3-Methylcyclohex-2-enone Derivatives as Initiators of Cyclisation. Part 1. Introduction and Synthesis of 2-Substituted 3-Methylcyclohex-2-enones

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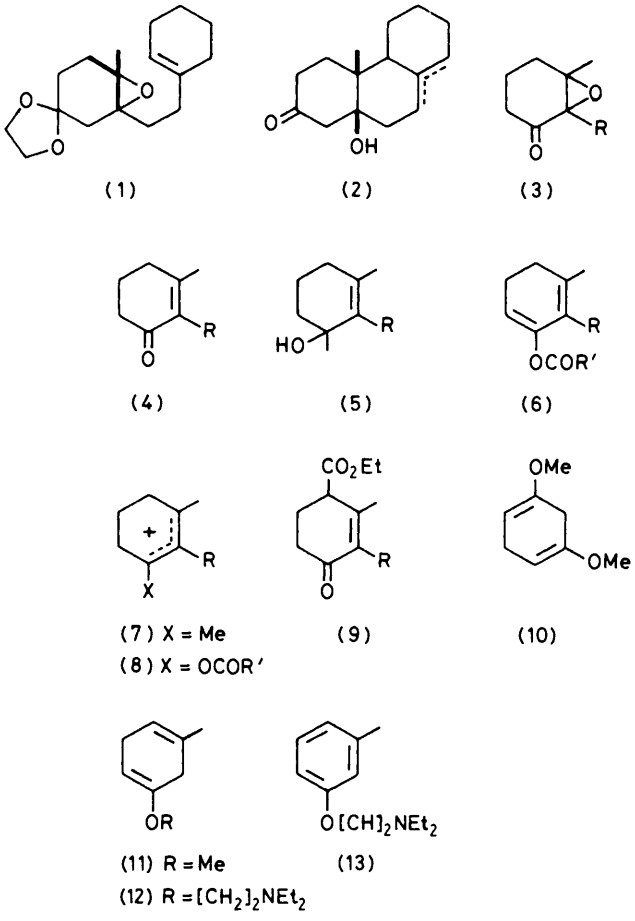
A series of C-2 substituted 3-methylcyclohex-2-enones has been prepared using the Hagemann ester route. A new synthesis of these compounds has been developed which involves the alkylation of the *N,N*-diethylaminoethyl ether of 1-hydroxy-5-methylcyclohexa-1,5-diene. The cyclohexenones have been converted into the corresponding α,β-epoxyketones using alkaline hydrogen peroxide.

The efficient cyclisation of the epoxide (1) to the tricyclic products [1] (2) prompted us to study cyclisation of the synthetically more accessible epoxides (3), readily available from 2-substituted 3-methylcyclohex-2-enones (4). It was also apparent that the cyclohexenones could be converted into the corresponding alcohol (5) and the dienol acylates (6). These have been shown by Johnson [2] and by Harding [3] to be good precursors for the allylic ions (7) and (8) which, in turn, are efficient initiators of cyclisation. This flexibility offered by the 3-methylcyclohex-2-enone unit suggested facile synthetic routes provided that the cyclohexenones could be prepared in high yield. The classical route is by alkylation of Hagemann's ester (9); this has been developed by Smith and Rouault [4,5] with useful modifications provided by Marshall *et al.*[6] and Johnson *et al.*[3] The major disadvantage of the Hagemann's ester route is the formation of minor (10—20%) amounts of C-4 alkylation products; [5] in addition, we have found with reactive (*e.g.* prop-2-ynyl halides) significant amounts of di-alkylated product are formed. In our hands the overall yields seldom exceeded 50% and in certain cases we were unable to obtain any alkylation product; these results caused us to examine other routes.

We first investigated alkylation of the enolate derived from 3-methylcyclohex-3-enone and lithium di-isopropylamide; [7] satisfactory alkylation could be achieved using reactive halides but no product was obtained with 4-bromobut-1-ene. The route from cyclohexane-1,3-dione suffers from the drawback that the dione can be alkylated in good yield only with reactive halides. However, Piers and Grierson [8] solved this problem by alkylation of the nucleophile formed from the diene (10) and LiBu^t. The sequence, hydrolysis to dione,[8] enol ether formation,[9] reaction with MgMgI, and hydrolysis gives the cyclohexenone with excellent yields at all stages. In an effort to reduce the number of steps we attempted metallation of (11) with Bu^{n}Li–HMPA–THF [conditions which are satisfactory for (10)] but without success. The greater acidity of (10) is presumably due to a solvating effect of the ethereal oxygens on the lithium. Geometrically this interaction must be distinct from that in the well-established *o*-methoxyaryl-lithiums where the dihedral angle between C–O and C–Li must be *ca.* 0°; in the cyclohexadienyl case the dihedral angle would be either *ca.* 60° (sp^3 hybridisation) or *ca.* 90° (sp^2 hybridisation). Given these assumptions the most likely structure for the lithio-derivative of (10) is that of an aggregate with *inter*-molecular co-ordination of Li and O. We therefore sought a derivative of (11) in which there was an increased possibility of co-ordination for Li. An obvious candidate is (12) which was readily prepared by Birch reduction of (13).[10] Metallation with Bu^{n}Li–HMPA–THF at −78 °C, addition of alkylating agent, warming to room temperature, and hydrolysis of the product with Me_2CO–2M-HCl under N_2 gave good (60—90%) yields of C-2 alkylated 3-methylcyclohex-2-enones. Bromides are satisfactory alkylating agents when they are allyl, prop-2-ynyl, homoallyl, or phenethyl derivatives; when these structural features are not present, best results are obtained using the iodides. One unexpected bonus is that the diethylaminoethyl group in (12) appears to stabilise the cyclohexadiene to aerial oxidation; (12) can be stored at 0 °C for months without it becoming contaminated with (13).



The cyclohexenones were all converted in high yield into the corresponding α,β-epoxy-ketones using the method of

Table. 2-Substituted 3-methylcyclohex-2-enones and related epoxides prepared *

R (E ≡ the epoxide)	Alkylating agent	Method of preparation (% yield)	Combustion analyses (%) Found C	Found H	Required C	Required H	Accurate mass measurements Found	Required
$[(CH_2)_2CH{=}CH_2]$	RBr	H, A(84%)					164.1198	164.1201
E			73.5	9.1	73.3	8.8		
$[(CH_2)_2CH{=}CHMe]$	RBr [12]	H, A(86%)						
E			73.8	9.3	74.2	9.3		
$[(CH_2)_2C{=}CMe]$	$ROSO_2C_7H_7$ [13]	M, A(60%)					176.1203	176.1201
E							192.1145	192.1150
$[(CH_2)_2CH{=}CMe_2]$	RBr [12]	H, A(79%)					192.1511	192.1514
E							208.1411	208.1463
$[(CH_2)_2C_6H_4$-*p*-OMe]	RBr ‡	A(78%)					244.1460	244.1463
$[CH_2CH{=}CH_2]$	RBr	H	79.8	9.5	80.0	9.2		
E			72.8	8.6	72.3	8.4		
$[CH_2CMe{=}CH_2]$	RCl	H					164.1196	164.1201
E			72.8	8.8	73.3	8.8		
$[CH_2CH{=}CHMe]$	RBr		79.9	10.1	80.4	9.7	164.1196	164.1201
E			73.0	9.0	73.3	8.8		
$[(CH_2)_2CMe{=}CH_2]$	$ROSO_2C_7H_7$ [14]	H	80.4	10.0	80.8	10.1		
E			74.4	9.3	74.2	9.3		
$[(CH_2)_2C{\equiv}CH]$	RBr [15]	M					342.1323	342.1328 †
E							178.0990	178.0994
$[(CH_2)_2C_6H_4OMe$-*m*]	RBr [16]	H					244.1458	244.1463
E							260.1409	260.1412
$[(CH_2)_2CH{=}CH{\cdot}(CH_2)_2CMe{=}CH_2]$	RBr §	M					232.1825	232.1827
E							248.1774	248.1776

* The alkylations were carried out using three procedures: H, the NaOEt–EtOH procedure of Smith and Rouault; M, the modification (NaH, PhMe), due to Marshall *et al.*; and A, the new procedure described in this paper. All compounds gave ^{1}H n.m.r. spectra compatible with the structures proposed, the enones showing 3H(s) at τ 8.00 ± 0.05, and the epoxides 3H(s) at τ 8.50 ± 0.05. Accurate mass measurements were carried out on samples judged to be single compounds by the criteria of t.l.c. and/or g.l.c.

† Characterised as 2,4-dinitrophenylhydrazone.

‡ Prepared by $LiAlH_4$ reduction of *p*-methoxyphenylacetic acid followed by bromination.

§ Prepared from 2,3-dichlorotetrahydrofuran by the sequence 3-methylbut-3-enylmagnesium chloride, Na–NH_3 reduction, bromination.

House and Wasson.[11] The various compounds prepared are listed in the Table and studies on their cyclisation are discussed in the following papers.

Experimental

Birch Reduction of (13).—The amine [11] (13) (10.35 g), anhydrous ethanol (13.11 g), and ether (25 ml), were added to a 1 l three-necked flask fitted with a Me_2CO–solid CO_2 condenser. Ammonia (*ca.* 300 ml) was distilled into the flask and small freshly cut pieces of sodium added until the blue colour persisted for 40 min. The condenser was removed and a 1 : 1 ethanol–water mixture (50 ml) added. After the ammonia had evaporated, brine (100 ml) was added and the mixture extracted with ether. After drying, the ether extract was concentrated to give the *diene* (12) (9.20 g), b.p. (bath) 120 °C/0.1 mmHg, τ ($CDCl_3$) 4.68 (1 H, m), 5.43 (1 H, m), 6.26 (2 H, t), 7.38 (10 H, m), 8.36br (3 H, s), and 8.98 (6 H, t) (Found: M^+, 209,1786. $C_{13}H_{23}NO$ requires *M*, 209.1780).

2-(*But*-3-*enyl*)-3-*methylcyclohex*-2-*enone*.—The enol ether (12) (3.09 g, 14.8 mmol) was added to THF (20 ml, freshly distilled) in a 3-necked flask under a N_2 atmosphere. The solution was cooled to −78 °C and n-butyl-lithium (15 mmol) in hexane added *via* a septum cap. After the mixture had been stirred for 1 h, HMPA (2.65 g, 14.8 mmol) in THF (5 ml) was added when the orange solution changed to crimson. 4-Bromobut-1-ene (2 g) in THF (5 ml) was added. After 5 min the cooling bath was removed and the mixture allowed to warm to ambient temperature. After addition of brine (30 ml) the aqueous solution was extracted with ether and the ethereal layer dried to give, after evaporation of the solvent, the alkylated product which was dissolved in acetone (15 ml) and 2M-HCl (8 ml) added. The mixture was set aside overnight under an N_2 atmosphere after which the acetone was evaporated and brine (40 ml) added. Work-up in the usual way gave the ketone [3; R = $(CH_2)_2CH = CH_2$] (2.03 g) (84%), b.p. 75 °C (bath)/1.5 mmHg, identical with a sample prepared by the Hagemann ester route.[3]

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