Reactions of Lithiated Pyruvaldehyde Acetals with Oxiranes; Part II

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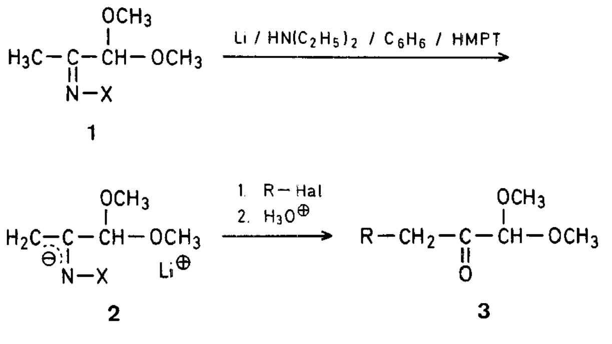
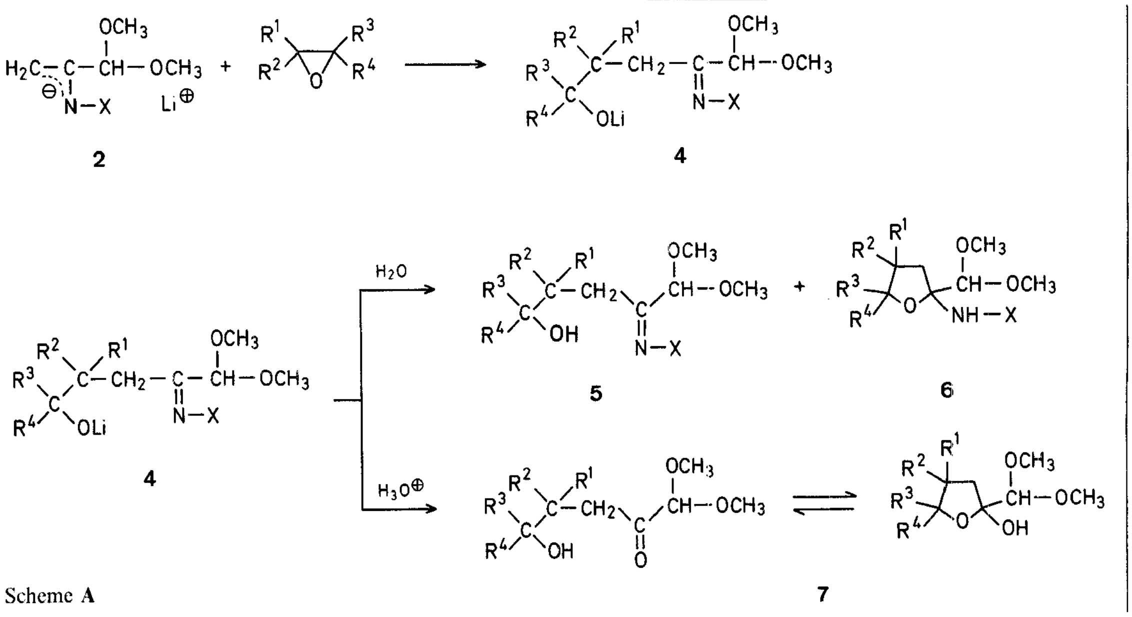
We have recently shown that the imines and hydrazones derived from the pyruvaldehyde dimethyl acetal (**1**) are easily metallated at −65° by using very powerful bases i.e. the activated lithium dialkylamides generated *in situ* from lithium and a secondary amine in benzene/hexamethylphosphoric triamide medium[1].



The alkylation of **2** followed by acid hydrolysis leads to the pyruvaldehyde homologues **3** in good yields.

δ-Hydroxy-keto-aldehydes **7** should be obtained in a simple and rapid route from the condensation reaction of epoxides with the anions of **2** (Scheme A).



Scheme A

In fact, epoxides react easily with the anions of **2** but, in contrast with the alkylations which occur at −50°, the opening of the epoxide ring occurs only at higher temperatures. An active compound such as ethylene oxide reacts at −30° and the most stable epoxide i.e. cyclohexane oxide is opened at −10°. The ring opening of the 2,3-epoxybutane is more difficult and the yields are never better than 51 %, even on addition of lithium bromide. When unsymmetric epoxides are reacted, the attack always takes place on the less hindered carbon atom.

Neutral hydrolysis of **4** yields **5** and also the tetrahydrofuran **6**. The imines and hydrazones react to give different ratios of **5** and **6**. Our main results concerning the metallated imines **2** (X = cyclohexyl) are listed in Table 1.

Neutral hydrolysis of the metallated imine **4** gives exclusively the 2-aminotetrahydrofuran **6**. A small quantity of **5** arises from the reaction with ethylene oxide. In the reaction with cyclohexene oxide the formation of **5**, after addition of lithium bromide, does not exceed 10%. Conventional lithium dialkylamide (butyllithium and diethylamine in ether/tetrahydrofuran medium) does not give significantly different results.

Homologues of pyruvaldehyde dimethyl acetal react in the same way since the reaction of the metallated imine **8** with propylene oxide leads exclusively to **9**.

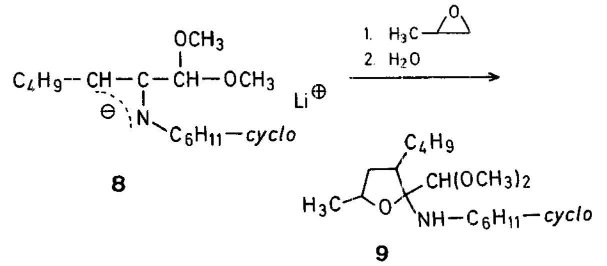


Table 2 contains the data concerning hydrazones, and the following comments should be noted.

(a) Neutral hydrolysis of the metallated hydrazones **4** yields a mixture of **5** and **6**. Addition of lithium bromide to the reaction mixture or substitution of conventional lithium dialkylamide in a mixture of diethyl ether/tetrahydrofuran for the activated amide does not affect the ratios of **5** and **6**.

(b) The reactions with the cyclohexene oxide are noteworthy: thus, neutral hydrolysis of the imine **4** only gives the cyclic form **6**, while neutral hydrolysis of the hydrazone **4** yields the open form **5** in a nearly pure state.

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Table 1. Preparation of Compounds **5** and **6** ($R^1 = H$, X = cyclohexyl), Scheme A

Entry	Product R^2	R^3	R^4	Reaction temperature	Yield [%]	b.p./torr of **5**+**6**	Composition [%][a] of **5**	of **6**	Molecular formula[b]
1	H	H	H	−30°	73	98°/0.3	10–15	85–90	$C_{13}H_{25}NO_3$ (243.3)
2	H	H	CH_3	−30°	79	105°/0.3	0	100	$C_{14}H_{27}NO_3$ (257.4)
3	H	H	C_2H_5	−30°	75	105°/0.1	0	100	$C_{15}H_{29}NO_3$ (271.4)
4	H	H	C_2H_5	−20°	85	120°/0.8	0	100[c]	$C_{15}H_{29}NO_3$ (271.4)
5	H	CH_3	CH_3	−30°	70	90°/0.1	0	100	$C_{15}H_{29}NO_3$ (271.4)
6	CH_3	H	CH_3	−10°	51	105°/0.1	0	100	$C_{15}H_{29}NO_3$ (271.4)
7	$-(CH_2)_4-$		H	−10°	86	135°/0.05	10	90[d]	$C_{17}H_{31}NO_3$ (297.4)
8	$-(CH_2)_4-$		H	−10°	84	150°/0.5	0	100	$C_{17}H_{31}NO_3$ (297.4)
9	H	H	C_6H_5	−30°	68	150°/0.1	0	100	$C_{19}H_{29}NO_3$ (319.4)

[a] Determined by N.M.R.

[b] All products gave satisfactory microanalyses (C ± 0.27%, H ± 0.28%, N ± 0.25%).

[c] Normal dialkylamide, not activated form.

[d] In the presence of lithium bromide.

Table 2. Preparation of Compounds **5** and **6** [$R^1 = H$, $X = N(CH_3)_2$], Scheme A

Entry	Product R^2	R^3	R^4	Reaction temperature	Yield [%]	b.p./torr of **5**+**6**	Composition [%][a] of **5**	of **6**	Molecular formula[b]
10	H	H	CH_3	−30°	71	108°/18	50–55	45–50	$C_{10}H_{22}N_2O_3$ (218.3)
11	H	CH_3	CH_3	−20°	74	110°/15	15–20	80–85	$C_{11}H_{24}N_2O_3$ (232.3)
12	H	CH_3	CH_3	−15°	69	76°/0.5	5–10	90–95[c]	$C_{11}H_{24}N_2O_3$ (232.2)
13	$-(CH_2)_4-$		H	−10°	78	103°/0.2	95	5	$C_{13}H_{26}N_2O_3$ (258.4)
14	$-(CH_2)_4-$		H	−10°	75	110°/0.5	95	5[d]	$C_{13}H_{26}N_2O_3$ (258.4)
15	H	H	C_6H_5	−30°	73	132°/0.5	40–45	55–60	$C_{15}H_{24}N_2O_3$ (280.4)

[a] Determined by N.M.R.

[b] All products gave satisfactory microanalyses (C ± 0.27%, H ± 0.28%, N ± 0.25%).

[c] Normal dialkylamide, not activated form.

[d] In the presence of lithium bromide.

Table 3. Preparation of Compounds **7** ($R^1 = H$)

Entry	Starting material	R^2	R^3	R^4	Hydrolysis reagent	Yield [%]	b.p./torr	Composition [%][a] linear	cyclic	Molecular formula[b]
16	**4** (X = *cyclo*-C_6H_{11})	$-(CH_2)_4-$		H	tartaric acid	71	112°/0.2	40	60	$C_{11}H_{20}O_4$ (216.3)
17	**6** (X = *cyclo*-C_6H_{11})	$-(CH_2)_4-$		H	tartaric acid	100	112°/0.2	40	60	$C_{11}H_{20}O_4$ (216.3)
18	**5** [$X = N(CH_3)_2$]	$-(CH_2)_4-$		H	hydrochloric acid	100	112°/0.2	40	60	$C_{11}H_{20}O_4$ (216.3)
19	**6** (X = *cyclo*-C_6H_{11})	H	H	C_6H_5	tartaric acid	92	123°/0.2	0	100	$C_{13}H_{18}O_4$ (238.3)

[a] Determined by N.M.R.

[b] All products gave satisfactory microanalysis (C ± 0.27%, H ± 0.28%, N ± 0.25%).

(c) Acid hydrolysis of **4** yields **7**. This hydrolysis is carried out at 0° with tartaric or hydrochloric acid solution. Compounds **5** and **6** give **7** quantitatively in acid medium. The amino tetrahydrofuran **6** (entry 8) and the open-chain hydrazone **5** (entry 13) both derived from cyclohexene oxide give the same δ-hydroxyaldehyde **7** (entries 17 or 18); on the other hand, **6** (entry 9) obtained with styrene oxide gives the cyclic compound **7** (entry 19) in acid medium (Table 3).

(d) The composition assigned to the mixtures (**5**+**6** and open chain **7**+cyclic **7**) was determined essentially by ^1H- and ^{13}C-N.M.R.

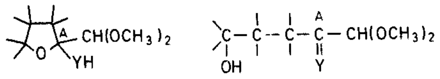
The typical ranges of chemical shifts are listed in Table 4. Overlapping of the lines in ^1H-N.M.R. spectra renders the integration difficult. The ratios of the mixture are therefore obtained with the aid of the ^{13}C-N.M.R. spectra recorded in the noise decoupled mode, with addition of a relaxation reagent $Cr(acac)_3$. In these conditions the heights of the lines are a good approximation for the signal intensities and the proportions of compounds may be evaluated. Moreover, the comparison of the ratios in the same spectrum gives comparable results.

^1H- and ^{13}C-N.M.R. spectra were recorded with a Varian XL 100-12 spectrometer fitted with 620 F computer using approximately 30% $CDCl_3$ solutions. The chemical shifts were measured at 303 K and referred to internal TMS. Acquisition times; ^1H: 4 s, ^{13}C: 0.8 s.

Preparation and Reaction of Activated Lithium Diethylamide with Hydrazones or Imines 1; Preparations of Compounds 5, 6, and 9: A mixture of diethylamine (4.05 g, 0.055 mol), hexamethylphosphoric triamide (12 ml), anhydrous benzene (11 ml), and hammer-wrought lithium (0.39 g, 0.055 mol) is stirred under nitrogen until the metal has completely dissolved. The temperature is maintained at 20° and dry tetrahydrofuran (15 ml) is added to the dark red solution. The solution is then cooled to −60° and the hydrazone or imine (**1**; 0.05 mol) in dry tetrahydrofuran (15 ml) is added slowly. The mixture is allowed to stand for 1 h at −60° to −50°, and then a solution of the epoxide (0.05 mol) in dry tetrahydrofuran

Table 4. ^{1}H- and ^{13}C-N.M.R. Data for Compounds **5**, **6**, **7**, and **9**

Compound	^{1}H-N.M.R. δ [ppm]	^{13}C-N.M.R. δ [ppm]
5 (X = cyclohexyl) entries 1–9	3.32 (H_3CO); 4.37–4.44 (—O—$\overset{\vert}{\mathrm{C}}$H—O)	165.3 [C(A)][a]; 109.5–109.1 (O—$\overset{\vert}{\mathrm{C}}$H—O); 58.6–58.5 (C-1, cyclohexyl); 54.6 (H_3CO)
6 (X = cyclohexyl) entries 1–9	3.40–3.45 (H_3CO); 4.10–4.27 (O—$\overset{\vert}{\mathrm{C}}$H—O)	107.5–107.2 (O—$\overset{\vert}{\mathrm{C}}$H—O); 98.8–97.3 [C(A)][a]; 56.5–56.0 (H_3CO); 50.1–49.7 (C-1, cyclohexyl)
5 [X = $N(CH_3)_2$] entries 10–15	4.48–4.40 (O—$\overset{\vert}{\mathrm{C}}$H—O); 3.32–3.30 ($H_3CO$); 2.44–2.42 [$N(CH_3)_2$]	167.2–166.7 [C(A)][a]; 108.4–107.1 (O—$\overset{\vert}{\mathrm{C}}$H—O); 54.7–54.6 ($H_3CO$); 48.0–46.9 [$N(CH_3)_2$]
6 [X = $N(CH_3)_2$] entries 10–15	4.17–4.16 (O—$\overset{\vert}{\mathrm{C}}$H—O); 3.42–3.34 ($H_3CO$); 2.40 [$N(CH_3)_2$]	106.6–106.0 (O—$\overset{\vert}{\mathrm{C}}$H—O); 100.7–99.0 [C(A)][a]; 55.7–55.2 (H_3CO); 50.5–50.3 [$N(CH_3)_2$]
7 (linear) entries 16–19	4.51 (O—$\overset{\vert}{\mathrm{C}}$H—O); 3.38 ($H_3CO$)	205.8 [C(A)][a]; 107.5–104.1 (O—$\overset{\vert}{\mathrm{C}}$H—O); 54.6 ($H_3CO$)
7 (cyclic) entries 16–19	4.32–4.13 (O—$\overset{\vert}{\mathrm{C}}$H—O); 3.50–3.44 ($H_3CO$)	107.5–104.1 (O—$\overset{\vert}{\mathrm{C}}$H—O); 85.0–83.2 [C(A)][a]; 56.8–55.8 (H_3CO)
9	4.13–4.03 (O—$\overset{\vert}{\mathrm{C}}$H—O); 3.46–3.34 ($H_3CO$)	108.2–103.8 (O—$\overset{\vert}{\mathrm{C}}$H—O); 97.9–97.7 [C(A)][a]; 58.1–55.3 (H_3CO); 50.7–49.0 (C-1, cyclohexyl)

[a]


Y = N—C_6H_{11}—*cyclo*, N—$N(CH_3)_2$, O

(70 ml) is added dropwise at the temperature given in Tables 1 and 2. The solution is then allowed to warm to room temperature and stirring is continued for 5–6 h. The reaction mixture is hydrolysed with cold water and extracted with ether. The ether layer is dried ($MgSO_4$), the solvent is removed under reduced pressure, and the residue is distilled.

For compound **9** a reaction temperature of −20° is used; yield: 66%; b.p. 120°/0.05 torr.

Preparation of Compounds 7 from 5 or 6:

Compound **5** or **6** in dry tetrahydrofuran (15 ml) is shaken for 2 min with 2 normal hydrochloric acid (10 ml) or for 5 h at 0° with tartaric acid (8 g in 50 g water). The solution is then extracted with ether, the organic layer is neutralised with sodium hydrogen carbonate, washed with water, and dried ($MgSO_4$). The solvent is removed under reduced pressure and the residue distilled (Table 3).

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** Laboratoires associés au C.N.R.S.

[1] T. Cuvigny, H. Normant, *Synthesis* **1977**, 198.

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