Preparation of Acetals of α-Epoxyketones and Their Chemoselective Hydrolysis Into α-Epoxyketones by Acidic Moist Silica Gel

Pascal Lescure, François Huet*

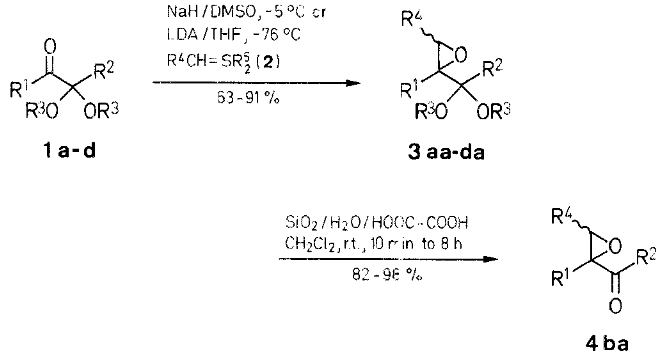
Laboratoire des Carbocycles, U.A. CNRS 478, Bâtiment 420, Université de Paris-Sud, F-91405 Orsay Cedex, France

Sulfur ylides react with monoacetals of α-dicarbonyl compounds to give the expected epoxyacetals in satisfactory to high yields. These lead to α-epoxyketones by chemoselective hydrolysis by acidic moist silica gel.

α-Epoxyketones, which are interesting intermediates in organic synthesis,[1] are usually prepared by epoxidation of α,β-unsaturated ketones;[2,3] however, especially in the case of α-methyleneketones, yields may be lowered by several unwanted reactions.[4] Other methods such as oxidation of α-epoxyalcohols,[5,6] reaction of α-halogenoketones with aldehydes in basic medium,[3] and peroxide oxidation of Mannich base derivates[4] are also used. On the other hand, the corresponding acetals are usually prepared by epoxidation of α,β-unsaturated acetals.[6,7]

As monoacetals of α-dicarbonyl compounds **1** are easily available,[8] we attempted to prepare epoxyacetals **3** by reaction of compounds **1** with sulfur ylides, which are useful reagents for the formation of epoxides from carbonyl compounds and do not react with acetals.[9] Reactions with an excess of ylide, necessitated by the low reactivity of compounds **1**, effectively gave epoxides **3** in satisfactory to high yield (Table 1).

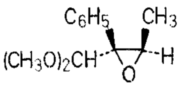
However, in reactions between α,α-dimethoxyacetophenone **1a** and diphenylsulfonium ethylide **2b** and between 2,2-dimethoxycyclopentanone **1d** and dimethylsulfonium methylide **2a**, yields were lowered with recovery of starting material. As expected,[9] reactions with ylide **2b** gave both geometric isomers, with low stereoselectivity; however it is worthy of note that each pure stereoisomer could be obtained by column chromatography.

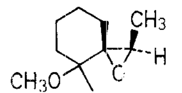


1	R^1	R^2	R^3
a	C_6H_5	H	CH_3
b	CH_3	C_2H_5	C_2H_5
c	$-(CH_2)_4-$		CH_3
d	$-(CH_2)_3-$		CH_3

2	R^4	R^5
a	H	CH_3
b	CH_3	C_6H_5

Stereochemical assignments were based either on those of the corresponding hydrolysis products [for **3cb** (*SR-RS*) and **3'cb** (*RR-SS*); see below] or on ^{1}H-NMR data (Table 1) [for **3ab** (*SR-RS*) and **3'ab** (*RR-SS*); in epoxides a phenyl group has a shielding effect towards a *cis* methyl group or a *cis* proton as observed in several cases and particularly in spectra of *cis*- and *trans*-2-methyl-3-phenyloxiranes[11]].


3ab (*SR-RS*)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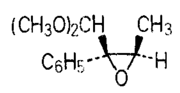
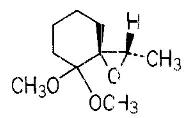

3'ab (*RR-SS*)


3'cb (*SS-RR*)

Compounds **3** bear two functions which are sensitive to acidic hydrolysis. Fortunately a treatment in mild conditions with acidic moist silica gel[10] afforded α-epoxyketones **4** in high yield (Table 2). Compounds **4cb** and **4'cb** were obtained diastereomerically pure from isolated acetals **3cb** and **3'cb**. Stereochemical assignments were based on ^{1}H-NMR spectra in the presence of $Eu(fod)_3$.[12] The a values in the linear area of $\delta = a[Eu(fod)_3]/[\text{Epoxyketone}]$ were determined for the methyl group and epoxidic protons. These values are 6.2 and 18.9, respectively, for **4cb** and 13.6 and 2.0 for **4'cb** (paramagnetic shifts are larger for the methyl group and epoxidic protons *cis* to the carbonyl group than for the *trans* ones).

Epoxyacetals 3aa, 3ca, 3da; General Procedure:

Sodium hydride (288 mg of 50% mineral oil dispersion, 6 mmol) is washed under nitrogen with (3 × 2 ml) by swirling, allowing the hydride to settle and decanting. After the last decantation, the remaining hexane is evaporated by a stream of nitrogen, and dry dimethyl sulfoxide (4 ml) is added. The mixture is stirred at 70–75 °C under nitrogen until the gas evolution ceases (ca. 30 min). After cooling to room temperature and addition of tetrahydrofuran (8 ml), the mixture is cooled to – 5 °C and a solution of trimethylsulfonium iodide (1.306 g, 6.4 mmol) in dimethyl sulfoxide (5.2 ml) is introduced over a period of 3 min. After 5 min stirring at – 5 °C neat α-ketoacetal **1** (4 mmol) is added dropwise at the same temperature. After 2 h at – 5 °C and 2 h at room temperature, water (36 ml) is added. Extraction with dichloromethane (3 × 20 ml)

Table 1. Reaction of α-Ketoacetals **1** With Ylides **2a** and **2b** to Give Epoxyacetals **3**

α-keto-acetals	Ylides	Epoxy-acetals	Yield[a] (%)	Molecular Formula[b]	IR (CCl_4)[c] (cm^{-1})	^{1}H-NMR (CCl_4/TMS)[d] δ (ppm)	MS[e] m/e (%)
1a	**2a**	**3aa**	84	$C_{11}H_{14}O_3$ (194.2)	1110, 1080, 1025	2.55 (d, 1H, J = 6.3 Hz); 3.01 (d, 1H, J = 6.3 Hz); 3.34 (s, 3H); 3.38 (s, 3H); 4.33 (s, 1H); 7.20–7.60 (m, 5H)	47 (33); 51 (20); 75 (100); 77 (23); 91 (24)
1a	**2b**	**3ab** and	63 (**3**/**3′** = 2)[f]	$C_{12}H_{16}O_3$ (208.3)	1120, 1090, 1080	0.92 (d, 3H, J = 5.4 Hz); 3.19 (q, 1H, J = 5.4 Hz); 3.29 (s, 3H); 3.34 (s, 3H); 4.14 (s, 1H); 7.30–7.60 (m, 5H)	47 (20); 75 (100); 77 (23)
		3′ab			1120, 1085	1.44 (d, 3H, J = 5.4 Hz); 2.75 (q, 1H, J = 5.4 Hz); 3.29 (s, 3H); 3.44 (s, 3H); 4.22 (s, 1H); 7.25–7.70 (m, 5H)	59 (37); 75 (100); 77 (24); 150 (31)
1b	**2a**	**3ba**	68	$C_{10}H_{20}O_3$ (188.3)	1155, 1075, 1050	0.82 (t, 3H, J = 7.2 Hz); 1.11 (t, 6H, J = 6.3 Hz); 1.24 (s, 3H); 1.63 (q, 1H, J = 7.2 Hz); 1.69 (q, 1H, J = 7.2 Hz); 2.18 (d, 1H, J = 7.2 Hz); 2.78 (d, 1H, J = 7.2 Hz); 3.35 (q, 2H, J = 6.3 Hz); 3.47 (q, 2H, J = 6.3 Hz)	43 (63); 57 (100); 75 (99); 103 (41); 131 (94); 143 (40)
1c	**2a**	**3ca**	84	$C_9H_{16}O_3$ (172.2)	1170, 1110, 1050	1.58 (m, 8H); 2.22 (d, 1H, J = 5.4 Hz); 2.83 (d, 1H, J = 5.4 Hz); 3.11 (s, 3H); 3.16 (s, 3H)	39 (58); 41 (73); 43 (50); 55 (82); 57 (45); 101 (100); 172 (M$^+$, 2.3)
1c	**2b**	**3cb** and	91 (**3**/**3′** = 2.1)	$C_{10}H_{18}O_3$ (186.3)	1105, 1050	1.20 (d, 3H, J = 5.4 Hz); 1.57 (m, 8H); 3.10 (s, 3H); 3.17 (s, 3H); 3.25 (q, 1H, J = 5.4 Hz)	55 (63); 59 (30); 98 (36); 101 (100); 114 (71); 186 (M$^+$, 3.6)
		3′cb			1105, 1055	1.49 (d, 3H, J = 5.4 Hz); 1.54 (m, 8H); 2.55 (q, 1H, J = 5.4 Hz); 3.16 (s, 3H); 3.19 (s, 3H)	41 (34); 55 (69); 59 (57); 98 (34); 101 (100); 114 (71); 186 (M$^+$, 0.6)
1d	**2a**	**3da**	61[g]	$C_8H_{14}O_3$ (158.2)	1145, 1095, 1070, 1050	1.79 (m, 6H); 2.45 (d, 1H, J = 6.3 Hz); 2.83 (d, 1H, J = 6.3 Hz); 3.15 (s, 3H); 3.23 (s, 3H)	39 (50); 41 (44); 42 (34); 43 (76); 55 (70); 71 (26); 101 (100)

[a] Isolation by column chromatography gave pure products (oils).
[b] Satisfactory microanalysis obtained C ±0.28, H ±0.23.
[c] Perkin-Elmer 682.
[d] Perkin-Elmer R 32 (90 MHz).
[e] Girdel-Nermag R 10-10 or GC/MS Hewlett-Packard 5992A.
[f] 73%, taking the recovered **1a** (14%) into account.
[g] 75%, taking the recovered **1d** (19%) into account.

Table 2. Hydrolysis of Epoxyacetals **3** into α-Epoxyketones **4**

Epoxy-acetals	Epoxy-ketones	Yield[a] (%)	Molecular Formula[b]	IR (CCl_4) (cm^{-1})	^{1}H-NMR (CCl_4/TMS) (ppm)	MS m/e (%)
3ba	**4ba**	85	$C_6H_{10}O_2$ (114.1)	1715	0.99 (t, 3H, J = 7.2 Hz); 1.44 (s, 3H); 2.23 (q, 2H, J = 7.2 Hz); 2.71 (d, 1H, J = 5.4 Hz); 2.85 (d, 1H, J = 5.4 Hz)	43 (29); 57 (100); 114 (M$^+$, 10)
3ca	**4ca**	82	$C_7H_{10}O_2$ (126.2)	1735	1.91 (m, 8H); 2.54 (d, 1H, J = 6.3 Hz); 2.93 (d, 1H, J = 6.3 Hz)	39 (62); 41 (100); 42 (92); 55 (82); 68 (60); 98 (46); 126 (M$^+$, 33)
3cb	**4cb**	98	$C_8H_{12}O_2$ (140.2)	1730	1.30 (d, 3H, J = 5.4 Hz); 1.87 (m, 6H); 2.30–2.60 (m, 2H); 3.07 (q, 1H, J = 5.4 Hz)	39 (84); 41 (99); 55 (100); 56 (78); 125 (82); 140 (M$^+$, 36)
3′cb	**4′cb**	87	$C_8H_{12}O_2$ (140.2)	1730	1.14 (d, 3H, J = 5.4 Hz); 1.50–2.70 (m, 8H); 2.89 (q, 1H, J = 5.4 Hz)	39 (85); 41 (91); 42 (54); 55 (100); 56 (70); 125 (62); 140 (M$^+$, 27)

[a] Yield in pure product (oil).
[b] Satisfactory microanalysis obtained C ±0.20, H ±0.27.

drying with magnesium sulfate and evaporation affords crude **3**, which is purified by column chromatography on silica gel (ether/pentane, 10:90) (Table 1).

4,5-Epoxy-4-methyl-3-pentanone Diethylacetal (3ba):

As the α-ketoacetal **1b** is less reactive than others, preparation of **3ba** requires slightly different conditions. A more concentrated solution is used (2 molar solution of sodium methylsulfinyl carbanion), introduction of solid trimethylsulfonium iodide, as well as an excess of reagents (10 mmol of sodium hydride and 10.4 mmol of trimethylsulfonium iodide for 4 mmol of **1b**) (Table 1).

Epoxyacetals 3ab, 3′ab, 3cb, 3′cb; General Procedure:

A solution of lithium diisopropylamide (4.5 mmol) is prepared by dropwise addition of diisopropylamine (0.470 g, 4.65 mmol) to a stirred solution of *n*-butyllithium (a 2.0 molar solution in hexane; 2.25 ml, 4.5 mmol) in tetrahydrofuran (10 ml), at −5 °C, under nitrogen. After 15 min, the mixture is cooled to −76 °C and a slurry of ethyldiphenylsulfonium tetrafluoroborate (1.450 g, 4.80 mmol) in tetrahydrofuran (40 ml) is added. After 45 min a solution of α-ketoacetal **1** (3 mmol) in tetrahydrofuran (1 ml) is added dropwise. After 1.5 h the reaction mixture is poured into water (40 ml). Extraction with dichloromethane (5 × 40 ml), drying with magnesium sulfate and evaporation of the solvents affords crude **3**. Column chromatography on silica gel (ether/pentane, 10:90) gives the individual pure geometric isomers.

Hydrolysis of Epoxyacetals 3 to Epoxyketones 4; General Procedure: Silica gel (Merck 60, 0.063–0.200 mm, 2 g) is stirred (ca. 2 min) with dichloromethane (4 ml) and 10% aqueous oxalic acid solution (0.2 g). Epoxyacetal **3** (1 mmol) is added, and the reaction mixture is stirred for 25 min for **3ba**, 8 h for **3ca**, 1.5 h for **3cb** or 10 min for **3'cb**. The solid phase is separated by suction filtration on a sintered glass funnel, and the solid is washed several times with dichloromethane. Evaporation of the solvent gives the epoxyketone **4** (Table 2).

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