A New Very Mild K₂CO₃-catalysed One-pot Two-carbon Ring Expansion of Cyclopentanones

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Cyclic α-carbonyl-substituted cyclopentanones undergo, in a one-pot process, an unprecedented K₂CO₃-catalysed cascade Michael addition-regioselective aldol cyclisation-reverse Dieckmann reaction with α,β-unsaturated aldehydes in methanol or ethanol at room temperature to afford stereoselectively substituted cycloheptane derivatives.

We have recently found a very mild and general one-pot high yield preparation of synthetically valuable hydroxybicyclo[3.2.1]octanones 1 by K₂CO₃–acetone promoted facile tandem Michael addition-regioselective aldol cyclisation of substituted Dieckmann esters with α,β-unsaturated aldehydes.[1] In this paper, we describe a very mild preparation of highly substituted cycloheptane derivatives by a new base-catalysed one-pot two-carbon homologation of α-carbonyl-substituted cyclopentanones.

Whereas the one-carbon ring expansion is well documented,[2] the two-carbon analogue represents a rare family of reactions. The well-known Stork-Landesman procedure[3] and the reaction between enamines and substituted acetylenes[4] constitute two important approaches. More recently, the acetalisation of cyclopentanones with a carbonyl function at the C-3-position of an α-side chain[5] and the four-step preparation of 2-methylcycloheptan-1,5-dione starting from 2-methylcyclopentan-1,3-dione have been published.[6] In both cases the reactive intermediates are bicyclo[3.2.1]octane derivatives, which are known to give a facile fragmentation reaction leading to cycloheptanes.[7]

Our own work on the synthetic exploitation of 2-hydroxybicyclo[3.2.1]octan-8-one ring systems 1[1] allowed us to find that these substrates evolved very cleanly, by a reverse-Dieckmann reaction[8] promoted by K₂CO₃ in methanol, to the corresponding substituted cycloheptane derivatives 2 (Scheme 1).

This result prompted us to surmise that the overall cascade Michael addition-regioselective aldol cyclisation-reverse Dieckmann reaction, would be possible in a one-pot process starting from cyclopentanones 3 and α,β-unsatured aldehydes 4. Indeed, the expected one-pot ring expansion takes place under mild conditions in methanol or ethanol at room temperature in the presence of a catalytic amount of K₂CO₃ (Scheme 2).
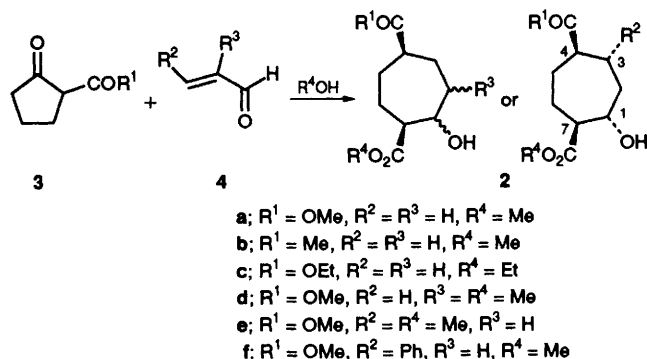
The method has been applied to several α,β-unsaturated aldehydes and gives satisfactory results with β-ketoesters or with 2-acetylcyclopentan-1-one (Table 1). All reactions are unoptimized but give reproducible results under the conditions reported above.†

An excess of K₂CO₃ reduces drastically the yield of the transformation as shown by the obtention of 2a in only 36% yield when 2 equiv. or more are used. This is probably owing

to the formation of the fully characterized cycloheptene derivative 5a, which rapidly decomposes in the reaction conditions (Fig. 1). Other bases such as Cs₂CO₃ and tetramethylguanidine (TMG) can be used without significant change in reaction time and yields. Finally, when the reaction of 3c with 4a is run in methanol (R⁴ = Me) a complete transesterification occurs leading exclusively to 2a.

Cycloheptanes 2a–d‡ are obtained as a mixture of epimers in the ratio 1.5:1 with respect to the hydroxy substituent and the cyclic structure has been confirmed by an INADEQUATE 2D NMR[9] study, which clearly established the carbon connectivity unique to structure 2.

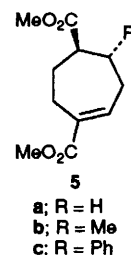Interestingly, in the case of 2e and 2f only one diastereoisomer having the hydroxy *trans* to the two methoxycarbonyl

3   **4**   **2**

a; R¹ = OMe, R² = R³ = H, R⁴ = Me
b; R¹ = Me, R² = R³ = H, R⁴ = Me
c; R¹ = OEt, R² = R³ = H, R⁴ = Et
d; R¹ = OMe, R² = H, R³ = R⁴ = Me
e; R¹ = OMe, R² = R⁴ = Me, R³ = H
f; R¹ = OMe, R² = Ph, R³ = H, R⁴ = Me

Scheme 2 *Reagents and conditions:* K₂CO₃ (0.25–0.5 equiv.), MeOH or EtOH, room temp., 6–72 h 36–94%

Table 1 Synthesis of substituted cycloheptanes

Cyclopentanone 3	Aldehyde 4	t/h	Product 2	Yield (%)
a	a	6	a	94
b	b	24	b	42
c	c	48	c	84
d	d	28	d	36
e	e	17	e	54
f	f	72	f	68

5

a; R = H
b; R = Me
c; R = Ph

1   a; R = OMe   **2**
          b; R = Me
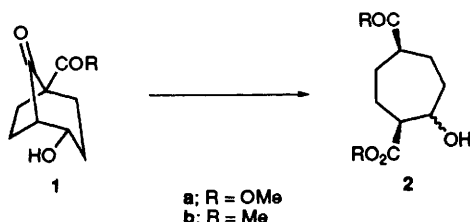
Scheme 1 *Reagents and conditions:* K₂CO₃ (1 equiv.), MeOH, room temp., 2–18 h, 70–96%

† All new compounds gave satisfactory analytical and/or spectral data.

‡ *E.g.:* **2a** (two diastereoisomers): colourless oil, R_f = 0.40 (diethyl ether–pentane, 7:3); IR (neat) v/cm^{-1} 3480, 2950, 2890, 1730; ¹H NMR (200 MHz, CDCl₃) δ 1.58–2.18 (8 H, m), 2.41–2.60 (3 H, m), 3.64 (3 H, s), 3.69 (3 H, s), 3.94–4.00 (1 H, m); ¹³C NMR (50 MHz, CDCl₃) δ 23.6, 23.7, 24.7, 25.2, 27.2, 28.9, 32.4, 33.6, 42.9, 43.7, 51.1, 51.3, 51.37, 51.4, 52.9, 53.7, 72.3, 73.3, 175.6, 176.0.

functions and *cis*, respectively to the methyl or to the phenyl substituent, can be isolated.§ This result can be explained assuming the concomitant formation and the rapid degradation of **5b** and **5c** from the others epimers **5**.

The stereochemistry of this one-pot, three-step transformation is determined by the stereoselectivity of the Michael addition,[10] which constitutes the first step of the overall process and allows the preparation of highly substituted and stereodefined cycloheptane derivatives with high synthetic potentialities.

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§ Extensive NMR study including selective irradiations and NOE DIFF experiments has unambiguously established the proposed structure. *E.g.*: **2e**: White crystals, m.p. = 60–62 °C, R_f = 0.21 (diethyl ether–pentane, 9:1); IR (CCl$_4$) v/cm^{-1} 3540, 2960, 2880, 1735; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.88 (3 H, d, *J* 6.6 Hz), 1.54–1.67 (2 2-H, m), 1.67–1.86 (2 5-H + 2 6-H, m), 1.98 (3-H, m), 2.09 (4-H, dt, *J* 10.4, 5.3 Hz), 2.32 (7-H, ddd, *J* 9.8, 8.2, 4.8 Hz), 3.58 (3 H, s), 3.63 (3 H, s), 3.94 (1-H, td, *J* 9.8, 2.5 Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 22.7 (q), 23.9 (t), 27.8 (t), 31.9 (d, C3), 42.2 (t), 51.6 (q), 51.7 (d, C4), 51.9 (q), 53.7 (d, C7), 73.0 (d, C1), 175.9 (s), 176.5 (s).

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