Azeotropic Transesterification of β-Keto Esters

Jens Christoffers*[a] and Neclâ Önal[a]

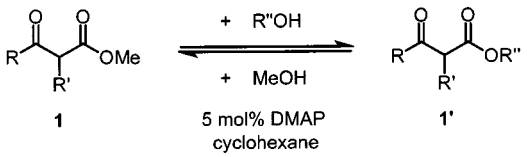
Keywords: Alcohols / Azeotropes / Esters / β-Keto esters / Transesterifications / Synthetic methods

Transesterifications of methyl β-keto carboxylates catalyzed by DMAP with various high boiling alcohols can be accomplished in refluxing cyclohexane in a Dean-Stark trap. The MeOH formed is removed completely from the reaction mixture as an azeotrope leading to quantitative conversions. The starting materials are converted in stoichiometric ratio, which makes the purification of the product very simple and results in high yields.

Introduction

β-Keto esters are valuable building blocks in organic synthesis and are classically prepared by Claisen condensation; the cyclic congeners are prepared by its intramolecular version, the Dieckmann condensation.[1] If the alcohol component of the β-keto ester is ethanol, methanol or another cheap material, the Claisen condensation is the method of choice for the preparation, because the loss of one equivalent of the alcohol can be taken into account. Direct esterification of β-keto acids is of course impossible, since these species decarboxylate readily. There are a number of alternative routes to access β-keto esters in the literature, for example the acylation of ketones with chloroformates,[2] the alcoholysis of diketene,[3] and the acylation of Meldrum′s acid.[4]

Particularly useful is the preparation of β-keto esters by transesterification of methyl β-keto carboxylates **1**, since the latter are usually easily accessible by Claisen condensation (Scheme 1). The transesterification is an equilibrium, which can be catalyzed by Brönstedt base[5] or most effectively by DMAP[6] and distannoxanes.[7] However, a catalyst cannot overcome thermodynamics; thus, an excess[8] of either the starting materials **1** or R′′OH has to be applied to achieve reasonable yields of the product **1′**.

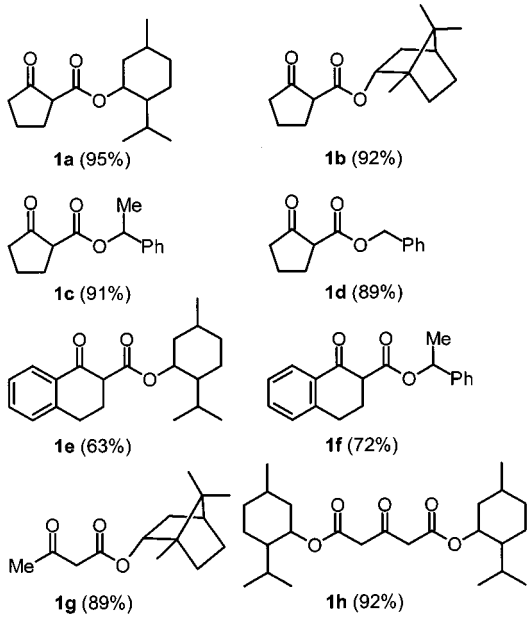


Scheme 1. Azeotropic transesterification of methyl β-keto carboxylates

Results and Discussion

The most elegant way to drive the equilibrium in Scheme 1 to the side of the product would be the removal of the formed MeOH from the reaction mixture. We have found a way to solve this problem in a simple way: MeOH forms an azeotrope with cyclohexane in the vapor phase, but is not miscible at ambient temperature in the condensed phase. Moreover, MeOH has a higher density than cyclohexane. Consequently, MeOH can be removed by azeotropic distillation in a Dean-Stark trap from a transesterification reaction. There is an obvious analogy to the removal of water in an azeotropic esterification reaction, and it is quite remarkable that this principle has, to the best of our knowledge, so far never been applied in organic synthesis. It is important to note that this method works exclusively with MeOH/cyclohexane. Other combinations of alcohols and hydrocarbons turned out not to be suitable.

Scheme 2 shows a list of products which we have prepared by this azeotropic transesterification methodology of corresponding methyl β-keto carboxylates. The configurations of products in Scheme 2 are not specified for simplicity. In the case of **1c** and **1f** racemic 1-phenylethanol was added; for **1a**, **1b**, **1e**, **1g**, and **1h** enantiopure (−)-menthol and (−)-*endo*-borneol was used. The products were gener-



Scheme 2. Products and yields obtained by azeotropic transesterification

[a] Technische Universität Berlin, Institut für Organische Chemie, Sekretariat C 3,
Straße des 17. Juni 135, D-10623 Berlin, Germany,
Fax: (internat.) + 49-30/723-1233,
E-mail: jchr@wap0105.chem.tu-berlin.de

  1434−193X/00/0408−1633 $ 17.50+.50/0

ally obtained as mixtures of enol tautomers and two diastereotopic (except for **1g** and **1h**) keto tautomers.

Importantly, all these conversions proceeded with nearly stoichiometric amounts of starting materials (1.0 equiv. methyl ester **1**, 1.1 equiv. alcohol R′′OH). The use of DMAP (0.05 equiv.) as the catalyst turned out to give very satisfying results. Isolated yields are very good as shown in Scheme 2, except for **1e** and **1f**, in which steric congestion prevents a quantitative conversion. Even the double transesterification of dimethyl acetone-1,3-dicarboxylate (2.2 equiv. of menthol were applied here) gives product **1h** with very good yield. Since no large excess of one of the starting materials needs to be removed after conversion, the purification of products is simply accomplished by distillation in vacuo, which allows us to perform reactions on a large scale.

Conclusion

In summary, transesterifications of methyl β-keto carboxylates catalyzed by DMAP with various high boiling alcohols can be accomplished in refluxing cyclohexane in a Dean-Stark trap. The formed MeOH is removed completely from the reaction mixture as an azeotrope leading to quantitative conversions. The starting materials are reacted in a stoichiometric ratio, which makes the purification of the product very simple and results in high yields.

Experimental Section

General: Column chromatography was accomplished with Merck silica gel (Type 60, 0.063−0.200 mm) using *tert*-butyl methyl ether (MTB) and hexanes (PE). Multiplicity assignments of ^{13}C NMR resonances were made using DEPT experiments. All starting materials were commercially available.

General Procedure for the Transesterification: A mixture of β-keto methyl ester (1.0 equiv.), the alcohol (1.1 equiv.) and DMAP (0.05 equiv.) in cyclohexane (1 mL/mmol keto ester) was heated overnight in a Dean-Stark trap. All volatile materials were removed in vacuo and the residue distilled under high vacuum (bulb-to-bulb over a 10 cm Vigreux column or kugelrohr) or chromatographed on SiO_2 (PE/MTB).

(−)-Menthyl 2-Oxocyclopentane-1-carboxylate (1a):[6c] Methyl cyclopentanone-2-carboxylate (7.10 g, 50.0 mmol), (−)-menthol (8.60 g, 55.0 mmol) and DMAP (305 mg, 2.50 mmol) were converted in cyclohexane (50 mL) according to the general procedure to yield the title compound (12.6 g, 47.3 mmol, 95%) as a colorless oil which solidified slowly below 25 °C after chromatography (PE/MTB 5:1, R_f = 0.38). − $[\alpha]_D^{23}$ = −91.0 (c = 12.5 g/L, $CHCl_3$). − $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): two diastereoisomers, partly doubled signal set, δ = 15.9 (CH_3), 16.2 (CH_3), 20.7 (CH_3), 20.8 (CH_3), 21.0 (CH_2), 21.9 (CH_3), 23.1 (CH_2), 23.4 (CH_2), 25.7 (CH), 26.1 (CH), 27.3 (CH_2), 27.4 (CH_2), 31.4 (CH), 34.2 (CH_2), 37.9 (CH_2), 38.05 (CH_2), 40.66 (CH_2), 40.68 (CH_2), 46.80 (CH), 46.89 (CH), 54.79 (CH), 55.10 (CH), 75.3 (CH), 75.3 (CH), 169.0 (C), 169.0 (C), 212.3 (C), 212.4 (C). − $C_{16}H_{26}O_3$ (266.38): calcd. C 72.14, H 9.84; found C 72.18, H 9.31.

(−)-*endo*-Borneyl 2-Oxocyclopentane-1-carboxylate (1b): Methyl cyclopentanone-2-carboxylate (7.10 g, 50.0 mmol), (−)-*endo*-borneol (8.50 g, 55.0 mmol) and DMAP (305 mg, 2.50 mmol) were converted in cyclohexane (50 mL) according to the general procedure to yield the title compound (12.2 g, 46.1 mmol, 92%) as a colorless oil after kugelrohr distillation at 0.1 mm (oven temp. 150 °C). − $[\alpha]_D^{23}$ = −30 (c = 9.6 g/L, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): two diastereoisomers, ratio 1:1, partly doubled signal set, δ = 0.80 (s, 3 H), 0.83 (s, 3 H), 0.85 (s, 6 H), 0.88 (s, 6 H), 0.98 (ddd, J = 13.8 Hz, J = 6.2 Hz, J = 3.4 Hz, 2 H), 1.16−1.34 (m, 4 H), 1.63−2.36 (m, 20 H), 3.15 (t, J = 8.8 Hz, 2 H), 4.85−4.98 (m, 2 H). − $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): two diastereoisomers, partly doubled signal set, δ = 13.3 (CH_3), 13.4 (CH_3), 18.7 (CH_3), 19.6 (CH_3), 20.9 (CH_2), 26.96 (CH_2), 27.03 (CH_2), 27.3 (CH_2), 27.4 (CH_2), 27.85 (CH_2), 27.88 (CH_2), 36.5 (CH_2), 36.7 (CH_2), 37.9 (CH_2), 38.0 (CH_2), 44.8 (CH), 47.8 (C), 48.8 (C), 48.9 (C), 54.7 (CH), 54.9 (CH), 80.7 (CH), 80.8 (CH), 169.6 (C), 169.7 (C), 212.1 (C), 212.2 (C). − IR (ATR): $\tilde{\nu}$ = 1756 cm^{-1} (s), 1725 (vs). − $C_{16}H_{24}O_3$ (264.36): calcd. C 72.69, H 9.15; found C 72.61, H 9.07. − HRMS: calcd. 264.1725, found 264.1724.

***rac*-1-Phenylethyl 2-Oxocyclopentane-1-carboxylate (1c):** Following the general procedure methyl cyclopentanone-2-carboxylate (7.10 g, 50.0 mmol) was converted with *rac*-1-phenyl ethanol (6.72 g, 55.0 mol) and DMAP (305 mg, 2.49 mmol) in cyclohexane (50 mL) to give the title compound (10.6 g, 45.6 mmol, 91%) as a colorless oil after kugelrohr distillation at 0.1 mm (oven temp. 175 °C). − ^1H NMR (200 MHz, $CDCl_3$): mixture of two diastereoisomers, ratio 1:1, double signal set, δ = 1.55 (d, J = 6.7 Hz, 3 H), 1.58 (d, J = 6.5 Hz, 3 H), 1.77−1.97 (m, 2 H), 2.03−2.20 (m, 2 H), 2.20−2.35 (m, 8 H), 3.17 (t, J = 8.8 Hz, 1 H), 3.19 (t, J = 8.8 Hz, 1 H), 5.90 (q, J = 6.6 Hz, 1 H), 5.96 (q, J = 6.5 Hz, 1 H), 7.25−7.37 (m, 10 H). − $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): two diastereoisomers, partly doubled signal set: δ = 20.8 (CH_2), 22.10 (CH_3), 22.13 (CH_3), 27.2 (CH_2), 27.3 (CH_2), 38.0 (CH_2), 54.6 (CH), 54.7 (CH), 73.2 (CH), 73.3 (CH), 125.8 (CH), 126.0 (CH), 127.7 (CH), 127.8 (CH), 128.36 (CH), 128.40 (CH), 141.2 (C), 141.3 (C), 168.4 (C), 168.7 (C), 211.9 (C), 212.1 (C). − IR (ATR): $\tilde{\nu}$ = 1754 cm^{-1} (vs), 1724 (vs). − $C_{14}H_{16}O_3$ (232.28): calcd. C 72.39, H 6.94; found C 72.12, H 7.08. − HRMS: calcd. 232.1099; found 232.1102.

Benzyl 2-Oxocyclopentane-1-carboxylate (1d):[9] Methyl cyclopentanone-2-carboxylate (9.93 g, 69.8 mmol), benzyl alcohol (8.31 g, 76.8 mmol) and DMAP (427 mg, 3.50 mmol) were converted in cyclohexane (50 mL) according to the general procedure to yield the title compound (13.5 g, 61.9 mmol, 89%) as a colorless oil after distillation (bp. 150 °C at 0.1 mm). − $C_{13}H_{14}O_3$ (218.25): calcd. C 71.50, H 6.47; found C 71.51, H 6.46.

(−)-Menthyl 1-Tetralone-2-carboxylate (1e):[2] Following the general procedure methyl 1-tetralone-2-carboxylate (2.55 g, 12.5 mmol) was converted with (−)-menthol (2.15 g, 13.7 mmol) and DMAP (77 mg, 0.6 mmol) in cyclohexane (60 mL) to give the title compound (2.59 g, 7.87 mmol, 63%) as a colorless oil after chromatography (PE/MTB 5:1, R_f = 0.51). − $[\alpha]_D^{23}$ = −72 (c = 8.4 g/L, $CHCl_3$). − ^1H NMR (200 MHz, $CDCl_3$): mixture of enol and keto tautomer (two diastereoisomers with one set of signals), ratio enol/keto = 9:1, enol tautomer: δ = 0.78 (d, J = 6.9 Hz, 3 H), 0.90 (d, J = 7.0 Hz, 3 H), 0.90−1.14 (m, 3 H), 0.93 (d, J = 6.4 Hz, 3 H), 1.35−1.75 (m, 4 H), 1.90 (td, J = 7.0 Hz, J = 2.7 Hz, 1 H), 2.04−2.18 (m, 1 H), 2.50−2.60 (m, 2 H), 2.78−2.87 (m, 2 H), 4.83 (td, J = 10.8 Hz, J = 4.4 Hz, 1 H), 7.14−7.35 (m, 3 H), 7.74−7.81 (m, 1 H), 12.57 (s, 1 H). − $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): enol tautomer (major isomer, ca. 90%): δ = 16.5 (CH_3), 20.5 (CH_2), 20.57 (CH_3), 21.9 (CH_3), 23.6 (CH_2), 26.5 (CH), 27.6

(CH_2), 31.3 (CH), 34.2 (CH_2), 41.0 (CH_2), 47.0 (CH), 74.3 (CH), 97.1 (C), 124.1 (CH), 126.4 (CH), 127.2 (CH), 123.0 (C), 130.3 (CH), 139.1 (C), 164.8 (C), 172.2 (C); other signals (two diastereoisomeric keto tautomers, rel. intensity each ca. 5%) δ = 15.8 (CH_3), 16.1 (CH_3), 20.63 (CH_3), 23.0 (CH_2), 23.2 (CH_2), 25.7 (CH), 26.0 (CH), 26.3 (CH_2), 26.8 (CH_2), 27.3 (CH_2), 27.6 (CH_2), 34.1 (CH_2), 40.5 (CH_2), 40.6 (CH_2), 46.7 (CH_2), 54.6 (CH), 54.7 (CH), 75.2 (CH), 126.7 (CH), 127.5 (CH), 128.6 (CH), 131.8 (C), 133.5 (CH), 143.3 (C), 143.4 (C), 169.53 (C), 169.7 (CH), 193.0 (C). − $C_{21}H_{28}O_4$ (328.45): calcd. C 76.79, H 8.59; found C 76.99, H 8.55.

***rac*-1-Phenylethyl 1-Tetralone-2-carboxylate (1f):** Following the general procedure methyl 1-tetralone-2-carboxylate (10.4 g, 50.0 mmol) was converted with *rac*-1-phenyl ethanol (6.72 g, 55.0 mmol) and DMAP (305 mg, 2.49 mmol) in cyclohexane (50 mL) to give the title compound (10.6 g, 36.0 mmol, 72%) as a colorless oil after chromatography (PE/MTB 5:1, R_f = 0.48). − ^{1}H NMR (200 MHz, $CDCl_3$): mixture of keto (two diastereoisomers with one set of signals) and enol tautomer, ratio enol/keto = 2:1; enol tautomer: δ = 1.62 (d, *J* = 6.6 Hz, 3 H), 2.60−2.70 (m, 2 H), 2.86−2.89 (m, 2 H), 6.04 (q, *J* = 6.6 Hz, 1 H), 7.19−7.40 (m, 8 H), 7.76−7.81 (m, 1 H), 12.42 (s, 1 H); keto tautomer: δ = 1.56 (d, *J* = 6.4 Hz, 3 H), 2.28−2.59 (m, 2 H), 2.89 (q, *J* = 5.5 Hz, 2 H), 3.64 (dd, *J* = 9.5, J = 4.9 Hz, 1 H), 5.98 (q, *J* = 6.7 Hz, 1 H), 7.19−7.40 (m, 8 H), 8.07 (d, *J* = 7.8 Hz, 1 H). − $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): keto (two diastereoisomers) and enol tautomer (triple signal set): δ = 20.5 (CH_2), 22.0 (CH_3), 22.1 (CH_3), 22.6 (CH_3), 26.3 (CH_2), 26.4 (CH_2), 27.4 (CH_2), 27.5 (CH_2), 27.7 (CH_2), 54.4 (CH), 54.6 (CH), 72.4 (CH), 73.2 (CH), 73.3 (CH), 97.0 (C), 124.2 (CH), 125.8 (CH), 126.0 (CH), 126.5 (CH), 126.8 (CH), 127.3 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 129.9 (C), 130.5 (CH), 131.8 (C), 133.7 (CH), 139.3 (C), 141.2 (C), 141.8 (C), 143.48 (C), 143.51 (C), 165.2 (C), 169.3 (C), 169.5 (C), 171.9 (C), 193.0 (C), 193.1 (C). − IR (ATR): $\tilde{\nu}$ = 1737 cm^{-1} (s), 1686 (s). − $C_{19}H_{18}O_3$ (294.35): calcd. C 77.53, H 6.16; found C 77.34, H 6.27. − HRMS: calcd. 294.1256; found 294.1255.

(−)-*endo*-Borneyl 3-Oxobutanoate (1g):[3][4d,5,7] Methyl 3-oxobutanoate (5.00 g, 43.1 mmol), (−)-*endo*-borneol (7.31 g, 47.4 mmol) and DMAP (263 mg, 2.16 mmol) were converted in cyclohexane (70 mL) according to the general procedure to yield the title compound (9.18 g, 38.5 mmol, 89%) as a colorless oil after kugelrohr distillation at 0.1 mm (oven temp. 175 °C). − $[\alpha]_D^{23}$ = −38.9 (*c* = 10.2 g/L, $CHCl_3$). − $C_{14}H_{22}O_3$ (238.33): calcd. C 70.54, H 9.31; found C 70.26, H 9.30.

(−)-Dimenthyl 1,3-Acetonedicarboxylate (1h): Dimethyl 1,3-acetonedicarboxylate (5.00 g, 28.7 mmol), (−)-menthol (9.88 g, 63.2 mmol) and DMAP (176 mg, 1.44 mmol) were reacted in cyclohexane (40 mL) for 3 days according to the general procedure to yield a crude material (13.1 g), from which DMAP and excess menthol were removed by kugelrohr distillation at 0.1 mm (oven temp. 150 °C). Further distillation at 250 °C (oven temp.) yielded the title compound (11.2 g, 26.4 mmol, 92%) as a colorless oil. − $[\alpha]_D^{23}$ = −87 (*c* = 6.6 g/L, $CHCl_3$). − ^{1}H NMR (400 MHz, $CDCl_3$): mixture of keto and mono-enol tautomer (ratio: 7:1); keto tautomer: δ = 0.76 (d, *J* = 6.9 Hz, 3 H), 0.86−0.91 (m, 1 H), 0.89 (d, *J* = 7.1 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.92−1.10 (m, 2 H), 1.32−1.60 (m, 2 H), 1.62−1.71 (m, 2 H), 1.82−1.91 (m, 1 H), 1.98−2.05 (m, 1 H), 3.56 (A-part of an AB-system, *J* = 15.9 Hz, 1 H), 3.60 (B-part of an AB-system, *J* = 15.9 Hz, 1 H), 4.73 (td, *J* = 11.0 Hz, *J* = 4.4 Hz, 1 H); mono-enol tautomer: δ = 3.20 (s, 2 H), 5.10 (s, 1 H), 12.17 (s, 1 H); all other signals are hidden by the major tautomer. − $^{13}C\{^1H\}$ NMR (50 MHz, $CDCl_3$): mixture of keto and mono-enol tautomer; keto tautomer: δ = 16.0 (CH_3), 20.63 (CH_3), 21.9 (CH_3), 23.15 (CH_2), 26.0 (CH), 31.3 (CH), 34.0 (CH_2), 40.5 (CH_2), 46.7 (CH), 49.1 (CH_2), 75.5 (CH), 166.2 (C=O), 195.4 (C=O); mono-enol tautomer: δ = 16.1 (CH_3), 16.3 (CH_3), 20.56 (CH_3), 23.24 (CH_2), 23.4 (CH_2), 26.1 (CH), 40.8 (CH_2), 41.2 (CH_2), 46.8 (CH), 46.9 (CH), 74.0 (CH), 75.3 (CH), 91.9 (CH), 167.2 (C), 168.0 (C), 171.9 (C); all other signals are hidden by the major tautomer. − IR (ATR): $\tilde{\nu}$ = 1733 cm^{-1} (vs). − $C_{25}H_{42}O_5$ (422.61): Calcd. C 71.05, H 10.02; found C 70.96, H 10.23. − HRMS: calcd. 423.3110; found 423.3111 (M + H^+).

Acknowledgments

We are grateful to the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft for support of this work. J. C. thanks the Deutsche Forschungsgemeinschaft for a fellowship and Prof. Dr. S. Blechert for his support.

[1] F. Toda, T. Suzuki, S. Higa, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3521−3522.
[2] D. S. Brown, B. A. Marples, P. Smith, L. Walton, *Tetrahedron* **1995**, *51*, 3587−3606.
[3] [3a] F. Korte, F. Wüsten, *Liebigs Ann. Chem.* **1961**, *647*, 18−22.[3b] T. Mukaiyama, T. Yamada, T. Nagata, K. Imagawa, *Chem. Lett.* **1993**, 327−330.
[4] [4a] A. N. Meldrum, *J. Chem. Soc.* **1908**, *93*, 598−601.[4b] D. Davidson, S. A. Bernhard, *J. Am. Chem. Soc.* **1948**, *70*, 3426−3428.[4c] Y. Oikawa, K. Sugano, O. Yonemitsu, *J. Org. Chem.* **1978**, *43*, 2087−2088.[4d] J. L. Marco, N. Martin, A. Martinez-Grau, C. Seoane, A. Albert, F. H. Cano, *Tetrahedron* **1994**, *50*, 3509−3528.
[5] A. Shimomura, J. B. Cohen, *J. Chem. Soc.* **1922**, *121*, 883−887.
[6] [6a] D. F. Taber, J. C. Amedio, Y. K. Patel, *J. Org. Chem.* **1985**, *50*, 3618−3619. − [6b] J. C. Gilbert, T. A. Kelly, *J. Org. Chem.* **1988**, *53*, 449−450. − [6c] C. P. Decicco, R. N. Buckle, *J. Org. Chem.* **1992**, *57*, 1005−1008. −
[7] J. Otera, T. Yano, A. Kawabata, H. Nozaki, *Tetrahedron Lett.* **1986**, *27*, 2383−2386.
[8] C. Mottet, O. Hamelin, G. Garavel, J.-P. Depres, A. E. Greene, *J. Org. Chem.* **1999**, *64*, 1380−1382.
[9] J. Christoffers, U. Rößler, T. Werner, *Eur. J. Org. Chem.* **2000**, 701−705.

Received December 1, 1999
[O99657]