Synthetic Approach to Medium-sized Cycloalkanones. A One-pot Three-carbon Ring Expansion of Carbocyclic β-Keto Esters

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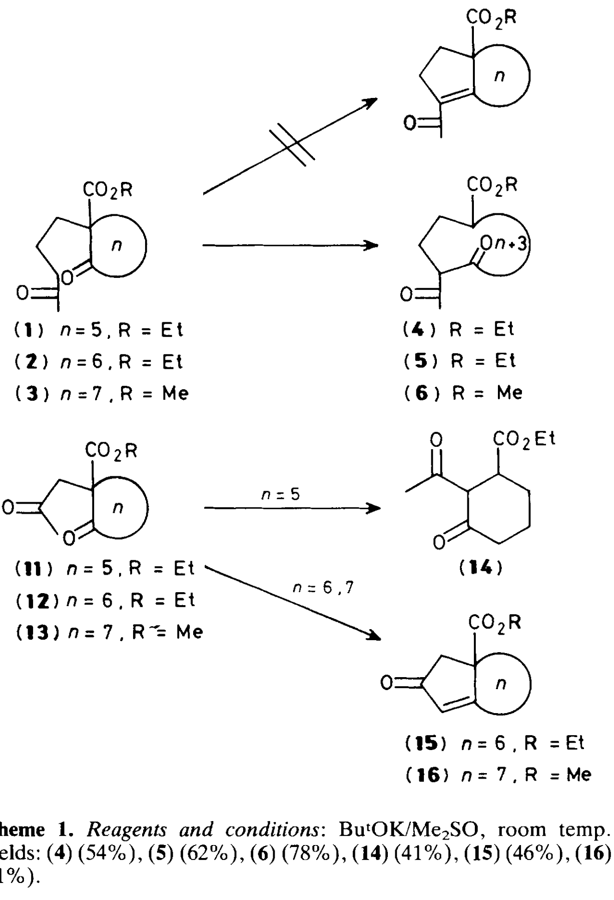
By treatment with Bu^{t}OK in Me$_2$SO, carbocyclic β-keto-esters (5-, 6-, and 7-membered rings) with a 4-oxopentyl function at the α-position afforded three-carbon ring expansion products (8-, 9-, and 10-membered rings, respectively).

New syntheses of medium-sized rings[1] are attractive to organic chemists because, at present, there are only limited synthetic procedures available. Recent approaches have involved the fragmentation of a cross-piece bond in ring systems composed of two or more small rings, *e.g.* Grob fragmentation.[2]

Here we report a one-pot three-carbon ring expansion by treatment of carbocyclic β-keto esters, having a 4-oxopentyl moiety at the α-position, with Bu^{t}OK in Me$_2$SO at room temperature. This carbon zip reaction[3] involves aldol and retro-aldol condensation.[4] Treatment of (**3**) (7-membered ring)† with Bu^{t}OK (1.2 equiv.) in Me$_2$SO at room temperature afforded a three-carbon ring expansion product (**6**) (10-membered ring) in 78% yield.‡ This one-pot reaction was applied to the 5-membered ring β-keto esters (**1**) and (**2**), and the ring expansion products (**4**) and (**5**) were obtained in 62 and 54% yields respectively (Scheme 1). The cyclized dehydration products were not obtained in contrast to the result obtained by Nakashita and Hesse[5] which concerned the reaction of α-nitro-cyclopentanone and -cyclohexanone with methyl 3-oxopent-4-enoate.



Scheme 1. *Reagents and conditions*: Bu^{t}OK/Me$_2$SO, room temp. Yields: (**4**) (54%), (**5**) (62%), (**6**) (78%), (**14**) (41%), (**15**) (46%), (**16**) (41%).

Treatment of (**3**) with Bu^{t}OK (1.2 equiv.) in tetrahydrofuran (THF) at −78 °C gave the normal aldol condensation product (**7**), with a small amount of (**6**). Compound (**7**) could be converted to (**6**) by treatment with Bu^{t}OK. This result suggests that the three-carbon ring expansion process is thermodynamically preferable to the dehydration process. The stereochemistry of (**7**) was established by Baeyer–Villiger oxidation with CF_3CO_3H and subsequent methanolysis with K_2CO_3/MeOH to convert it to the five membered lactone (**9**). Facile formation of (**9**) indicates that the methyl ketone in (**7**) should be *cis* relative to the angular methyl ester. By treatment with 2,2-dimethoxypropane/*p*-$MeC_6H_4SO_3H$, (**9**) was converted to the acetonide (**10**), indicating the methyl ketone in (**7**) to be *cis* relative to the angular OH. Thus, the above aldol condensation at −78 °C provides a simple method for the construction of *cis*-fused carbocyclic ring systems with the methyl ketone in the *cis*-position (Scheme 2). It is noteworthy that (**7**) was easily converted to the bicyclo-[4.4.1]undecanone derivative (**17**) under reductive conditions

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† Compounds (**1**)—(**3**) were prepared *via* alkylation of the corresponding carbocyclic β-keto ester with 5-chloropentan-2-one ethylene acetal in the presence of Bu^{t}OK in Me$_2$SO and subsequent treatment with 10% HCl in MeOH. Compounds (**11**)—(**13**) were obtained by similar alkylation with allyl chloride followed by Wacker oxidation.

‡ All yields refer to isolated and purified compounds. An $FeCl_3$ test on (**4**), (**5**), (**6**), and (**14**) was positive, indicating the presence of a 1,3-diketone.

Selected spectroscopic data for (**4**): i.r. (neat) 1740, 1710, 1440 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 1.28 (3H, t, *J* 7.2 Hz), 2.24 (3H, s), 3.40 (1H, t, *J* 6.9 Hz), 4.18 (2H, q, *J* 7.2 Hz); ^{13}C n.m.r. ($CDCl_3$) δ 14.2 (q), 20.7 (t), 26.1 (t), 27.4 (t), 29.0 (q), 29.4 (t), 38.0 (t), 48.9 (d), 59.8 (d), 61.5 (t), 169.6 (s), 202.9 (s), 213.5 (s); mass spec. *m/z* 240 (M^+), 194, 166.

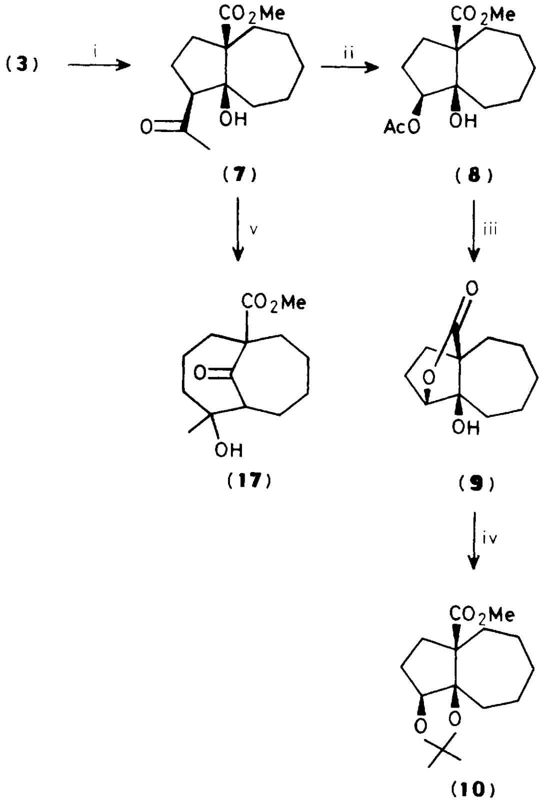
For (**5**): i.r. (neat) 1710 (br), 1640 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 1.28 (3H, t, *J* 7.2 Hz), 2.24 (3H, s), 3.40 (1H, t, *J* 7.1 Hz), 4.18 (2H, q, *J* 7.2 Hz); ^{13}C n.m.r. ($CDCl_3$) δ 14.1 (q), 25.0 (t), 25.3 (t), 25.9 (t), 27.2 (t), 28.8 (q), 34.1 (t), 42.1 (t), 50.5 (d), 59.9 (d), 61.3 (t), 169.7 (s), 203.2 (s), 212.7 (s); mass spec. *m/z* 254 (M^+), 209.

For (**6**): i.r. (neat) 1740—1690 (br), 1635 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 2.24 (3H, s), 3.42 (1H, dd, *J* 7.4, 14.6 Hz), 3.74 (3H, s); ^{13}C n.m.r. ($CDCl_3$) δ 24.2 (t), 25.1 (t), 25.9 (t), 28.7 (q), 29.4 (t), 29.8 (t), 31.4 (t), 43.0 (t), 51.8 (q), 52.4 (d), 59.6 (d), 170.1 (s), 202.9 (s), 215.5 (s); mass spec. *m/z* 254 (M^+), 223.

For (**7**): i.r. (neat) 3460, 1710, 1690 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 2.22 (3H, s), 2.97 (1H, dd, *J* 7.6, 10.7 Hz), 3.71 (3H, s); mass spec. *m/z* 254 (M^+), 236.

For (**14**): i.r. (neat) 1710 (br), 1600 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 1.26 (3H, t, *J* 7.3 Hz), 3.46 (1/2 H, br), 4.14 (2H, q, *J* 7.3 Hz), 16.00 (1/2 H, s); mass spec. *m/z* 212 (M^+), 170.

For (**17**): i.r. (neat) 3460, 1690 cm^{-1}; ^{1}H n.m.r. ($CDCl_3$) δ 1.22 (3H, s), 3.71 (3H, s), 3.77 (1H, s, OH); ^{13}C n.m.r. ($CDCl_3$) δ 22.7 (q), 25.4 (t), 26.1 (t), 27.2 (t), 30.5 (t), 30.8 (t), 34.0 (t), 43.9 (t), 51.2 (d), 51.8 (q), 66.5 (s), 81.5 (s), 176.4 (s), 218.5 (s); mass spec. *m/z* 254 (M^+), 236.



Scheme 2. *Reagents and conditions*: i, Bu^{t}OK/THF, −78 °C, 64%; ii, CF_3CO_3H/CH_2Cl_2, 61%; iii, K_2CO_3/MeOH, 85%; iv, $Me_2C(OMe)_2$/*p*-$MeC_6H_4SO_3H$/dimethylformamide, 81%; v, L-Selectride/THF, 80% or $NaBH_4$/MeOH, −78 °C, 25%.

using L-Selectride or $NaBH_4$ at −78 °C.§ Ring expansions in (**1**)—(**3**) may proceed *via* aldol condensation [such as (**7**)] followed by a retro-aldol reaction, which may be caused by the stereoelectronic repulsion between the ester, OH, and methyl ketone in a *cis*-configuration.

For further application of this zip reaction, carbocyclic β-keto esters (**11**)—(**13**), having a 2-oxopropyl moiety were subjected to the ring expansion conditions. In the case of compound (**11**), the three-carbon ring expansion product was not obtained, but a one-carbon expansion product (**14**) was obtained in 41% yield. Interestingly, (**12**) and (**13**) afforded only the cyclized dehydration products (**15**) and (**16**) without any formation of one- or three-carbon ring expansion products.

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§ The structure of (**17**) was suggested by a referee. Compound (**17**) was obtained as the major product, in addition to a small amount of reduction products. Reaction of (**7**) with lithium acetylide also afforded (**17**), and the addition product was not obtained. Treatment of (**17**) with Bu^{t}OK afforded (**6**).