Synthesis of 4,4-Disubstituted Cyclohexenones by the Baeyer–Villiger Fragmentation of 1-Methoxybicyclo[2.2.2]oct-5-enones

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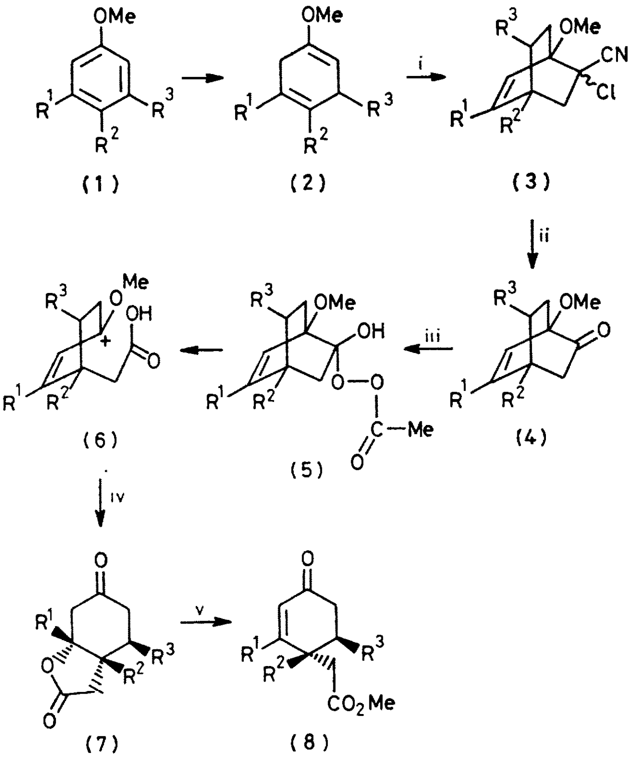
Summary The sodium acetate-buffered, peracetic acid oxidation of various 1-methoxybicyclo[2.2.2]oct-5-enones, prepared by hydrolysis of the adducts derived from dihydroanisole derivatives and α-chloroacrylonitrile, leads to 4-substituted cyclohex-2-en-1-one 4-acetic acid derivatives.

4,4-Disubstituted cyclohexenone derivatives are useful intermediates in natural products synthesis and several elegant synthetic methods have been reported.[1] The approach described here is based on the fragmentation of a bicyclo[2.2.2]octane derivative, a principle established previously by Birch[2] and Raphael.[3] The Baeyer–Villiger fragmentation of norbornenone and bicyclo[2.2.2]octenone was recognised by Meinwald[4] a number of years ago, and other examples have been reported more recently.[5,6] The Baeyer–Villiger oxidation of various norbornenone derivatives followed by allylic rearrangement of the resulting lactones has been used effectively in the stereoselective synthesis of substituted cyclopentenes.[7]

Our own work was based on the assumption that fragmentation should be the preferred mode of reaction of the intermediate (**5**), upon Baeyer–Villiger oxidation† of the ketones (**4**), owing to the formation of the stable cationic intermediate (**6**), which in turn would solvolyse to a cyclohexenone (Scheme). This was found to be the case when the reaction was carried out with sodium acetate-buffered peracetic acid in acetic acid, but not with other peroxycarboxylic acids. The lactones (**7**) were obtained after acidic work up of the reaction mixture. These lactones could be converted into the cyclohexenones (**8**) upon treatment with sodium hydroxide and dimethyl sulphate or the cyclohexenones could be obtained directly by working up the Baeyer–Villiger reaction with an excess of sodium hydroxide and dimethyl sulphate. The results are in the Table.



a; $R^1 = R^3 = H, R^2 = Me$
b; $R^1 = Me, R^2 = R^3 = H$
c; $R^1 = R^2 = Me, R^3 = H$
d; $R^1 = R^2 = R^3 = Me$
e; $R^1 = R^2 = R^3 = H$

Scheme. *Reagents*, i, $CH_2{=}C(Cl)CN$, ii, $Na_2S.9H_2O$–KOH–EtOH–H_2O, iii, $MeCO_3H$–$MeCO_2H$–$MeCO_2^-$, iv, H_3O^+, v, Me_2SO_4–NaOH.

Table

	B.p. of ketone (**4**) /°C (*p*/mmHg)	% Yield from (**3**)	M.p. of Lactone (**7**)/°C	% Yield from (**4**)†	B.p.[a] of cyclohexenone (**8**) /°C (*p*/mmHg)	% Yield from (**4**)†
a	Ref. 8	75	74—75	56	50 (12)	74
b	Ref. 9	46	—	—	125 (0·2)	69
c	78—80 (0·2)	43	—	—	100 (0·1)	59
d[b]	70[a] (0·1)	55	104—105	17	110 (0·1)	52
e	Ref. 8	50	—	—	Ref. 11	85

[a] Kugelrohr oven temperature. [b] Stereochemical assignment by analogy with the results reported in ref. 10.

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† The reaction conditions for the oxidation of (**4**) were as follows. To a solution of the ketone (**4**) in acetic acid containing sodium acetate (100 mg/ml) was added 1 mol. equiv. of 40% peracetic acid and the mixture was heated at 50 °C for 3 h. After cooling the mixture to room temperature peracetic acid (1 mol. equiv.) was added, and the reaction was allowed to proceed to completion at room temperature (up to 4 days).

The ketones (**4**) were obtained by the hydrolysis of the adducts (**3**) using a solution containing 1 mol. equiv. of $Na_2S.9H_2O$ and 2 mol. equiv. of KOH in 95% $EtOH-H_2O$. This was found to be an improvement over the general procedure by Evans[8] and Monti.[9] A limiting factor is the fact that the adducts (**3**) are efficiently formed only from the cycloaddition of α-chloroacrylonitrile to those Birch reduction products (**2**) in which $R^2 = H$ or Me.

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