Ring Cleavage Reaction based on Intermolecular Aldol Condensation

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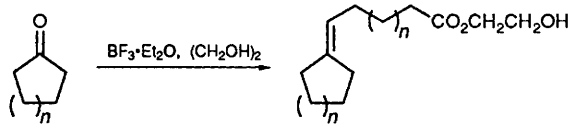
Acetalization of carbonyl groups in cyclic ketones using BF_3–ethylene glycol brought about ring cleavage reactions *via* an intermolecular aldol condensation.

Previously, we reported ring cleavage and reconstruction[1] *via* aldol condensation followed by Grob fragmentation[2] under acetalization conditions (BF_3–ethylene glycol). This reaction, based on an intramolecular aldol condensation, prompted us to study intermolecular aldol condensations followed by fragmentation. Reaction of simple cyclic ketones with BF_3–ethylene glycol proceeded as for the intramolecular reaction to afford the ethylene glycol half esters in 30–70% yields (Table 1). Moderate yields were obtained for five- and six-membered rings; with larger rings the yield and the rate of reaction were reduced.

The structures† of the products were established on the basis of spectroscopic data: *e.g.* the ^1H NMR spectrum of the product in entry 1 included an unsaturated proton signal at δ 5.33 (1H, m), and signals due to the ethylene glycol half ester at δ 3.82 (2H, m, CH_2O) and 4.22 (2H, m, CO_2CH_2). The IR [ν_{max}/cm^{-1} 3400 (OH) and 1700 (ester)] and mass spectra [*m/z* 212 (M^+)] also supported this structure. Scheme 1 shows a tentative reaction mechanism.

As a further application of this reaction, we studied ring cleavage reactions based on a crossed intermolecular aldol condensation using cyclopentanone as the enolate donor and substituted benzaldehydes as the enolate acceptor. In accord with our expectation, crossed aldol condensation and subsequent ring cleavage occurred to afford the *trans* ethylene glycol half esters; the *cis*-isomers were not detected (Table 2).‡ The structures† were determined from spectroscopic data, as exemplified by the product in entry 1. The ^1H NMR spectrum showed ethylene glycol half ester signals at δ 3.81 (2H, m, CH_2O) and 4.21 (2H, m, CH_2OCO), and *trans*-unsaturated proton signals at δ 6.15 (1H, dt, *J*/Hz 15.9, 6.1) and 6.42 (1H, d, *J*/Hz 15.9); ν_{max}/cm^{-1} 3400 (OH), 1730 (ester), and 1640 (aromatic); *m/z* 234 (M^+). As shown in Table 2, except for entry 2, electron-releasing functions

Table 1 Ring cleavage–aldol condensation[a]

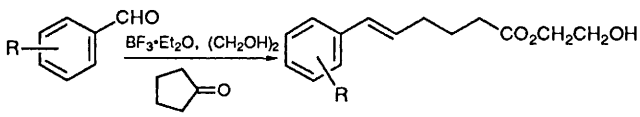


Entry	*n*	Yield (%)
1	1	70
2	2	75
3	3	45
4	8	30

[a] A mixture of the cyclic ketone and BF_3·Et_2O (7 equiv.) in CH_2Cl_2 was stirred at 0 °C for 3–5 h under Ar atmosphere, then ethylene glycol (5 equiv.) was added and the mixture stirred for 2–3 h (150 h for entry 4) at room temp.

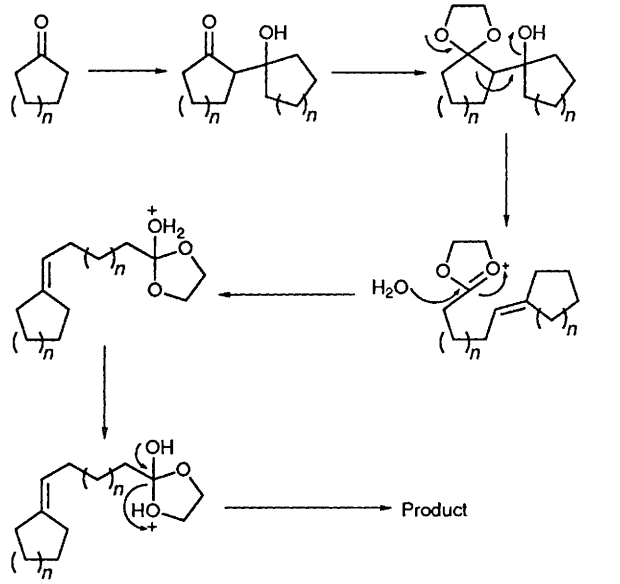
† Each product was obtained as a colourless oil. Selected spectroscopic data of representative products. Table 1, entry 2: ν_{max}/cm^{-1} (neat) 3450, 1740 and 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.84 (2H, m, CH_2O), 4.22 (2H, m, CO_2CH_2) and 5.37 (1H, m, =CH–); ^{13}C NMR ($CDCl_3$) δ 174.2 (CO), 137.7 (=C–), 120.9 (=CH–), 65.9 (CH_2O), 61.4 (CH_2O), 37.9, 34.2, 28.8, 28.3, 27.3, 25.3, 25.0, 23.1, 22.6 (all CH_2); *m/z* 240 (M^+), 179, 149 and 95. Table 2, entry 2: ν_{max}/cm^{-1} (neat) 3450, 1730, 1600 and 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76–3.84 (5H, m, CH_3O, CH_2O), 4.15–4.24 (2H, m, CO_2CH_2), 6.07–6.23 (1H, dt, *J*/Hz 15.8, 6.0, =CH–) and 6.65–7.43 (5H, m, –CH=, ArH); ^{13}C NMR ($CDCl_3$) δ 174.0 (CO), 156.4 (=C– ×2), 130.1, 128.1, 126.5, 125.6 (ArCH), 120.7 (=CH–), 110.9 (=CH–), 66.0 (CH_2O), 61.3 (CH_2O), 55.5 (OCH_3), 33.5, 32.8 and 24.6 (CH_2); *m/z* 264, 202, 160 and 147.

Table 2 Crossed aldol condensation[a]



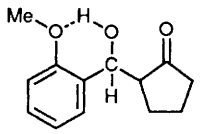
Entry	R=	Yield (%)
1	H	61
2	*o*-MeO	59
3	*p*-MeO	29
4	*o*-Me	32
5	*p*-Cl	24
6	(*o*, *m* or *p*)-NO_2	0

[a] A mixture of the aldehyde, BF_3·Et_2O (3 equiv.) and cyclopentanone (1 equiv.) in CH_2Cl_2 was stirred at 0 °C for 3–5 h under Ar, then ethylene glycol (5 equiv.) was added and the mixture stirred for 15–20 h at room temp. Substrates were not recovered, and unidentified polymers were obtained.

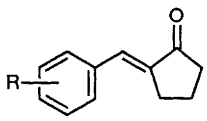


Scheme 1

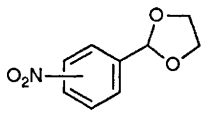
‡ It is not clear whether the *trans*-isomer was formed directly or *cis*–*trans*-isomerisation occurred under the conditions used.



(A)



(B)



(C)

resulted in poor yields, possibly owing to the instability of the intermediary aldol, which may be readily dehydrated to the enone (**B**)§ because of the participation of the electron-releasing function. It is likely that the intermediate from *o*-methoxybenzaldehyde (entry 2) would be stabilized by the formation of an intramolecular hydrogen bond [structure (**A**)] and undergo acetalization followed by Grob fragmentation. It is noteworthy that *o*-, *m*- or *p*-nitrobenzaldehydes afforded only the acetal (**C**),[5] and ring cleavage was not observed at all. Based on the hard–soft acid–base concept, ethylene glycol is a hard base and enol carbon atoms soft. The carbonyl carbon of benzaldehyde is considered to be softer than the normally hard carbonyl function, because of resonance effects. Thus, the intermolecular aldol condensation of cyclopentanone and benzaldehyde proceed to induce the fragmentation *via* acetalization. In contrast, the carbonyl carbon of nitrobenzaldehyde seems to be harder, and prefers the formation of the acetal to the aldol condensation.

§ Structures (**B**) and (**C**) were supported by spectroscopic data.

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