An Easy Transformation of Ketones into α,α-Epoxymethylketones by Hydrogen Peroxide Oxidation of Mannich Base Derivates

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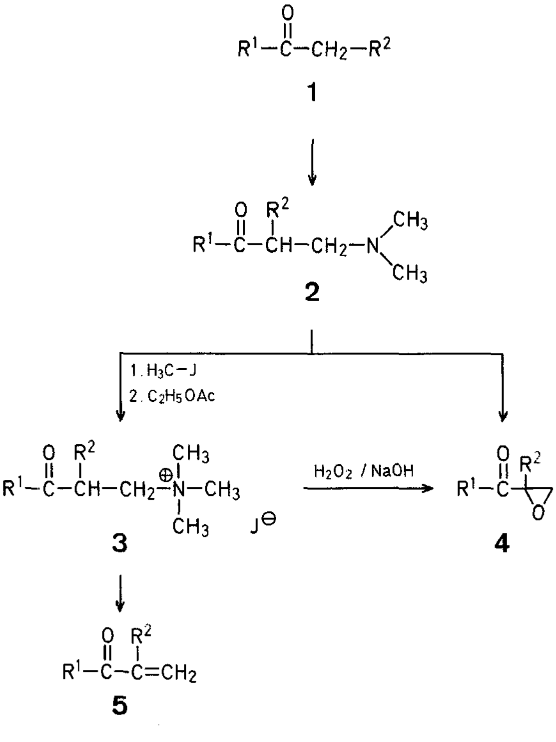
Although α-epoxyketones are usually prepared from conjugated enones[1], oxidation of α-methyleneketones is more complicated due to dimerisation, polymerisation[2], retro-aldolisation[3] and Baeyer-Villiger processes[4]. Such α-epoxyketones, when formed, can be further oxidized or rearranged[4-7] and, in most cases, can only be isolated in low yields. In other cases, the epoxidation of allylic alcohols followed by chromic acid oxidation has been preferred to the direct oxidation of the conjugated enones[8].

For another purpose, we needed various α-epoxyketones formally derived from α-methyleneketones and have investigated the oxidation[9] of Mannich bases or the corresponding ammonium salts with hydrogen peroxide in alkaline medium and we show here that this method, which does not require previous isolation of the α-methyleneketones **5**, is general and convenient for the transformation of ketones **1** into the corresponding α-epoxyketones **4**.



The Mannich bases **2**, easily prepared from the corresponding ketones[10], gave rise to the corresponding salts **3** on treatment with iodomethane. Whereas treatment of Mannich bases **2** by hydrogen peroxide/sodium hydroxide permitted isolation of epoxyketones **4** in only low yields together with unreacted starting material **2** (30 and 70% from **2b**, respectively), the direct oxidation of ammonium salts **3** dissolved in a mixture of methanol and water allowed isolation of epoxyketones **4** in good yields (Table).

The purity of the isolated epoxyketone was very sensitive to the conditions used for the reaction: especially to the pH of the solution and to the addition rate of ammonium salt **3** to the oxidant (see experimental); the temperature range also was critical: at low temperature, formation of enone **5** was favored, at high temperature, other competitive reactions took place. Furthermore, when **3b** was treated with hydrogen peroxide/sodium hydroxide in water, water/acetonitrile, or in a two-phase system (water/dichloromethane) instead of water/methanol, **5b** was isolated as the main product (72, 70, and more than 90%, respectively). When it was sufficiently stable (e.g. **5b** or **5g**), enone **5** was oxidized to the α-epoxyketone **4** in about the same yield and stereoselectivity as obtained when the starting material **3** was used. One could conclude that the main advantage of this epoxidation method is the production of a very reactive enone *in situ* in a concentration low enough to avoid polycondensation. However, under our experimental con-

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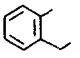
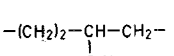
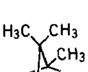
Table. 3-Oxoalkyltrimethylammonium Iodides 3 and α,α-Epoxymethylketones 4

Ketone 1			Ammonium Salt 3			Epoxyketone 4					
No.	R^1	R^2	Yield [%]	m.p. [°C][a]	Molecular formula[b] or Lit. m.p.	Oxidation temperature	Yield [%]	b.p. [°C]/torr or m.p. [°C]	Molecular formula[b]	^{1}H-N.M.R. (CCl_4) δ [ppm]	M.S. m/e (M^{+})
1a	C_2H_5	CH_3	63	149°/260°	155°/260°[12]	−10 to 0°C	72	65°/1	$C_6H_{10}O_2$ (114.1)	0.98 (t, 3H, $J=7$ Hz); 1.42 (s, 3H); 2.05–2.48 (2q, 2H, $J=7$ Hz); 2.71–2.88 (AB q, 2H, $J=5.5$ Hz)	114
1b	n-C_4H_9	n-C_3H_7	80	124°/255°	$C_{13}H_{28}JNO$ (341.3)	+10 to +20°C	74[c]	80°/0.3	$C_{10}H_{18}O_2$ (170.2)	0.8–1.7 (m, 14H); 2.1–2.4 (m, 2H); 2.75–2.83 (AB q, 2H, $J=5$ Hz)	170
1c	C_6H_5	CH_3	90	138°	158°[d,13]	− 5 to +5°C	65[c]	80°/0.1	$C_{10}H_{10}O_2$ (162.2)	1.60 (s, 3H); 2.78 (s, 2H); 8.1–7.3 (m, 5H_{arom})	162
1d			69	175° (dec)	$C_{13}H_{18}JNO$ (331.3)	−10 to 0°C	62	70–71°	$C_{10}H_8O_2$ (160.2)	3.15–3.38 (AB q, 2H, $J=7.5$ Hz); 3.46 (s, 2H); 7.9–7.1 (m, 4H_{arom})	160
1e	—$(CH_2)_4$—		61	154°/255°	136°/200°[14], 154°/258°[12]	−10 to 0°C	38	60°/1	[15]	1.6–2.6 (m, 8H); 2.53–2.85 (AB q, 2H, $J=6$ Hz)	126
1f	 $-(CH_2)_2-\underset{C_4H_9\text{-}t}{\underset{\vert}{CH}}-CH_2-$		68	166°/255°	$C_{14}H_{28}JNO$ (353.3)	−10 to 0°C	65[c]	oil[f]	$C_{11}H_{18}O_2$ (182.3)	0.93 (s, 9H); 1.2–2.6 (m, 7H); 2.51–3.21 (AB q, 2H, $J=5.5$ Hz)	182
1g			30[g]	242°	$C_{14}H_{26}JNO$ (351.3)	+10 to +20°C	60[h]	oil[f]	$C_{11}H_{16}O_2$ (180.3)	0.93, 0.98 (2s, 9H); 1.2–1.1 (m, 5H); 2.71–2.95, 2.90–3.01 (2 AB q, 4H, $J=6.5$ Hz)	180
1f	$C_6H_5CH_2$	C_6H_5	75	140°/260°	145°[16]	+20°C	75[i]	oil	—	2.81–3.08 (AB q, 2H, $J=5.5$ Hz); 3.68 (s, 2H); 7.5–7.2 (m, 10H_{arom})	238

[a] These salts are quite unstable as indicated by the reported melting points in the literature. Usually two melting points were described when measured on an oil bath. We are almost sure that the lower one corresponds to a decomposition (bubbles were observed) and the higher one corresponds to impure trimethylammonium iodohydrate (m.p. 263°C). When measured on a Kofler apparatus only the lower melting point was observed at higher temperature (2-15°C) which corresponds to decomposition of the salt. Furthermore the melting point is very sensitive to the rate of heating.

[b] The microanalysis for new compounds were in agreement with the calculated values: C ±0.26; H ±0.10; N ±0.10, except for **4e** C −0.4; **3f** C −0.5.

[c] Homogeneity checked by G.L.C. on two columns, 2% SE 30 and 30% OV 17 on WAWDMCS.

[d] m.p. for (+) isomer.

[e] Probably *trans* structure in agreement with the large value of δ for the AB system.

[f] Purified by chromatography on florisil.

[g] The conjugated enone which is particularly stable in this case can also be isolated in high yield (62%) from the Mannich condensation.

[h] *endo*/*exo* = 43/57.

[i] The best yields were obtained by using phase transfer conditions[11] with the enone. The epoxyketone which contained about 20% of unreacted enone was identical to an authentic sample prepared by chromic oxidation of the corresponding epoxyalcohol.

ditions or when using a phase-transfer system[11], we were unable to oxidise the very unstable α-methyleneketones such as **5e** or **5f**. It seems probable that the first step consists of a substitution of the ammonium group by the hydroperoxide anion to give the same hydroperoxi e intermediate as in the direct epoxidation of the enone.

3-Oxoalkyltrimethylammonium Iodides 3; General Procedure:

The Mannich bases **2**, prepared according to Ref.[10] are hydrolysed with 10% potassium carbonate solution and extracted with dichloromethane. The organic solution is dried with magnesium sulfate and iodomethane in excess is added. After 24h in the dark, the mixture is concentrated and compound **3** precipitated by addition of ethyl acetate. The ammonium salt is generally used without further purification; it can be crystallised, however, from a mixture of methanol/ethyl acetate.

α,α-Epoxymethylketones 4; Typical Procedure (0.001-0.1 mol Scale):

A solution of compound **3b** (17 g, 0.05 mol) in methanol/water (170 ml of each) is added over a period of 5 h to a vigorously stirred mixture of 1 molar sodium hydroxide in 1:1 methanol/water (100 ml) and 30% hydrogen peroxide (50 ml, 0.55 mol). The temperature is kept between 10 and 20°C. The mixture is then diluted with water (500 ml) and extracted with ether (4 × 200 ml). The organic layer is washed with saturated sodium chloride solution (4 × 100 ml) and dried with sodium sulfate. Elimination of the solvent affords **4b** (80%) with a purity higher than 90%. Compounds **4** can be distilled, crystallised, or chromatographed on florisil (eluent: dichloromethane/ether 99/1–90/10).

If the experiment is carried out at pH 9.2 (Borax buffer) instead of in the pH range 11–13, no compound **4b** is detected. If compound **3b** is added over a period of 1 h instead of 5 h, the yield of **4b** decreases to 60%.

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[1] L. F. Fieser, M. Fieser, *Reagents for Organic Synthesis*, Vol. I, John Wiley & Sons, New York, 1967, p. 466.

[2] Z. Y. Kyi, *Sci. Sin.* **4**, 297 (1955); *C. A.* **50**, 11347 (1956).
J. L. Gras, *Tetrahedron Lett.* **1978**, 2111.

[3] H. O. House, R. L. Wasson, *J. Org. Chem.* **22**, 1157 (1957).

[4] S. D. Levine, *J. Org. Chem.* **31**, 3189 (1966).
G. Le Guillanton, *Bull. Soc. Chim. Fr.* **1969**, 2781.
D. L. Koffen, D. G. Korzan, *J. Org. Chem.* **36**, 390 (1971).

[5] R. D. Temple, *J. Org. Chem.* **35**, 1275 (1970).

[6] Y. Ogata, Y. Sawaki, Y. Shimizu, *J. Org. Chem.* **43**, 1760 (1978).

[7] G. R. Treves, H. Stange, R. A. Olofson, *J. Am. Chem. Soc.* **89**, 6257 (1967).
W. Reusch, P. Mattison, *Tetrahedron* **23**, 1953 (1967).

[8] J. L. Pierre, *Ann. Chim. (Paris)* **1**, 159 (1966).

[9] J. W. Ager, F. W. Eastwood, R. Robinson, *Tetrahedron Suppl. no. 7*, **1966**, 277.
D. S. Schneider, F. W. Eastwood, *Aust. J. Chem.* **25**, 2185 (1972).

[10] Y. Jasor, M. Gaudry, M. J. Luche, A. Marquet, *Tetrahedron* **33**, 295 (1977).

[11] O. L. Chapman, T. C. Hess, *J. Org. Chem.* **44**, 962 (1979).

[12] A. N. Kost, V. V. Ershov, *Zh. Obshch. Khim.* **27**, 1722 (1957); *C. A.* **52**, 3782 (1958).

[13] A. F. Casy, J. L. Myers, *J. Chem. Soc.* **1964**, 4639.

[14] K. Dimroth, K. Resin, H. Zetzsch, *Ber. Dtsch. Chem. Ges.* **73**, 1399 (1940).

[15] P. Chautemps, J. L. Pierre, *Tetrahedron* **32**, 549 (1976).

[16] W. Wilson, Z. Y. Kyi, *J. Chem. Soc.* **1952**, 1321.

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