Bromination of Ketones in the Presence of Epoxides as a Method for Regiospecific Synthesis of Bromo-ketones

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Regioselective free-radical introduction of bromine at the α-position of an unsymmetrical ketone has been achieved simply by photocatalytic bromination in the presence of 1.2-epoxycyclohexane. Under these conditions functionalization of steroid ketones is also observed. The selectivity of these reactions is due to the epoxide which, by scavenging the halogen acid produced during the reaction, inhibits any ionic acid-catalysed bromination of the ketone. Whereas the more highly substituted ketones are brominated easily, the less substituted ones are unchanged because of competing free-radical ring opening of the epoxide.

In view of the usefulness of α-halogenocarbonyl compounds as synthetic intermediates, we sought suitable conditions for the bromination of unsymmetrical ketones which would influence the regioselectivity of the electrophile in a simple, direct way.[1,2] However, the factors which govern regioselectivity in this system are still obscure. Notwithstanding the choice of various experimental conditions (halogenating reagent, solvent, light) and attempts to predict products on the basis of kinetic or thermodynamic control, low yields or mixtures difficult to separate were commonly obtained.[3-6] On the

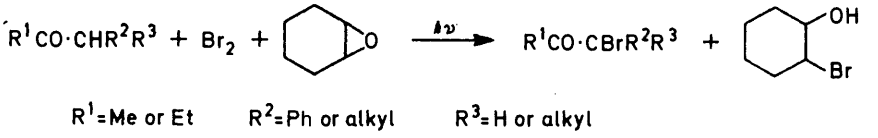
[1] V. Calò, L. Lopez, G. Pesce, and P. E. Todesco, *Tetrahedron*, 1973, **29**, 162.
[2] V. Calò, L. Lopez, and G. Pesce, *J.C.S. Perkin II*, 1976, 247.
[3] H. O. House, 'Modern Synthetic Reactions,' Benjamin, New York, 1965.
[4] E. W. Garbisch, *J. Org. Chem.*, 1965, **30**, 2109.
[5] J. Hooz and J. N. Bridson, *Canad. J. Chem.*, 1972, **50**, 2387.
[6] Y. Jasor, M. Gaudry, and A. Marquet, *Bull. Soc. chim. France*, 1973, 2735 and previous papers in this series.

other hand, the halogenation of enol derivatives (synthesis of which is time consuming and often difficult) suffers the disadvantage that acidic by-products may catalyse equilibration of starting material or of product bromo-ketone.[7-9]

In a preliminary communication [10] we reported that treatment of some alkyl benzyl ketones with bromine in the presence of 1,2-epoxycyclohexane as hydrobromic acid scavenger results in a fast photocatalytic process and leads to almost exclusive benzylic bromination. We have now studied the factors affecting this reaction in an attempt to achieve a simple regiospecific synthesis of various bromo-ketones.

RESULTS

Bromination of ketones with bromine in carbon tetrachloride during irradiation with a 100 W tungsten lamp in the presence of 1,2-epoxycyclohexane proceeds as in Scheme 1, giving monobrominated ketone in which



SCHEME 1

bromine has entered exclusively the benzylic or the more highly substituted α-position. Bromination under the same conditions, but in the dark, stopped after a rapid, small initial halogen uptake. The results are reported in the Table.

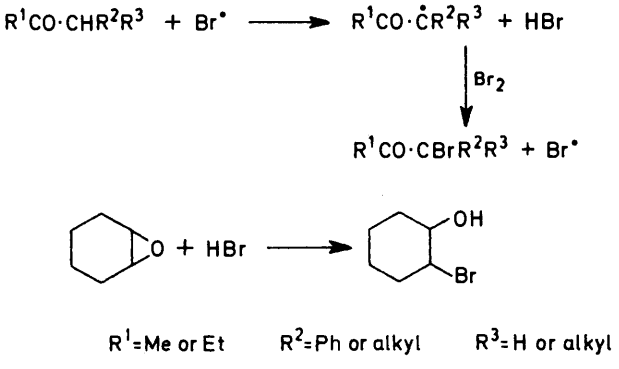
The extent of substitution α to the carbonyl group plays a decisive role in this reaction. Ketones with at least a tertiary or a benzylic α-carbon atom are brominated at this position exclusively. With less substituted ketones (butan-2-one or acetone) the reaction occurs in a different manner, yielding a mixture of 2-bromocyclohexanol and 2-bromocyclohexanone, together with the starting ketone.

The choice of the solvent is also important. In diethyl ether as solvent the reaction invariably yields only 2-bromocyclohexanol and the starting ketone.

In order to see whether the regioselectivity of bromination also applied to steroidal ketones, we studied the reactions of 5α- and 5β-pregnane-3,20-dione. Under our conditions regioselective introduction of bromine occurred at the 17-position; 2-bromocyclohexanol and 2-bromocyclohexanone were also produced.

DISCUSSION

It appears that in the presence of the epoxide, in carbon tetrachloride, the bromination of the more highly substituted ketones occurs by a mechanism different from that generally accepted, which involves an acid-catalysed rate-determining enolization followed by a rapid reaction of the enol with the halogen.[11-16] In fact under our conditions the concentration of hydrobromic acid, which would catalyse the enolization of the ketone, is very low because of the very fast reaction of the acid with the epoxide to give the bromohydrin. The inhibition of the reaction in the dark excludes the possibility of the products being derived from an ionic addition of bromine to the enol. Thus the photocatalysis and the product distribution suggest a free-radical process, which, for the more highly substituted ketones, could be represented as in Scheme 2. Any regioselectivity must occur in the abstraction of hydrogen by a bromine atom. The exclusive formation of one regioisomer strengthens the concept [17] that delocalization of the unpaired electron due to the carbonyl group is small, and that other groups (*e.g.* phenyl or alkyl) attached to the reaction centre, through their superior stabilizing power, will dictate the course of the reaction. When such groups are present in both the α- and the α′-positions (*e.g.* benzyl isopropyl



SCHEME 2

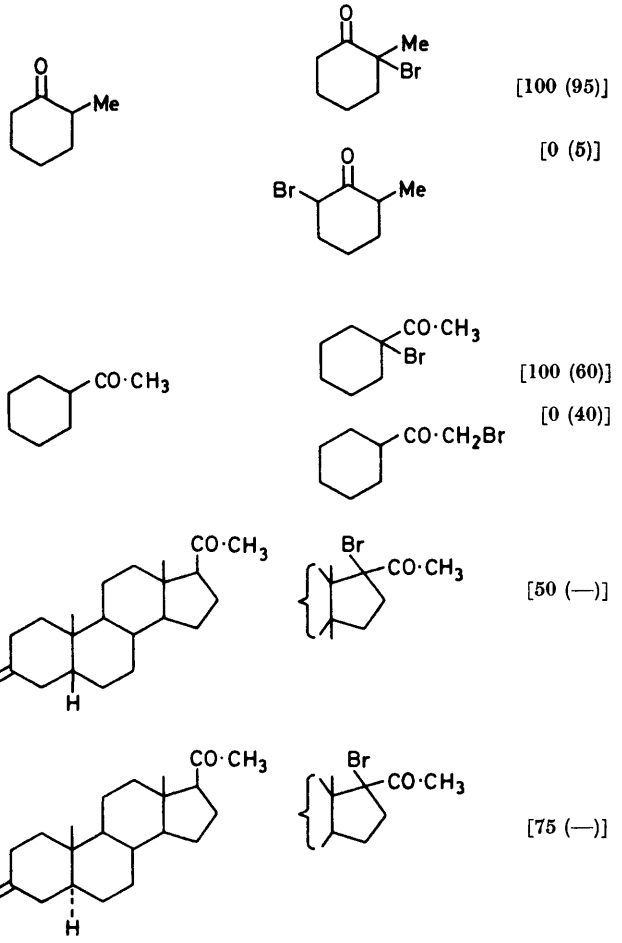
ketone) a lack of regiospecific halogenation is observed. The preponderance of the stabilization effect due to alkyl groups is in accord with the high ratios of 3- to 1-bromo-derivative found in the bromination of butan-2-one with *N*-bromosuccinimide [18,19] in carbon tetrachloride, and the detection of only the more substituted oxoalkyl radical from the reaction between alkanones and di-t-butyl peroxide.[20] With less substituted ketones, such as

[7] H. Piotrowska, W. Wojnarowski, B. Waegell, and G. Ourisson, *Bull. Soc. chim. France*, 1965, 3511.
[8] K. A. Hill and P. L. Stotter, *J. Org. Chem.*, 1973, **38**, 2576.
[9] R. H. Reuss and A. Hassner, *J. Org. Chem.*, 1974, **39**, 1785.
[10] V. Calò and L. Lopez, *J.C.S. Chem. Comm.*, 1975, 212.
[11] E. S. Gould, 'Mechanism and Structure in Organic Chemistry,' Holt, Rinehart, and Winston, New York, 1959.
[12] R. P. Bell and K. Yates, *J. Chem. Soc.*, 1962, 1927.
[13] C. Rappe, *Acta Chem. Scand.*, 1968, **22**, 219, and references therein.
[14] J. E. Dubois and J. Toullec, *Tetrahedron Letters*, 1971, 3373.
[15] J. Toullec and J. E. Dubois, *Tetrahedron Letters*, 1971, 3377.
[16] R. A. Cox and J. Warkentin, *Canad. J. Chem.*, 1972, **50**, 3242.
[17] D. M. Camaioni, H. F. Walter, and D. W. Pratt, *J. Amer. Chem. Soc.*, 1973, **95**, 4057.
[18] C. Rappe and R. Kumar, *Arkiv Kemi*, 1965, **23**, 475.
[19] N. C. Deno and R. Fishbein, *J. Amer. Chem. Soc.*, 1973, **95**, 7445.
[20] A. G. Davies and B. Muggleton, *J.C.S. Perkin II*, 1976, 502.

butan-2-one or acetone, in the absence of an efficient stabilizing group attached to the radical centre, the bromination of epoxycyclohexane competes favourably with the halogenation of the ketone, and a mixture of

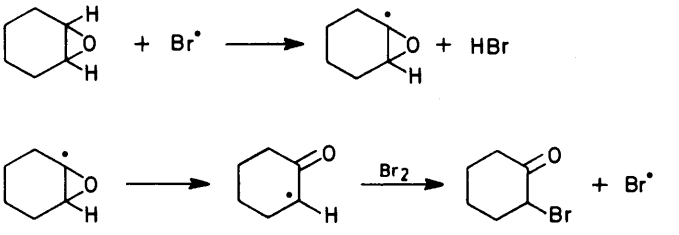
Bromination of ketones with and without added epoxycyclohexane in CCl_4 at 20 °C

Ketone	Brominated products (%)	
$ArCH_2{\cdot}CO{\cdot}CH_3$	$ArCHBr{\cdot}CO{\cdot}CH_3$	[100 (95) [a]]
	$ArCH_2COCH_2Br$	[0 (5)]
$ArCH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_3$	$ArCHBr{\cdot}CO{\cdot}CH_2{\cdot}CH_3$	[100 (60)]
	$ArCH_2{\cdot}CO{\cdot}CHBr{\cdot}CH_3$	[0 (40)]
$ArCH_2{\cdot}CO{\cdot}CHMe_2$	$ArCHBr{\cdot}CO{\cdot}CHMe_2$	[66 (23)]
	$ArCH_2{\cdot}CO{\cdot}CBrMe_2$	[34 (77)]
$CH_3{\cdot}CO{\cdot}CHMe_2$	$CH_3{\cdot}CO{\cdot}CBrMe_2$	[100 (90)]
	$CH_2Br{\cdot}CO{\cdot}CHMe_2$	[0 (10)]
$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_3$	$CH_3{\cdot}CO{\cdot}CHBr{\cdot}CH_3$	[*b* (87)]
	$CH_2Br{\cdot}CO{\cdot}CH_2{\cdot}CH_3$	[*b* (13)]
$Me_2CH{\cdot}CO{\cdot}CH_2Bu$	$Me_2CBr{\cdot}CO{\cdot}CH_2Bu$	[100 (77)]
	$Me_2CH{\cdot}CO{\cdot}CHBrBu$	[0 (23)]



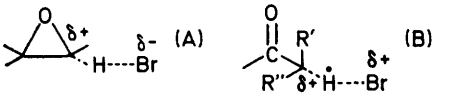
[a] Product distribution in parentheses refers to bromination in the dark and without added epoxide. [b] See text.

2-bromocyclohexanone, 2-bromocyclohexanol, and starting ketone is obtained. Although little is known [21] about the reactions between bromine and epoxides, there is some chemical and spectroscopic evidence for the existence and subsequent rearrangement of oxiranyl radicals.[22] Since in the dark there is no reaction between bromine and the epoxide under our reaction conditions, we suggest a free-radical process for ring fission of the epoxide (Scheme 3).†



SCHEME 3

We offer the following explanation for the preferential bromination of the epoxide relative to the less substituted ketones. It is known [23] that the bromine atom is less electrophilic and more selective than chlorine; thus with bromine the hydrogen abstraction step, which is rate-determining, occurs later along the reaction co-ordinate, *i.e.* involves a greater extent of bond breaking in the transition state, and hence would be susceptible to polar effects. If the transition states for the bromination of an epoxide and a ketone are delineated as (A) and (B),



respectively, then provided that R′ and R″ attached to the incipient radical centre α to the carbonyl group cannot stabilize effectively such a polar transition state, the epoxidic oxygen should be more efficient than the carbonyl group in stabilizing the positively polarized α-carbon atom. For this reason the epoxide should be brominated faster than the less substituted ketones. If R′ and/or R″ can stabilize the positively polarized α-carbon atom in the transition state, as happens with the more highly substituted ketones, bromination of the ketone will predominate. Similarly, the inhibition of ketone bromination when diethyl ether is the solvent is not unexpected if the conclusions drawn from competitive brominations of ketones in the presence of the epoxide are valid. In other words, the polar effect reponsible for the preferential free-radical hydrogen abstraction from the epoxide should operate also for acyclic ethers, allowing free-radical bromination of the solvent. Subsequent reaction between the epoxide and the halogen acid produced during bromination of the solvent yields the bromohydrin (Scheme 4). It is noteworthy that the bromination of ketones in diethyl ether but in the absence of epoxide occurs as usual to give a mixture of isomeric bromides.

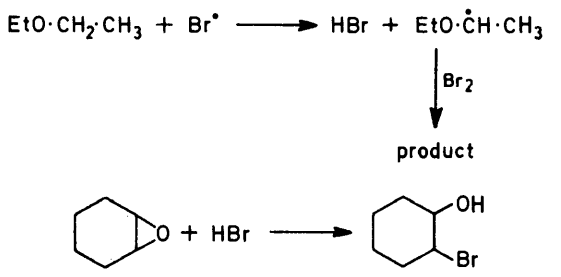
† Regioselectivity in the free-radical ring opening of epoxides by bromine is under investigation.

[21] M. M. Movsumzade, P. A. Gurbanov, A. L. Shabanov, and S. S. Berbutova, *Azerb. khim. Zhur.*, 1969, 58 (*Chem. Abs.*, 1969, **71**, 80771f).

[22] H. Itzel and H. Fisher, *Helv. Chim. Acta*, 1976, **59**, 880.

[23] For a discussion of the factors governing radical reactions see *e.g.* R. L. Huang, S. H. Goh, and S. H. Ong, 'The Chemistry of Free Radicals,' Arnold, London, 1974.

Our procedure for bromination of 5α- and 5β-pregnane-3,20-dione affords a simple * regioselective introduction of bromine in the 17-position, α to the 20-oxo-group, which is the more substituted α-position. However, besides the expected bromo-steroid and the bromocyclohexanol we isolated some 2-bromocyclohexanone



SCHEME 4

and starting ketone from the bromination of the 5β-epimer. Evidently in this case the bromination of the steroid and the free-radical reaction of the epoxide are competing reactions, notwithstanding the presence of a highly substituted position α to the 20-oxo-group. Probably steric effects are operating to retard abstraction of the 17-hydrogen atom.

EXPERIMENTAL

General Procedure for Bromination in the Presence of 1,2-Epoxycyclohexane.—(a) *In carbon tetrachloride.* Bromine and the ketone (each 0.06 mol) and epoxycyclohexane (0.1 mol) dissolved in carbon tetrachloride were irradiated at room temperature with a 100 W tungsten lamp for 0.5—2 h. The isomer composition was determined directly by g.l.c. of the reaction mixture (6 ft Silicone SE 30 on Chromosorb AW DMCS, 60—80 mesh). A calibration curve of peak height against composition was constructed by using mixtures of authentic brominated regioisomers prepared by known procedures. The isomer compositions from the brominations of benzyl isopropyl ketone and 2-methyloctan-3-one were determined by n.m.r. 1-Bromo-3-methyl-1-phenylbutan-2-one showed τ(CCl_4) 2.70 (m) 4.62 (s), 7.13 (q), 8.94 (s), and 9.00 (s). 3-Bromo-3-methyl-1-phenylbutan-2-one showed τ(CCl_4) 2.60—2.90 (m), 6.03 (s), and 8.21 (s). 2-Bromo-2-methyloctan-3-one showed τ(CCl_4) 5.83 (t), and 7.09 (q). 4-Bromo-2-methyloctan-3-one showed τ(CCl_4) 7.28 (t) and 8.20 (s). The total yields of bromo-ketones, isolated by preparative t.l.c. on silica gel (eluant hexane–ether, 5 : 2) were >90%, with traces of starting ketone and 2-bromocyclohexanol as by-products. Bromination of less substituted ketones (butan-2-one or acetone) under the same conditions yielded the starting ketone, 2-bromocyclohexanol, and 2-bromocyclohexanone.

The bromination of ketones in carbon tetrachloride without the epoxide was performed as above but in the dark. To avoid product equilibration due to the hydrobromic acid produced, immediately after the solution had become colourless solid sodium carbonate or epoxycyclohexane was added to neutralize the acid. The yields of bromo-ketones were in the range 70—85% with 5—15% of αα′-dibrominated products.

(b) *In diethyl ether.* The bromination of all the ketones tested, in ether with added epoxide as above, upon irradiation, yielded unchanged ketone and 2-bromocyclohexanol. Bromination [25] in the dark without the epoxide yielded in each case a mixture of brominated regioisomers whose composition differed from that obtained in carbon tetrachloride.

17-Bromo-5α-pregnane-3,20-dione.— 5α-Pregnane-3,20-dione (0.32 g), bromine (0.6 g, 1 mol. equiv.), and the epoxide (0.16 g, 1.5 mol. equiv.) were dissolved in carbon tetrachloride (50 ml), cooled (0 °C), and irradiated for 2 h as above. The solution was chromatographated (silica gel; ether–hexane–acetone, 1 : 1 : 0.04) and yielded the *bromo-derivative* (0.3 g, 75%), m.p. 161—164° (from ethanol) (Found: C, 63.65; H, 8.0; Br, 20.15. $C_{21}H_{31}BrO_2$ requires C, 63.8; H, 7.9; Br, 20.2%), τ(CCl_4) 7.64 (s, 21-H_3), 8.97 (s, 19-H_3), and 9.20 (s, 18-H_3).† Unchanged ketone, the bromohydrin, and a trace of unidentified material were the other products.

17-Bromo-5β-pregnane-3,20-dione.—Bromination of 5β-pregnane-3,20-dione under the same conditions yielded a *monobromo-product* (50%) m.p. 145—147° (from ethanol) (Found: C, 63.6; H, 7.9; Br, 19.55%), τ(CCl_4) 7.70 (s, 21-H_3), 8.97 (s, 19-H_3), and 9.24 (s, 18-H_3). Other products were the starting ketone, the bromohydrin, and 2-bromocyclohexanone.

Bromination of the two steroid ketones without the epoxide is very fast and yields a mixture of bromo-derivatives not containing the above bromo-steroids.

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* The usual bromination of these ketones under ionic conditions yields a complex mixture of bromo-ketones. Only recently, Breslow [24] has succeeded in functionalization of the steroid nucleus by using iodophenyl esters of 3-hydroxy-steroids.

† The 19-, 18-, and 21-H_3 n.m.r. signals for the starting 5β-ketone occur at τ(CCl_4) 9.00, 9.42, and 8.02, respectively. Though the bromination of the two steroids appears to be stereospecific, it was difficult to assign conclusively the 17α- or 17β-orientation to the bromine introduced (see ref. 2).

[24] B. B. Snider, R. J. Corcoran, and R. Breslow, *J. Amer. Chem. Soc.*, 1975, **97**, 6580.

[25] M. Gaudry and A. Marquet, *Bull. Soc. chim. France*, 1969, 4169.