co., Ltd, and Instrumental Analysis Center of Shanghai Jiao Tong University.

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