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An Efficient Procedure to α-Hydroxyaldehyde Dimethyl Acetals

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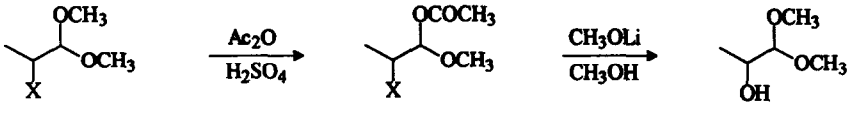
Abstract: *α-Hydroxyaldehyde dimethyl acetals are prepared efficiently by conversion of α-haloaldehyde dimethyl acetals into α-haloaldehyde hemiacetal acetates and subsequent methanolysis promoted by lithium methoxide.*

INTRODUCTION

α-Hydroxyaldehyde dimethyl acetals are utilized for the preparation of 2-keto acetals[1] and δ-dicarbonyl compounds,[2] and also as precursors of α-hydroxy aldehydes.[3,4] They are obtained by alcoholysis of the addition products of phenylsulfonyl methyl ether with carbonyl compounds,[5] by reaction of Grignard reagent on protected glyoxals,[6] by enol ether epoxydation in alcoholic solvents[7] and, more generally, by treating α-haloaldehydes with sodium methoxide in methanol.[8]

Recently we developed efficient methods to α-chloro-[9] and α-bromo-aldehyde dimethyl acetals,[10] and their conversion into α-hydroxyaldehyde dimethyl acetals appeared an appealing procedure. Despite the theoretical simplicity of the nucleophilic substitution of the α-halide atom by an hydroxyl anion, the reaction is virtually hindered by the two electron withdrawing methoxyl groups;[11] by reaction with potash[12] α-haloaldehyde dimethyl acetals indeed afford only small amounts of elimination products. The alternative route through the α-halo acetals deprotection is subjected to a difficult hydrolysis process[13] and also to unsatisfactory yields of the sodium methoxide attack on α-haloaldehydes.[8]

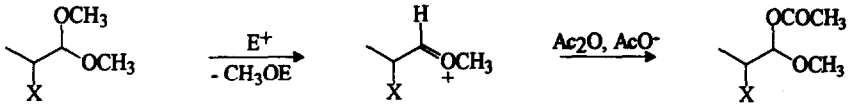
Now we report that α-hydroxyaldehyde dimethyl acetals are very easily prepared by transformation of α-haloaldehyde dimethyl acetals into the corresponding hemiacetal acetates and subsequent methanolysis promoted by lithium methoxide (Scheme 1). As far as we know, the only reported example of a comparable route is a poor yield conversion of 1-acetoxy-2-bromo-1-methoxyethane into 2-hydroxyethanal dimethylacetal by sodium methoxide in methanol.[14]



Scheme 1

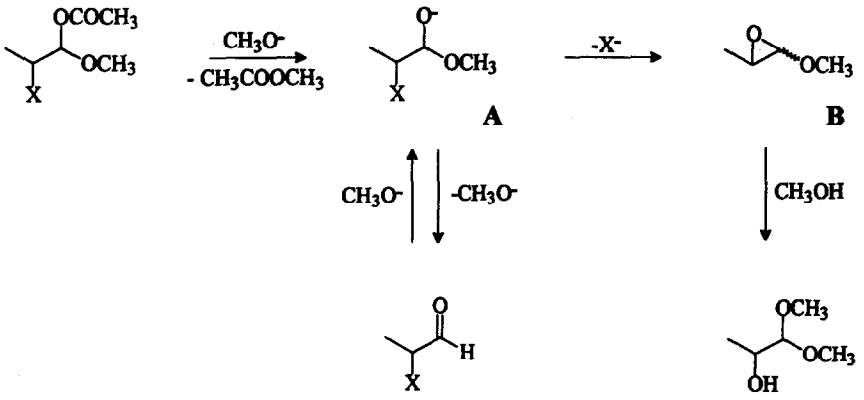
RESULTS AND DISCUSSION

The high yields (92-98%) preparation of α-haloaldehyde hemiacetal acetates was smoothly accomplished on treating α-halo acetals with catalytic amount of H_2SO_4 in acetic anhydride (Ac_2O). This is a well known reaction[15] that, as usually observed in acid catalysed reactions of acetals and outlined in Scheme 2 (the catalyst is here represented as E^+ since several electrophilic species are present in a Ac_2O solution of strong acids[15b]), involves an α-alkoxy-carbenium ion intermediate. Besides to be more easy than the acetal hydrolysis, this modification of protective group avoids handling of the irritant, bad smelling and unstable α-halo aldehydes.



Scheme 2

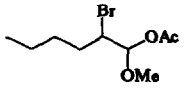
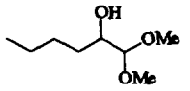
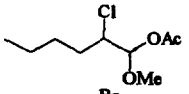
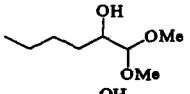
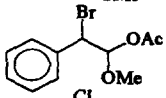
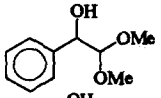
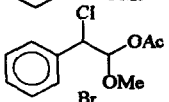
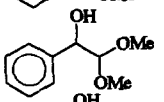
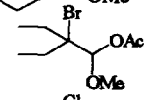
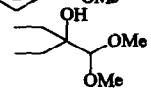
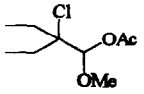
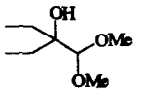
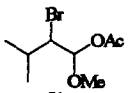
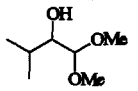
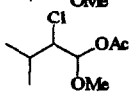
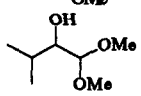
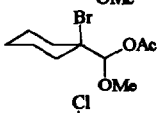
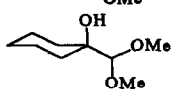
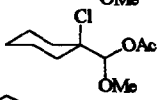
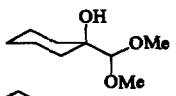
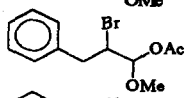
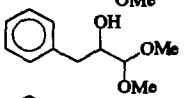
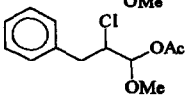
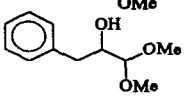
As expected, [16] hemiacetal acetates are promptly deprotected by methoxide anion, and the intermediate **A** should be transformed into the α-hydroxyaldehyde dimethyl acetals through the formation of an intermediate epoxyether **B**, according to a commonly accepted mechanism (Scheme 3).[8]



Scheme 3

Preliminary tests on 1-acetoxy-2-bromo-1-methoxyhexane showed that lithium methoxide was much better than the sodium salt, and that dilution was a critical parameter, since working with concentrations higher than those reported in the Experimental part, afforded significantly lower yields. It was also verified that a quick addition of α-bromo hemiacetal acetates to the methoxide solution at room temperature gave the best results, whereas the corresponding chlorinated substrates needed to be slowly dropped into the methoxide solution thermostatted at 55 °C. The two optimized procedures were tested on a number of α-haloaldehyde hemiacetal acetates obtaining very satisfactory conversions starting both from α-bromo- and from α-chloro-

Table : Preparation of α-Hydroxyaldehyde Dimethyl Acetals

Substrate	Product	Yield[a] (%)	Yield[b] (%)	Time (min)
		98 (96)[c]	96	45
		97 (97)[c]	94	40
		81	79	120
		79	77	120
		17	8	60
		77	73	60
		89	89	240
		95	94	45
		96	87	60
		99	96	60
		98	93	120
		98	97	60

a) Starting from 5 mmoles of substrate. b) Starting from 50 mmoles of substrate.
c) In parenthesis the yields starting from the parent α-haloaldheydes.

substrates; the same procedure was also applied to a larger scale preparation with only a little yields lowering (Table).

As reported in Scheme 3, the formation of the epoxyether **B** could involve a rapid equilibrium between intermediate **A** and the free α-haloaldehyde. To verify this equilibrium, we performed the acylal conversion in methanol-d_4. If the free aldheyde is not formed, only one labelled methoxyl group should have been detected in the recovered α-hydroxyaldehyde dimethyl acetal. An almost complete statistical distribution of methoxyl-d_3 in the acetal group was instead observed (see Experimental Section); the little difference from the theoretical value is due to the electron withdrawing effect of the α-halogen atom which stabilizes the tetrahedral intermediate **A**[17] and facilitates the formation of the epoxyether **B**; in agreement, the difference between the observed and theoretical values was higher for the α-chloro than for the α-bromo-derivative.

A free carbonyl intermediate is also supported by the identical yields obtained in the reaction of α-bromo- and α-chloro-hexanal with lithium methoxide in methanol (Table). This result also shows that the procedure can be effectively applied to α-haloaldehydes, providing better yields in α-hydroxyaldehyde dimethyl acetals than those usually obtained by their treatment with sodium methoxide in methanol.[8]

EXPERIMENTAL PART

^{1}H NMR spectra were recorded on a Bruker WP80 spectrometer. Mass spectra were obtained on a HP 5989A MS Engine. Reagents and solvents were standard grade commercial products and used without further purification. The α-haloacetals were prepared according to known procedures.[9,10]

General procedure for the preparation of α-haloaldehyde hemiacetal acetates. To a stirred solution of α-haloaldehyde dimethylacetal (50 mmoles) in acetic anhydride (130 mmoles), 96% H_2SO_4 (5 μl) was added. The reaction mixture, kept at room temperature, was monitored by GC and after 24-48 hours diluted with petroleum ether (b.p. 30-50°C) (50 ml). The organic phase was washed with water (3 x 30 ml), dried over Na_2CO_3 and evaporated; residual acetic anhydride was eliminated by a stream of nitrogen under reduced pressure (0.1 mmHg). The crude product was clean enough to be used without further purification.

Special case.- With 1-acetoxy-2-bromo-1-methoxy-3-methylbuthane the amount of 96% H_2SO_4 was 3.75 μl.

General procedures for the preparation of α-hydroxyaldehyde dimethyl acetals. *a) from α-bromoaldehyde hemiacetal acetates.* In a 25 ml round bottom flask, $LiOCH_3$ was prepared by cautious addition of LiH (5.1 mmol) to CH_3OH (4.2 ml). When sparkling stopped, the mixture was thermostatted at 20°C and the α-bromoaldehyde hemiacetal acetate (5 mmoles) was added all at once to the vigorously stirred solution. The reaction mixture was monitored by GC analysis and after full conversion diluted with water (20 ml) and extracted with $CHCl_3$ (2 x 10 ml). The organic phases were collected, dried over Na_2CO_3 and evaporated. The crude α-hydroxyaldehyde dimethyl acetal was purified by chromatography on silica gel, using a petroleum ether (b.p. 30-50°C) / diethyl ether gradient as eluent.[18]

b) from α-chloroaldehyde hemiacetal acetates. In a two-necked 25 ml round bottom flask, fitted with a condenser and a dropping funnel, a solution of $LiOCH_3$ (5.1 mmol) in CH_3OH (3.2 ml) was carefully prepared. The mixture was thermostatted at 54°C and a solution of α-chloroaldehyde hemiacetal acetate (5 mmoles) in CH_3OH (1 ml) was slowly dropped in. After complete conversion (GC monitoring) the reaction mixture was worked up as described above.

2-hydroxy-2-ethylbutanal dimethyl acetal

B.p.: 33-35°C / 0.1 mmHg.

^{1}H NMR (δ, $CDCl_3$): 0.70-1.05 (6H, m, 2 x CH_3-C); 1.35-1.65 (4H, m, 2 x C-CH_2); 3.50 (6H, s, 2 x -OCH_3); 4.10 (1H, s, -C<u>H</u>(OCH_3)$_2$).

IR (neat): 3520 (OH) cm^{-1}. MS (EI, 70 eV) *m/z*: 75 (100).

Found: C, 59.3; H, 11.2%. $C_8H_{18}O_3$ requires C, 59.23; H, 11.18%.

2-hydroxy-3-methylbutanal dimethyl acetal

B.p.: 70-72°C / 16 mmHg.

^{1}H NMR ($CDCl_3$): 0.90 (6H, d, 2 x -CH_3); 1.00 (6H, d, 2 x -CH_3); 1.60-2.10 (1H, m, -C<u>H</u>(CH_3)$_2$); 3.30-3.55 (1H, m, -C<u>H</u>-OH); 3.40 (6H, s, 2 x -OCH_3); 3.44 (6H, s, 2 x -OCH_3); 4.22 (1H, d, -C<u>H</u>(OCH_3)$_2$).

IR (neat): 3500 (OH) cm^{-1}. MS (EI, 70 eV) *m/z*: 75 (100).

Found: C, 56.7; H, 10.9%. $C_7H_{16}O_3$ requires C, 56.73; H, 10.88%.

1-hydroxycyclohexancarboxaldehyde dimethyl acetal

B.p.: 54-56°C / 0.15 mmHg.

^{1}H NMR ($CDCl_3$): 1.30-1.85 (10H, m, -C_6H_{10}); 3.50 (6H, s, 2 x -OCH_3); 3.95 (1H, s, -C<u>H</u>(OCH_3)$_2$).

IR (neat): 3490 (OH) cm^{-1}. MS (EI, 70 eV) *m/z*: 75 (100).

Found: C, 62.0; H, 10.5%. $C_9H_{18}O_3$ requires C, 62.04; H, 10.41%.

2-hydroxy-3-phenylpropanal dimethyl acetal

B.p: 92-94°C / 0.2 mmHg.

^{1}H NMR ($CDCl_3$): 2.85 (2H, m, Ph-CH_2-); 3.47 (6H, s, 2 x -OCH_3); 3.49 (6H, s, 2 x -OCH_3); 3.70-4.05 (1H, m, -C<u>H</u>-OH); 4.15 (1H, d, -C<u>H</u>(OCH_3)$_2$); 7.28 (5H, m, C_6H_5).

IR (neat): 3480 (OH) cm^{-1}. MS (EI, 70 eV) *m/z*: 75 (100).Found: C, 67.4; H, 8.3%. $C_{11}H_{16}O_3$ requires C, 67.32; H, 8.22%.

Preparation of d-labelled α-hydroxyhexanal dimethyl acetal. The reactions for both 1-acetoxy-2-bromo-1-methoxyhexane and the corresponding 2-chloro-derivative were performed in CD_3OLi-CD_3OD following the above described procedure. The isolated products were analyzed in GC-MS. The relative percentages of peaks m/z 81 [$(CD_3O)_2CH^+$] and m/z 78 [$(CH_3O)(CD_3O)CH^+$] for α-hydroxyhexanal dimethyl acetal from 1-acetoxy-2-bromo-1-methoxyhexane were 89.5 and 10.5% against the statistical values of 90.8 and 9.2%; the corresponding percentages for the acetal from the 1-acetoxy-2-chloro-1-methoxyhexane were 87.6 and 12.4%.

Preparation of α-hydroxyhexanal dimethyl acetal from 2-halohexanal. *a) from α-bromohexanal.* The substrate (5 mmoles) was added all at once to a $LiOCH_3$ (5.1 mmol) solution in CH_3OH (4.2 ml). The reaction mixture was monitored by GC and worked up as described above.

b) from α-chlorohexanal. The substrate (5 mmoles) was slowly dropped to a $LiOCH_3$ (5.1 mmol) solution in CH_3OH (4.2 ml) thermostatted at 54°C. After complete conversion (GC monitoring) the reaction mixture was worked up as described above.

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REFERENCES AND NOTES

1. Huet, F.; Lechevallier, A.; Conia, J. M. *Synth. Commun.*, **1980**, 83-87.
2. Poirier, J. M.; Hennequin, L.; Fomani, M. *Bull. Soc. Chim. Fr.*, **1985**, 436-448.
3. Kirrmann, A.; Druesne, F. *Compt. Rend.*, **1964**, 259, 3285-3287.
4. Avy, A. *Bull. Soc. Chim. Fr.*, **1931**, 12-18.
5. Mandai, T.; Hara, K.; Nakajima, T.; Kawada, M.; Otera, J. *Tetrahedron Lett.*, **1983**, 24, 4993-4996. See also: Ogura, K.; Tsuchihashi, G. *Tetrahedron Lett.*, **1972**, 2681-2684.
6. Thiam, M.; Chastrette, F. *Bull. Soc. Chim. Fr.*, **1992**, 161-167. Maglioli, P.; De Lucchi, O.; Delogu, G.; Valle, G. *Tetrahedron: Asimmetry*, **1992**, 3, 365-366.
7. Frimer, A. A. *Synthesis*, **1977**, 578-579. Spiteller, G. *Liebigs Ann. Chem.*, **1993**, 1245-1248.
8. Stevens, C. L.; Farkas, E.; Gillis, B. T. *J. Am. Chem. Soc.*, **1954**, 76, 2695-2698. Stevens, C. L.; Gillis, B. T. *J. Am. Chem. Soc.*, **1957**, 79, 3448-3451. Kirrmann, A.; Muths, R.; Riehl, J.-J. *Bull. Soc. Chim. Fr.*, **1958**, 1469-1474.
9. Bellesia, F.; Boni, M.; Ghelfi, F.; Grandi, R.; Pagnoni, U. M.; Pinetti, A. *Tetrahedron*, **1992**, 48, 4579-4587.
10. Bellesia, F.; Boni, M.; Ghelfi, F; Pagnoni, U. M. *Gazz. Chim. Ital.*, **1993**, 123, 629-631.
11. Creary, X.; Rollin, A. J. *J. Org. Chem.*, **1977**, 42, 4231-4238. Kirrmann, A.; Chancel, P.; Vignalou, M.; Federlin, P. *Bull. Soc. Chim. Fr.*, **1950**, 707-711.
12. Whol, A. *Chem. Ber.*, **1908**, 41, 3599-3612.
13. Boni, M.; Ghelfi, F.; Pagnoni, U. M.; Pinetti, A. *Synth. Commun.*, **1993**, 1915-1921.
14. Shostakovskii, M. F.; Kuznetsov, N. V.; Yang, C.-M.; Balezina, G. G. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1962**, 2220-2223 (*C.A.*, **1963**, 58, 13783a).
15. a) Akiyoshi, S.; Okuno, K. *J. Am. Chem. Soc.*, **1954**, 76, 693-694. See also: De Buyck, L.; Verhue, A. *Bull. Soc. Chim. Belg.*, **1993**, 102, 347-355. b) Bailey, W. F.; Rivera, A. D. *J. Org. Chem.*, **1984**, 4958-4964.
16. Bayer, O. in *Houben-Weil, Methoden der Organischen Chemie*, Georg Thieme Verlag: Stuttgart, 1954; vol. 7/1, pp. 442-445.
17. Creary, X. *J. Org. Chem.*, **1987**, 52, 5056-5030. Duhamel, P.; Cantacuzène, J. *Bull. Soc. Chim. Fr.*, **1962**, 1843-1846.
18. α-Hydroxyaldehyde dimethyl acetals were better purified by silica gel chromatography, since some degradation occurred on distillation.

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