Chloromethyl(dimethyl)sulfonium Trifluoromethanesulfonate — The Reagent for Preparation of Acetals of 2-Hydroxyaldehydes from Ketones under Basic Conditions

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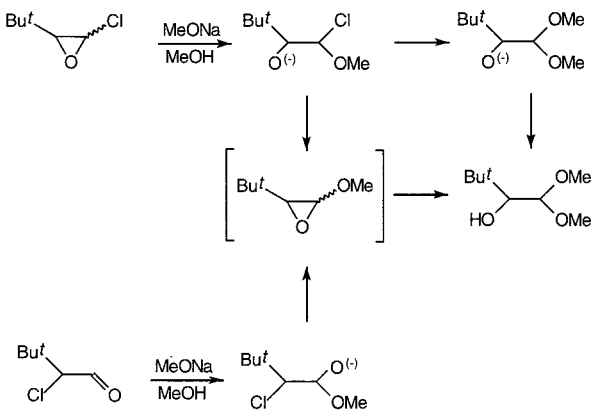
Abstract: 2-Hydroxyaldehydes dimethylacetals **5** are synthesized *via* reaction of chloromethyl(dimethyl)sulfonium trifluoromethanesulfonate (**1**) with ketones **2**, carried out in the presence of sodium methoxide in methanol. The corresponding 2-chloro- (**3a**) or 2-dimethylsulfonium-oxirane (**3b**) are presumably transient intermediates.

Some years ago, Griesbaum *et al*[1] reported that 2-*t*-butyl-3-chlorooxirane or 2-chloro-3,3-dimethylbutanal react with sodium methoxide in methanol to afford dimethylacetal of 2-hydroxy-3,3-dimethylbutanal. It has been suggested that, in the case of chlorooxirane, this product is formed *via* non-cyclic intermediates,[1] or *via* 2-*t*-butyl-3-methoxyoxirane, a common intermediate plausible for both substrates (Scheme 1).



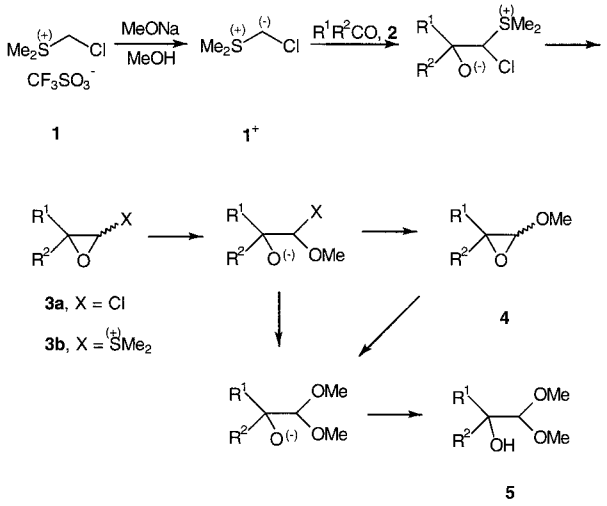
Scheme 1

The synthesis of the title compounds according to the method described above, requires either chlorooxirane or chloroaldehyde to be available in each particular case, yet some of the former are rather unstable,[2] while the latter have lachrymatory and skin irritant properties.

Therefore, we were looking for a more general approach to methyl acetals of 2-hydroxyaldehydes **5**, based on easily available substrates.[3] This approach consists of the reaction of ylide $\mathbf{1}^{+\cdot-}$, generated from salt **1** with ketones **2**, and subsequent cleavage of either oxiranes **3** thus formed by means of sodium methoxide (Scheme 2). However, none of α-halosulfonium salt, precursor of α-haloylide, is known to date.

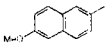
Preliminary efforts to synthesize chloromethyl(dimethyl) sulfonium salt from easily available chloromethyl methyl sulfide,[4] and methyl iodide or dimethyl sulfate, failed. The expected methylation of this sulfide at sulfur occurred if more active methylating agents like methyl trifluoromethanesulfonate (triflate) or trimethyloxonium tetrafluoroborate, were applied. After some experimentations, the crystalline salt **1** was obtained in yield of 85%.[5]

Preliminary experiments with salt **1** and simple carbonyl compounds like benzaldehyde or cyclopentanone, carried out in sodium methoxide-methanol system, failed to give the corresponding products **5**.[6] However, a simple stirring of 3,3-dimethyl-2-butanone (**2a**), and



Scheme 2

Table. Products **5** from reaction of salt **1** with ketones **2**

Entry	**2**, **5**		**2** / **1**	Yield[a]
	R^1	R^2	(mol / mol)	of **5** (%)
1	t-Bu	Me	5.0	**5a**, 56
2	Ph	CF_3	5.0	**5b**, 52[b]
3	Ph	Me	0.99	**5c**, 32
4	Ph	i-Bu	0.37	**5d**, 45
5	Ph	i-Pr	0.80	**5e**, 67
6		Me	0.90	**5f**, 42

[a] Of isolated products.

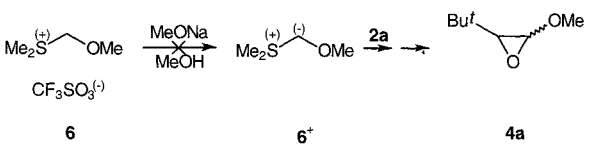
[b] At ratio of **2**/**1** = 2.0 yield is 28%.

phenones **2b-f** with **1** at rt for 5 days resulted in formation of expected products **5a-f** in 32 – 67% yields[7] (Table).

We have observed that isolation of pure acetals **5c-f** is facilitated if practically all ketones **2c-f** are consumed; therefore, the reactions with **2c-f** have been carried out with an excess of salt **1**. On the other hand, the experiments with phenone **2b** indicate that increase of **1**/**2b** molar ratio significantly improves yield of **5b** (Table, Entry 2).

The salt **1** can be deprotonated either at one of the methyl – or at the chloromethyl group, to generate methylide or chloromethylide $\mathbf{1}^{+-}$, respectively. Stabilization of the adjacent negative charge by a chlorine atom[8] should favour formation of $\mathbf{1}^{+\cdot-}$, in spite of a larger amount of methyl protons (statistical factor). Generation of methylide from **1** would result in methylene transfer to the carbonyl group of **2**, but such reaction course has not been observed.[9] Furthermore, adducts of $\mathbf{1}^{+\cdot-}$ to **2** may cyclize to oxiranes **3a** or **3b**, depending which group has been eliminated, but this step most probably does not affect the final result (Scheme 2).

Finally, the synthesis of methoxyoxirane **4**, a possible intermediate (Scheme 2), was attempted. Thus, dimethyl (methoxymethyl)sulfonium triflate (**6**) was prepared,[12] allowed to react with ketone **2a** and sodium methoxide in methanol, but neither oxirane **4a** nor acetal **5a** were produced, ca 90% of **2a** was recovered instead (Scheme 3).



6 6+ 4a

Scheme 3

This experiment shows that ylide 6^{+-} is possibly not generated under the conditions applied.[14]

To sum up, we have reported the first synthesis of sulfonium salt α-substituted with chlorine **1**, and demonstrated its usefulness for the preparation of methylacetals of 2-hydroxyaldehydes.

References and Notes

(1) Griesbaum, K.; Lie G. O.; Keul H. *J. Org. Chem.* **1984**, *49*, 679.

(2) Kirrmann, A.; Duhamel, P.; Nouri-Bimorhki, R. *Liebigs Ann. Chem.* **1966**, *691*, 33. Kirrmann, A.; Nouri-Bimorhki, R. *Bull. Soc. Chim. France* **1968**, 3213. McDonald, R. N. In *Mechanisms of Molecular Migration*; Thyagarajan, B. S, Ed.; Wiley: New York, 1971; vol. 3, p. 67.

(3) Alternatively, 2-hydroxyaldehyde dimethylacetals are prepared by reaction of the corresponding aldehydes with thianthrenium tetrafluoroborate followed by treatment of the initially formed 2-sulfoniumaldehydes with sodium methoxide in methanol: Schulz, M.; Kluge, R.; Michaelis, J. *Synlett* **1994**, 669.

(4) Bordwell, F. G.; Pitt, B. M. *J. Am. Chem. Soc.* **1955**, *77*, 572.

(5) Preparation of salt **1**: A protected from moisture solution of chloromethyl methyl sulfide[4] (10.1 g, 8.6 ml, 104 mmol) in dry CH_2Cl_2 (100 ml) was cooled to –78 °C, methyl triflate (17.4 g, 12.0 ml, 106 mmol) was added, and the mixture was kept at rt for 3 h. The volatile compounds were evaporated, and the solid residue was crystallized (AcOEt) to give **1** (23.0 g, 85%), colorless crystals of mp 50–51 °C. ^{1}H NMR (200 MHz, DMSO-d_6) δ 5.38 (s, 2H, CH_2Cl), 2.89 (s, 6H, Me_2S^+). Calcd. for $C_4H_8ClF_3O_3S_2$: C, 18.43; H, 3.09; Cl, 13.60; S, 24.60. Found: C, 18.14, H, 3.07; Cl, 13.65; S ,24.62. $\mathbf{1}^+\bullet BF_4^-$ (hygroscopic solid) was prepared in a similar way from chloromethyl methyl sulfide[4] and trimethyloxonium tetrafluoroborate, in 66% yield. ^{1}H NMR (200 MHz, DMSO-d_6) δ 5.37 (s, 2H, CH_2Cl), 2.89 (s, 6H, Me_2S^+).

(6) The dimethyl acetals or ketals of these carbonyls were main products.

(7) Preparation of **5**. General Procedure: Salt **1** (2.6 g, 10 mmol), ketone **1a-f** (Table 1) and methanol (5 ml) were magnetically stirred, while the solution of MeONa prepared from sodium (2.3 g, 100 mmol) and methanol (80 ml) was added. The mixture was stirred for 5 days, diluted with water (100 ml), extracted with Et_2O (3 × 50 ml), the organic extracts were washed with water and dried ($MgSO_4$). The solvent was evaporated and the residue purified by column chromatography on basic Al_2O_3, Brockmann grade V (eluent: hexane-CH_2Cl_2, gradient) to give **5** as colorless oils. In the case of **5f**, purification was repeated on silica gel (eluent: pentane-CH_2Cl_2, 1 : 1, then Me_2CO) (Table 1). ^{1}H NMR spectra of **5a-f** were measured at 200 MHz in $CDCl_3$.
5a: δ 4.19 (s, 1H, OCHO), 3.54 (s, 3H, OMe), 3.45 (s, 3H, OMe), 3.41 (s, 1H, OH), 1.06 (s, 3H, CMe), 0.92 (s, 9H, CMe_3). Calcd. for $C_9H_{20}O_3$: C, 61.33; H, 11.44. Found: C, 61.19; H, 11.41.
5b: δ 7.64 – 7.37 (m, 5H, ArH), 4.84 (s, 1H, OCHO), 3.58 (s, 3H, OMe), 3.24 (s, 3H, OMe). Calcd. for $C_{11}H_{13}F_3O_3$: C, 52.80; H, 5.24. Found: C, 52.72; H, 5.28.
5c: δ 7.55 – 7.25 (m, 5H, ArH) , 4.21 (s, 1H, OCHO), 3.43 (s, 3H, OMe), 3.33 (s, 3H, OMe), 2.69 (s, 1H, OH), 1.55 (s, 3H, CMe). Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.12; H, 8.19.
5d δ 7.53 – 7.23 (m, 5H, ArH), 5.28 (s, 1H, OCHO), 4.16 (s, 1H, OH), 3.41 (s, 3H, OMe), 3.36 (s, 3H, OMe), 1.97 – 1.66 (m, 2H, CH_2CH), 1.63 – 1.45 (m, 1H, CH_2CH), 0.79 (d, J = 6.56 Hz, 6H, CHMe_2). Calcd. for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.70; H, 9.29.
5e: δ 7.53 – 7.25 (m, 5H, ArH), 4.57 (s, 1H, OCHO), 3.51 (s, 3H, OMe), 3.45 (s, 3H, OMe), 3.39 (s, 1H, OH), 2.41 – 2.26 (m, 1H, CHMe_2), 0.83 (d, J = 6.92 Hz, 6H, CHMe_2). Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.54; H, 8.98.
5f: δ 7.95 – 7.11 (m, 6H, ArH), 4.28 (s, 1H, OCHO), 3.88 (s, 3H, OMe), 3.43 (s, 3H, OMe), 3.32 (s, 3H, OMe), 2.13 (s, 1H, OH), 1.63 (s, 3H, CMe). Calcd. for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30. Found: C, 69.50; H, 7.29.

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(9) Benzyldimethylsulfonium[10] and S-benzylthiolanium salt[11] are regioselectively deprotonated at methylene benzyl group by alkali metal hydroxides.

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(11) Borredon, M. E.; Delmas, M.; Gaset, A. *Tetrahedron* **1987**, *43*, 3945.

(12) Triflate **6** was prepared from methoxymethyl(methyl)sulfide[13] essentially as described for salt **1** in ref. 5.
6: yield ca 100%, mp 30 °C. ^{1}H NMR (200 MHz, DMSO-d_6) δ 4.41 (s, 2H, CH_2), 3.32 (s, 3H, OMe), 2.88 (s, 6H, Me_2S^+). Calcd. for $C_5H_{11}F_3O_4S_2$: C, 23.43; H, 4.33. Found: C, 23.30; H, 4.29.

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(14) Stirring of salt **6** with benzaldehyde, 50% aq sodium hydroxide and tetra-n-butylammonium hydrogen sulfate (according to the described reaction of trimethylsulfoxonium iodide with chalcone[15]) afforded phenyloxirane (yield ca 20%) as a sole product. This result indicates that **6** is preferentially deprotonated at the methyl group. In fact the oxygen atom may destabilize the neighbouring negative charge by p-p lone pair repulsion effect (+R-p orbital feedback mechanisms).[16]

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