Transesterification of 3-Oxo Esters with Allylic Alcohols

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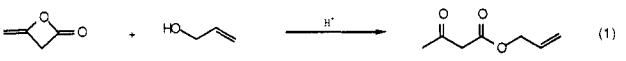
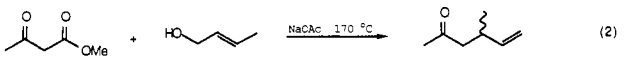
A consequence of our investigations of various aspects of the [3,3]sigmatropic rearrangements of allylic 3-oxo esters[1] was the requirement of an efficient method of synthesizing these compounds. We were surprised to find that no comprehensive method appears in the literature for the transesterification of methyl and ethyl β-keto esters with allylic alcohols.

Previous methods for the formation of allylic acetoacetates that are based on the acid-catalyzed opening of diketene[2] (eq 1) limit the range of available compounds to esters of acetoacetic acid. Potentially more general methods that rely on basic catalysis at higher temperatures either fail[3] or lead to decarboxylated rearrangement products (Carroll rearrangement, eq 2).[4,5]

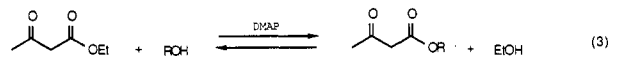


(1)



(2)

We were intrigued by the recently published method of Taber[6] that uses 4-(*N*,*N*-dimethylamino)pyridine (DMAP) in refluxing toluene to catalyze the transesterification of a series of simple methyl acetoacetates with a collection of high molecular weight aliphatic alcohols. The DMAP presumably promotes the establishment of a thermodynamic equilibrium (eq 3), which, in Taber's methodology,

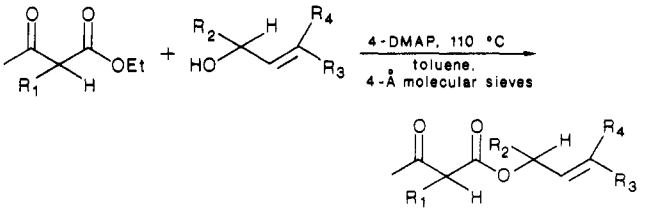


(3)

is driven to the right by use of an excess of the starting β-keto ester. A serious shortcoming of this technique appears when one has a β-keto ester and an allylic alcohol that are both synthetically "valuable".

Originally, we thought it possible that a modification of Taber's recipe that takes advantage of the known toluene–ethanol azeotrope[7] would be a more efficacious way to bias the equilibrium and might enable the use of stoichiometric quantities of reagents. However, in practice, problems with the slow rate of equilibrium and competitive entrainment of the allylic alcohol reduce the utility of this method. Fortunately, there is an effective solution. The ethanol can be removed from the system by simply performing the reaction in the presence of 4-Å molecular sieves.[8] By using this technology, we have synthesized the compounds listed in Table I from stoichiometric amounts of reagents and with good yields. In addition, the lower temperature of the reaction (110 °C) prevents the rearrangement originally seen by Carroll.[4]

Table I. Yields of Allylic β-Keto Esters

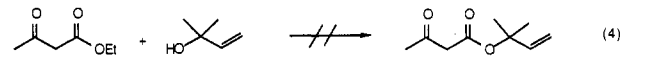


entry	R1	R2	R3	R4	yield,[a] %
1	H	H	H	H	45
2[b]	H	H	H	H	96
3	H	H	Me	H	94
4	H	H	Me	Me	86
5	H	Me	H	H	84
6	Me	H	H	H	32
7	Me	H	Me	H	83
8	Me	H	Me	Me	84
9	Me	Me	H	H	54

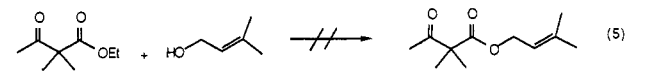
[a] Isolated yields. [b] Methyl acetoacetate and 3-Å molecular sieves.

Some facts about the transformation are noteworthy. First, allyl alcohol itself (entries 1 and 6) does not react well under the usual conditions (ethyl ester, 4-Å sieves). This is probably due to the fact that it is small enough to be absorbed by the 4-Å molecular sieves. However, this problem is easily addressed by using the methyl β-keto ester and 3-Å molecular sieves (entry 2).

Second, tertiary alcohols (eq 4) and nonenolizable ketones (eq 5) are unreactive in our hands. This may simply be a steric effect since ethyl 2-methyl-3-oxobutanoate requires a much longer reaction time than ethyl 3-oxobutanoate.[9] Also, the yield of the reaction decreases as one goes from a primary to a secondary allylic alcohol (entries 7–9), so it appears that steric constraints are important. Whether or not there is also an electronic effect is not known.

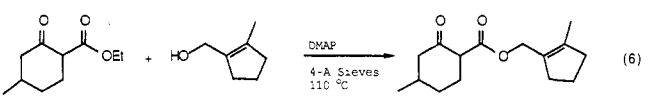


(4)



(5)

This appears to be the first general route to allylic β-keto esters. We are now applying this methodology to the synthesis of natural products by sequences involving the transesterification of cyclic β-keto esters with higher molecular weight allylic alcohols (e.g. eq 6). The yields of the transesterification in such cases remain above 80%.



(6)

Experimental Section

Infrared spectra were recorded with a Beckman IR-5A spectrophotometer as liquid samples between salt plates. ^1H and ^{13}C nuclear magnetic resonance spectra were measured at 360 MHz (Nicolet NT-360) or at 300 MHz (GE QE-300). Unless noted, $CDCl_3$ was used as an internal standard and deuterium lock.

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(9) With 1 equiv of DMAP, the reaction is complete for acetoacetates in 12 h and for 2-methylacetoacetates in about 36 h. Increasing the amount of DMAP decreases the reacton time.

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Chemical shifts are reported in ppm. Low-resolution electron-impact (EI) mass spectra were obtained with a Du Pont (CEC) 21-471 double-focusing mass spectrometer operating at 70 eV. Exact mass measurements were obtained on a Du Pont (CEC) 21-110 instrument. In cases where fragmentation precluded observation of a parent molecular ion using EI, chemical-ionization (CI) techniques were used instead. These spectra were recorded on a Finnigan-MAT TSQ-70 spectrometer at 70 eV with methane gas. High-pressure liquid chromatography was performed on a Waters 6000A instrument with two linked 2 ft × $^1/_4$ in. columns packed with LC Porasil (type A) silica gel. Combustion analyses (Atlantic Microlabs, Atlanta, GA) were obtained on samples that had been further purified by bulb-to-bulb distillation (Kugelrohr).

Skelly B was stirred over sulfuric acid for 24 h and over sodium carbonate for 12 h, filtered, and distilled. All other reagents and solvents were obtained from commercial sources and purified by standard methods.

General Procedure. A mixture of β-keto ester (5 mmol), allylic alcohol (5 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (5 mmol) was dissolved in sufficient toluene (ca. 200 mL) to ensure wetting of the 25 g of oven-dried molecular sieves (4 Å) that was subsequently added to the vessel. The mixture was then heated at reflux until no starting material was detectable by ^{1}H NMR spectroscopy; this typically required 12–36 h. After being cooled to room temperature, the solution was washed with saturated ammonium chloride (2 × 25 mL) and dried ($MgSO_4$). The toluene was removed by rotary evaporation, and the products were isolated by HPLC (1.5% EtOAc–98.5% Skelly B). Yields are reported in Table I. Spectral data are as follows.

2-Propenyl 3-oxobutanoate (1): ^{1}H NMR (300 MHz) δ 5.78 (m, 1 H), 5.14 (m, 2 H), 4.50 (d, 2 H), 3.35 (s, 2 H), 2.13 (s, 3 H); ^{13}C NMR (300 MHz) δ 199.8, 166.4, 131.4, 118.2, 65.4, 49.5, 29.6; IR 3050 (m), 2995 (m), 2930 (m), 1765 (s), 1740 (s), 1670 (s) cm^{-1}; LRMS (EI), *m/e* 85 (0.14), 84 (0.12), 58 (0.28), 57 (0.20), 43 (1.00), 41 (0.49), 39 (0.29); LRMS (CI), *m/e* 143 (M + 1, 0.44), 85 (1.00).

(*E*)-2-Butenyl 3-oxobutanoate (3): ^{1}H NMR (300 MHz) δ 5.65 (m, 2 H), 4.51 (d, 2 H), 3.40 (s, 2 H), 2.21 (s, 3 H), 1.67 (d, 3 H); ^{13}C NMR (300 MHz) δ 200.0, 167.0, 131.9, 124.6, 65.9, 50.0, 29.9, 17.5; IR 2980 (m), 2910 (m), 1760 (s), 1735 (s), 1670 (s) cm^{-1}; LRMS (EI), *m/e* 156 (M$^+$, 0.01), 85 (0.32), 71 (0.81), 69 (0.32), 58 (0.40), 57 (0.37), 55 (0.83), 54 (0.35), 43 (1.00), 42 (0.36), 41 (0.30), 39 (0.47); HRMS for $C_8H_{12}O_3$ calcd 156.07864, found 156.07902.

3-Methyl-2-butenyl 3-oxobutanoate (4): ^{1}H NMR (300 MHz) δ 5.21 (t, 1 H), 4.49 (d, 2 H), 3.31 (s, 2 H), 2.11 (s, 3 H), 1.62 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR (300 MHz) δ 200.0, 166.8, 139.2, 118.0, 61.8, 49.7, 29.6, 25.3, 17.6; IR 2995 (m), 2940 (m), 1760 (s), 1740 (s), 1670 (s) cm^{-1}; LRMS (EI), *m/e* 170 (M$^+$, 0.03), 103 (0.51), 86 (0.47), 85 (1.00), 71 (0.48), 69 (0.92), 68 (0.68), 67 (0.60), 58 (0.43), 57 (0.30), 53 (0.52), 43 (0.84), 42 (0.71), 41 (0.70), 40 (0.33), 30 (0.52); HRMS for $C_9H_{14}O_3$ calcd 170.09429, found 170.09487. Anal. Calcd: C, 63.51; H, 8.29. Found: C, 63.58; H, 8.30.

1-Methyl-2-propenyl 3-oxobutanoate (5): ^{1}H NMR (300 MHz) δ 5.78 (m, 1 H), 5.18 (m, 3 H), 3.38 (s, 2 H), 2.20 (s, 3 H), 1.28 (d, 3 H); ^{13}C NMR (300 MHz) δ 200.0, 166.2, 137.1, 116.2, 72.0, 50.2, 29.8, 19.7; IR 3060 (w), 2980 (m), 2940 (m), 1765 (s), 1740 (s), 1670 (m) cm^{-1}; LRMS (EI), *m/e* 85 (0.31), 71 (0.66), 58 (0.20), 57 (0.33), 55 (0.84), 43 (1.00), 39 (0.30); LRMS (CI), *m/e* 157 (M + 1, 0.03), 103 (1.00), 85 (0.85).

2-Propenyl 2-methyl-3-oxobutanoate (6): ^{1}H NMR (300 MHz) δ 5.82 (m, 1 H), 5.25 (m, 2 H), 4.52 (d, 2 H), 3.38 (q, 1 H), 2.21 (t, 3 H), 1.22 (d, 3 H); ^{13}C NMR (300 MHz) δ 202.7, 170.0, 131.5, 118.0, 65.3, 49.5, 29.4, 13.8; IR 3050 (m), 2985 (m), 2930 (m), 1755 (s), 1735 (s), 1670 (s) cm^{-1}; LRMS (EI), *m/e* 85 (0.85), 72 (0.35), 69 (0.89), 68 (0.55), 43 (1.00), 41 (0.62); LRMS (CI), *m/e* 157 (M + 1, 0.43), 99 (1.00).

(*E*)-2-Butenyl 2-methyl-3-oxobutanoate (7): ^{1}H NMR (360 MHz) δ 5.65 (m, 2 H), 4.50 (d, 2 H), 3.47 (q, 1 H), 2.19 (s, 3 H), 1.68 (d, 3 H), 1.29 (d, 3 H); ^{13}C NMR (300 MHz) δ 203.0, 170.1, 131.6, 124.5, 65.7, 53.4, 28.1, 17.4, 12.4; IR 2960 (m), 2920 (w), 1760 (s), 1730 (s), 1680 (m) cm^{-1}; LRMS (EI), *m/e* 170 (M$^+$, 0.04), 142 (0.37), 117 (0.34), 99 (0.59), 86 (0.64), 84 (0.71), 74 (0.66), 72 (0.84), 71 (0.50), 57 (0.51), 56 (0.81), 55 (1.00), 43 (0.90), 39 (0.52); HRMS for $C_9H_{14}O_3$ calcd 170.09429, found 170.09504. Anal. Calcd: C, 63.51; H, 8.29. Found: C, 63.54; H, 8.25.

3-Methyl-2-butenyl 2-methyl-3-oxobutanoate (8): ^{1}H NMR (360 MHz) δ 5.21 (t, 1 H), 4.50 (d, 2 H), 3.39 (q, 1 H), 2.09 (s, 3 H), 1.64 (s, 3 H), 1.58 (s, 3 H), 1.19 (d, 3 H); ^{13}C NMR (360 MHz) δ 203.1, 170.3, 139.5, 118.0, 62.0, 53.5, 28.1, 25.5, 17.8, 12.5; IR 2995 (m), 2960 (m), 1760 (s), 1735 (s), 1670 (w) cm^{-1}; LRMS (EI), *m/e* 85 (0.36), 72 (0.21), 69 (0.65), 68 (0.28), 67 (0.20), 57 (0.13), 43 (1.00), 41 (0.66), 39 (0.17); LRMS (CI), *m/e* 185 (M + 1, 0.01), 99 (0.08), 69 (1.00). Anal. Calcd: C, 65.19; H, 8.75. Found: C, 65.31; H, 8.76.

1-Methyl-2-propenyl 2-methyl-3-oxobutanoate (9): ^{1}H NMR (300 MHz) δ 5.66 (m, 1 H), 5.03 (m, 3 H), 3.44 (q, 1 H), 2.00 (s, 3 H), 1.19 (d, 3 H), 1.11 (d, 3 H); ^{13}C NMR (300 MHz) δ 202.9, 169.5, 136.9, 115.8, 71.6, 53.4, 29.3, 19.3, 13.6; IR 3050 (w), 2990 (m), 2960 (m), 1760 (s), 1740 (s), 1670 (m) cm^{-1}; LRMS (EI), *m/e* 99 (0.21), 74 (0.27), 72 (0.37), 57 (0.36), 55 (0.88), 43 (1.00); LRMS (CI), *m/e* 171 (M + 1, 0.05), 117 (1.00), 99 (0.72).

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Registry No. **1**, 1118-84-9; (*E*)-**3**, 82259-92-5; **4**, 21597-32-0; **5**, 25456-01-3; **6**, 111903-66-3; (*E*)-**7**, 111903-67-4; **8**, 111903-68-5; **9**, 111903-69-6; 4-DMAP, 1122-58-3; $MeCOCH_2CO_2Et$, 141-97-9; $MeCOCH(Me)CO_2Et$, 609-14-3; $HOCH_2CH{=}CH_2$, 107-18-6; $HOCH(Me)CH{=}CH_2$, 598-32-3; (*E*)-$HOCH_2CH{=}CHMe$, 504-61-0; $HOCH_2CH{=}CMe_2$, 556-82-1; $MeCOCH_2CO_2Me$, 105-45-3.

An Efficient Synthesis of (3*R*,4*R*)-3-(1(*R*)-Hydroxyethyl)-4-(benzoyloxy)-2-azetidinone from L-Threonine. Use of Phenylalkoxymethyl as a Novel N-Protecting Group

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The optically active azetidinone 1 is a valuable intermediate in the synthesis of penem[1] (15) and carbapenem[2] (14) antibiotics. While degradation of 6-aminopenicillanic acid[3] has been the traditional method of preparing 1, the

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