Organic Process Research & Development **1998**, *2*, 412−414

Technical Notes

Facile Synthesis of β-Keto Esters from Methyl Acetoacetate and Acid Chloride: The Barium Oxide/Methanol System[1]

Yoshifumi Yuasa* and Haruki Tsuruta

Technical Engineering Department, Fine Chemical Division, Takasago International Corporation, 1-5-1 Nishiyawata, Hiratsuka, Kanagawa, 254-0073, Japan

Yoko Yuasa

School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo, 192-0355, Japan

Abstract:

The synthesis of β-keto esters has been performed in good yield by reacting excess methyl acetoacetate with barium oxide, acylating the resulting barium complex with acid chloride, and then cleaving the α-acyl β-keto ester with methanol at a mild temperature. Using this new procedure, various β-keto esters were prepared. Thus, methyl 4-phenyl-3-oxobutanoate, methyl 3-phenyl-3-oxopropionate, methyl 4-cyclohexyl-3-oxobutanoate, and methyl 3-oxooctadecanoate were prepared from methyl acetoacetate and the corresponding acid chloride in 69%, 84%, 67%, and 74% yields, respectively.

β-Keto esters are known to be useful as intermediates in the synthesis of drugs, ceramides, biodegradable polymers, etc., and there have been reported a number of syntheses for β-keto esters.[2] For example, recently, Benetti et al.[2d] reviewed the synthesis of β-keto esters. In this review, numerous procedures were reported; in particular, the acylation of an acetoacetic ester at the C2 carbon, a well-known process, was discussed in detail. As the base component to be employed in this acylation process, NaH, $NaNH_2$, or alkali metal alcoholates are usually used.[3,4] However, the achieved yields are only of the order of 30−40%, because the β-keto ester formed during the condensation reaction has a higher reactivity than the starting compounds to be converted, which can lead to numerous secondary reactions. As an improvement in the base component in the reaction for condensing an acetoacetic ester with acid chloride, further, the use of magnesium alcoholates is suggested.[5] In practice, however, this method also has its difficulties because the commercially available magnesium alcholate is inadequate, so the magnesium alcoholate needed for the reaction always has to be freshly prepared. In addition, ammonolysis, which is used for the deacetylation of α-acyl β-keto esters to β-keto esters, produced acetamide as the byproduct in this cleavage process. Thus, the yield is reduced, and the posttreatment becomes troublesome. We have been studying a process for the acylation of acetoacetate and cleavage of the α-acylacetoacetic ester, particularly investigating the base component. We have found that the condensation of acetoacetic ester and acid chloride using barium oxide as a base component and then cleavage with an alcohol (MeOH) led to the β-keto ester in good yield, and we now report a process for the preparation of β-keto esters which is economically advantageous and applicable to industrial production.

We first tried the synthesis of methyl 4-phenyl-3-oxobutanoate (**3a**), which is a useful intermediate of allophenylnorstatine.[6] To prepare the barium chelate complex **1**, excess methyl acetoacetate in toluene was reacted with barium oxide, which was activated by the addition of a small amount of water, at 25−30 °C, and then the resulting barium chelate **1** was acylated to give an acylated complex (**2a**) with phenylacetyl chloride for 2 h at the same temperature. To deacetylate the complex **2a**, the suspension was then treated with 2 mol of methanol (based on phenylacetyl chloride) at 25−30 °C for 16 h. The deacylation of **2a** easily proceeded with addition of 2 equiv of methanol at a mild temperature. No methanol addition produced a very low yield. An increase in the reaction temperature (50 °C) did not contribute to increased yield. The resulting barium compound was treated with 5% H_2SO_4 solution to remove any insoluble $BaSO_4$. Subsequently, the excess methyl acetoacetate was recovered, and the β-keto ester **3a** could be purified by

* To whom correspondence should be addressed. Phone: 81-(0)463-21-7150. Fax: 81-(0)463-23-1655. E-mail: TIC00488@niftyserve.or.jp.

(1) This work has appeared in preliminary form: Sotoguchi, T.; Yuasa, Y.; Tachikawa, A.; Harada, S. JP Patent 10053561, 1998; *Chem. Abstr*. **1998**, *128*, 167178n.

(2) (a) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972. (b) Caine, D. In *Carbon−Carbon Bond Formation*; Augustine, R. L., Ed.; Marcel Dekker: New York, 1979; Vol. 1, pp 250−258. (c) Barton, D.; Ollis, W. D. *Comprehensive Organic Chemistry*, 1st ed.; Pergamon Press: Oxford, 1979; Vol. 2, pp 707−708 and 785−787. (d) Benetti, S.; Romagnoli, R.; Risi, C. D. R.; Spalluto, G.; Zanirato, V. *Chem. Rev*. **1995**, *95*, 1065 and references therein.

(3) Shriner, R. L.; Schmidt, A. G.; Roll, L. J. *Organic Syntheses*; Wiley: New York, 1943; Collect. Vol. II, p 266.

(4) Miller, W. H.; Roblin, R. O., Jr.; Astwood, E. B. *J. Am. Chem. Soc*. **1945**, *67*, 2197.

(5) Viscontimi, M.; Merckling, N. *Helv. Chim. Acta* **1952**, *35*, 2280.

(6) Sayo, N.; Yamasaki, T.; Kumobayashi, H.; Yuasa, Y.; Sotoguchi, T. US Patent 5581007, 1996; *Chem. Abstr*. **1996**, *125*, 276572v.

10.1021/op980044g CCC: $15.00
Published on Web 09/03/1998

Scheme 1

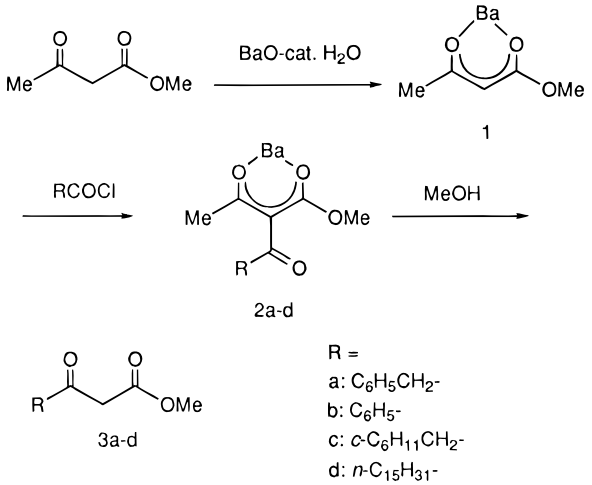

Table 1. **Yield of 3a upon varying the molar ratio of methyl acetoacetate**

run[a]	methyl acetoacetate (molar equiv)	yield of **3a** (%)[b]
1	2.0	58
2	4.0	69
3	6.0	65
4	8.0	64

[a] 1.2 equiv of BaO and 2.0 equiv of MeOH based on phenylacetyl chloride were used in all cases. [b] Isolated yield after purification by distillation.

Table 2. **Yield of 3a upon varying the molar ratio of BaO**

run[a]	BaO (molar equiv)	yield of **3a** (%)[b]
1	1.2	69
2	1.0	65
3	0.8	63
4	0.5	57

[a] 4.0 equiv of methyl acetoacetate and 2.0 equiv of MeOH based on phenylacetyl chloride were used in all cases. [b] Isolated yield after purification by distillation.

Table 3. **Yields of β-keto esters 3a−d[a]**

3	R	yield (%)[b]
a	$C_6H_5CH_2$	69
b	C_6H_5	84
c	*c*-$C_6H_{11}CH_2$	67
d	*n*-$C_{15}H_{31}$	74

[a] 1.2 equiv of BaO, 4.0 equiv of methyl acetoacetate, and 2.0 equiv of MeOH based on acid chloride were used in all cases. [b] Isolated yield after purification by distillation or recrystallization.

distillation at reduced pressure (Scheme 1). The optimized amounts of methyl acetoacetate and barium oxide were investigated and found to be 4 equiv and 1.2 equiv per mole of the acid chloride, respectively (see Tables 1 and 2). The utility of this new synthetic method was demonstrated for various β-keto ester compounds (see Table 3). This new reaction was also accomplised by using CaO or SrO. However, as the basicity of these alkaline earth metal oxides is weaker than that of BaO, more drastic reaction conditions, which involved refluxing several times, were needed.

In summary, it has been found that β-keto esters are obtained in good yields, 67−84%, by the acylation of methyl acetoacetate using barium oxide, acylating the resulting barium complex with acid chloride, and then cleaving the product with methanol at a mild temperature to form the β-keto ester. This method is suitable for the large-scale preparation of β-keto esters.

Experimental Section

All reagents and solvents were obtained from commercial sources and used without further purification. For determining the melting points, a Yanagimoto micromelting apparatus was used, and the values are uncorrected. Boiling points are given as uncorrected values. NMR spectra were obtained with a Bruker AM-400. ^{1}H and ^{13}C NMR were measured at 400 and 100 MHz, respectively. The NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard. The chemical shifts were given in δ (ppm). IR spectra were obtained with a Jasco IR-810. MS data were obtained with a Hitachi M-80A mass spectrometer at 70 eV. GC was done using a Hewlett Packard HP5890 II (column, silicon NB-1, 30 m × 0.25 mm, 0.25 μm; He gas, 1 kg/cm^2; oven temperature, 100−220 °C programmed at 5 °C/min; injection temperature, 250 °C; detector temperature, 250 °C). HPLC was done using a Hitachi L-6200 [column, Inertsil ODS-2; solvent, $CH_3CN/MeOH/H_2O$ = 47.5/47.5/5; flow rate, 1.0 mL/min; detector, Hitachi L-4000 (210 nm)].

Methyl 4-Phenyl-3-oxobutanoate (3a). Typical Procedure. To toluene (200 mL) was added BaO (37.8 g, 0.24 mol). After addition of H_2O (0.5 mL) and activation with vigorous stirring, methyl acetoacetate (92.9 g, 0.8 mol) was added dropwise at 25−30 °C over a period of 1 h. Into the solution was added dropwise phenylacetyl chloride (30.9 g, 0.2 mol) at the same temperature over a period of 1 h, and then stirring was continued for an additional 1 h. Next, MeOH (15 g, 0.47 mol) was added to the reaction mixture, which was then stirred for 16 h. After the pH value of the reaction mixture was adjusted to 1 using 5% H_2SO_4 solution, the insoluble barium salt was filtered off, and the organic layer was washed with 5% $NaHCO_3$ solution and brine. After the solvent was recovered, the oily residue (86.6 g) was distilled at reduced pressure to recover the methyl acetoacetate (45.7 g) and gave methyl 4-phenyl-3-oxobutanoate (29.5 g, 69%) as a colorless oil. The purity was 96% by GC: bp 122−123 °C/1 Torr (lit.[5] bp 125 °C/3 Torr); ^{1}H NMR 3.45 (2H, s, $COCH_2CO_2$), 3.70 (3H, s, CO_2CH_3), 3.82 (2H, s, $PhCH_2CO$), 7.19−7.36 (5H, s, aromH); ^{13}C NMR 48.5 (CH_2), 50.6 (CH_2), 52.9 (CH_3), 127.9 (CH), 129.4 (2×CH), 130.1 (2×CH), 133.8 (C), 168.1 (CO), 200.9 (CO); IR (neat) 1750, 1720, 1655, 1625, 1600, 1500 cm^{-1}; EI-MS (*m*/*e*, relative intensity) 192 (M^+, 42), 160 (8), 118 (55), 101 (43), 91 (100), 59 (26).

Methyl 3-Phenyl-3-oxopropanoate (3b). The product was recovered as a colorless oil (84%). The purity was 95% by GC: bp 118−120 °C/1 Torr (lit.[7] bp 90−92 °C/0.05 Torr); ^{1}H NMR 3.74 (3H, s, CO_2CH_3), 4.01 (2H, s,

(7) McElvain, S. M.; McKay, G. R., Jr. *J. Am. Chem. Soc.* **1956**, *78*, 6086.

PhCOCH_2CO$_2$), 7.41−7.79 (3H, m, aromH), 7.93−7.96 (2H, m, aromH); ^{13}C NMR 46.1 (CH_2), 52.9 (CH_3), 129.2 (2×CH), 129.3 (2×CH), 134.3 (CH), 136.5 (C), 168.4 (CO), 192.9 (CO); IR (neat) 1745, 1690, 1650, 1620, 1600, 1580 cm^{-1}; EI-MS (*m*/*e*, relative intensity) 178 (M^+, 9), 146 (26), 117 (70), 106 (9), 105 (100), 77 (38), 69 (3), 64 (1), 59 (2), 51 (9).

Methyl 4-Cyclohexyl-3-oxobutanoate (**3c**)**.** The product was recovered as a colorless oil (67%). The purity was 96% by GC: bp 95−98 °C/1.5 Torr (lit.[8] bp 80−81 °C/0.35 Torr); ^{1}H NMR 0.92−0.97 (2H, m), 1.13−129 (3H, m), 1.64−1.85 (6H, m), 2.40 (2H, d, J = 6.8 Hz, CH_2CO), 3.43 (2H, s, COCH_2CO$_2$), 3.74 (3H, s, CO$_2$CH_3); ^{13}C NMR 26.6 (CH_2), 26.7 (CH_2), 26.8 (2×CH_2), 33.7 (CH_2), 34.3 (CH), 50.2 (CH_2), 51.3 (CH_2), 52.9 (CH_3), 168.3 (CO), 203.0 (CO); IR (neat) 1750, 1715, 1650, 1625 cm^{-1}; EI-MS (*m*/*e*, relative intensity) 198 (M^+, 3), 125 (26), 117 (70), 116 (100), 97 (32), 85 (30), 74 (23), 64 (21), 55 (53), 43 (25).

(8) Kugatova-Schemyakina, G. P.; Andreev, V. M.; Anarkulova, L. S. *Zh. Org. Khim.* **1967**, *3*, 1213; *Chem. Abstr*. **1967**, *67*, 90429 g.

Methyl 3-Oxooctadecanoate (3d). This procedure was similar to that described above. After workup, the solvent was recovered in vacuo, and the residue was dissolved in MeOH and allowed to stand at −20 °C overnight. The precipitated crystals were filtered and dried and gave methyl 3-oxooctadecanoate as white crystals (74%). The purity was 95% by HPLC: mp 40−41 °C (lit.[5] mp 46 °C); ^{1}H NMR 0.81 (3H, t, J = 7 Hz, CH_3(CH$_2$)−), 1.18 (24H, m, 12×CH_2), 1.50−1.54 (2H, m, CH_2), 2.46 (2H, t, J = 7 Hz, CH_2CO), 3.37 (2H, s, COCH_2CO$_2$), 3.66 (3H, s, CO$_2$CH_3); ^{13}C NMR 14.8 (CH_3), 23.4 (CH_2), 24.2 (CH_2), 29.7 (CH_2), 30.0 (2×CH_2), 30.1 (CH_2), 30.3 (3×CH_2), 30.4 (2×CH_2), 32.6 (CH_2), 43.8 (CH_2), 49.7 (CH_2), 52.9 (CH_3), 168.4 (CO), 203.5 (CO); IR ($CHCl_3$) 1750, 1715 cm^{-1}; EI-MS (*m*/*e*, relative intensity) 312 (M^+, 2), 294 (2), 239 (13), 158 (4), 143 (6), 129 (24), 117 (33), 116 (100), 97 (11), 85 (11), 74 (11), 57 (20), 43 (32).

Received for review May 26, 1998.

OP980044G