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A NEW METHOD FOR NUCLEOPHILIC OXYMETHYLATION USING α-ALKOXYSILANES. SYNTHESIS OF UNSYMMETRICAL 1,2-DIOLS

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Desilylation of α-alkoxysilanes offers the convenient generation of carbinyl carbanions which react with a variety of carbonyl compounds giving mono-protected 1,2-diols of unsymmetrical type. Dehydration of these unsymmetrical diols leads to the regioselective formation of methyl ketones.

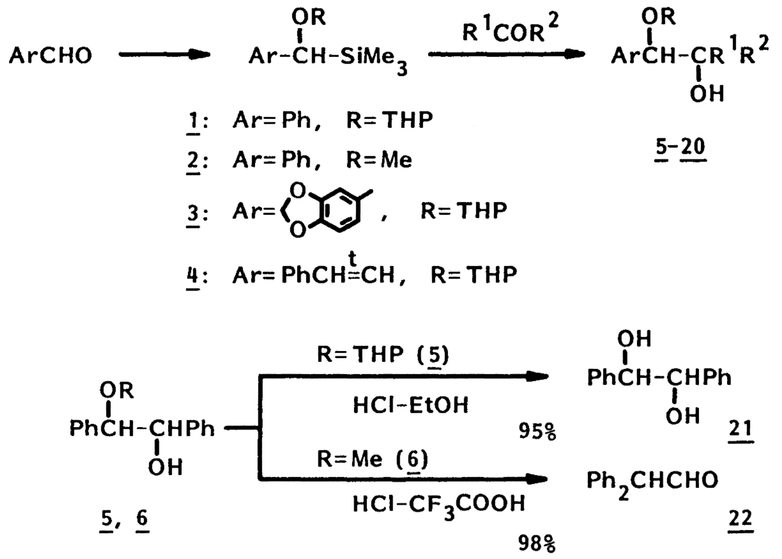
Nucleophilic oxymethylation of carbonyl functions is attractive as the preparative method of synthetically important 1,2-diols. The advantages of this process are the ready availability of a wide range of carbonyl compounds and the straightforward synthesis of unsymmetrical 1,2-diols. However, applications of this method in organic synthesis are quite limited since only a few types of reagents for carbinyl carbanion synthons are available now.1)

Deprotonation of allyl and vinyl ethers generates the alkoxy-substituted organometallics of unsaturation-stabilized type, which have been widely utilized in organic synthesis as excellent nucleophiles.2,3) Grignard reagents of α-halo ethers,4) α-stannyl alcohols and butyllithium,5) and α-stannyl ethers and butyllithium6) are also useful carbinyl carbanion equivalents.7) Some alkyl ethers can be deprotonated as well, but the anionic species generated frequently suffer from the Wittig rearrangement leading to the alcohols.8)

In this communication, we wish to present that α-alkoxysilanes are smoothly desilylated by a fluoride ion forming carbinyl carbanions which undergo nucleophilic oxymethylations onto various carbonyl compounds giving mono-protected 1,2-diols of unsymmetrical type.

The α-alkoxysilanes 1-4 were readily prepared from the corresponding aldehydes. Thus, the reductive silylation of benzaldehyde, piperonal, and cinnamaldehyde with lithium tetrakis(trimethylsilyl)aluminate9) or the Wittig rearrangement10) of benzyl trimethylsilyl ether gave fair yields of the corresponding α-hydroxysilanes.11) The hydroxy groups were protected as a tetrahydropyranyl (THP) ether with 2,3-dihydropyran in the presence of pyridinium p-toluenesulfonate12) at room temperature or as a methyl ether with dimethyl phosphite in the presence of p-toluenesulfonic acid13) at 90-100 °C.14)

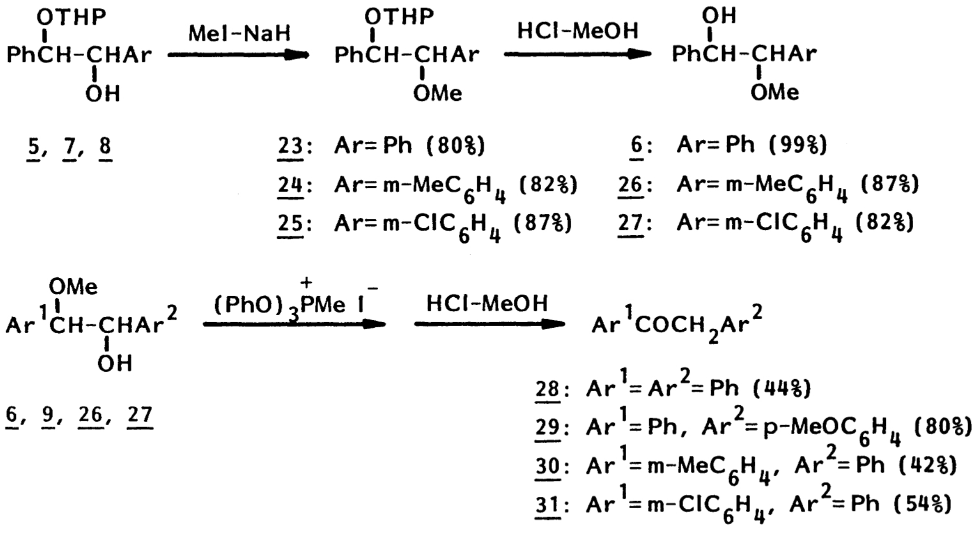
The reaction of 1 with benzaldehyde (1.5 equiv.) in dry dimethylformamide in the presence of CsF (one equiv.) under nitrogen at room temperature for 12 h and



Scheme 1.

the hydrolytic work-up gave the adduct 5 whose structure was confirmed on the basis of the spectral and analytical data.15) Similar reactions of the α-alkoxysilanes 1-4 with such carbonyl compounds as aromatic, α,β-unsaturated, heteroaromatic, aliphatic aldehydes, and ketones gave the adducts 6-20 (Scheme 1 and Table 1).

When the mono-protected 1,2-diol 5 was treated with a catalytic amount of HCl in ethanol at room temperature overnight, the tetrahydropyranyl moiety was removed giving 21 as an erythro-threo mixture (1:1). Although the methyl protected adduct 6 resisted a deprotection under the same conditions, the rearranged aldehyde 22 was obtained when 6 was heated in trifluoroacetic acid (at 70 °C for 40 min) in the presence of HCl. Thus, the protection as a tetrahydropyranyl ether is convenient for the synthesis of unsymmetrical 1,2-diols.16)



Scheme 2.

Table 1. Reactions of α-Alkoxysilanes with Carbonyl Compounds Leading to Mono-protected Unsymmetrical 1,2-diols 5-20

α-Alkoxysilanes 1-4		Carbonyl Compounds		Conditions[a)]		Products[b)]	Yield[c)]
Ar	R	R^1	R^2	Temp/°C	Time/h		%
Ph	THP	Ph	H	room temp	12	5	90
Ph	Me	Ph	H	90	16	6	74
Ph	THP	m-MeC$_6$H$_4$	H	room temp	21	7	69
Ph	THP	m-ClC$_6$H$_4$	H	room temp	21	8	72
Ph	Me	p-MeOC$_6$H$_4$	H	90	16	9	77
3,4-OCH$_2$OC$_6$H$_3$	THP	p-MeOC$_6$H$_4$	H	room temp	26	10	73
3,4-OCH$_2$OC$_6$H$_3$	THP	PhCH=CH (t)	H	room temp	21	11	72
PhCH=CH (t)	THP	p-MeOC$_6$H$_4$	H	room temp	16	12	63
Ph	Me	2-furyl	H	room temp	3	13	85
Ph	Me	2-thienyl	H	room temp	4	14	62
Ph	Me	2-pyridyl	H	room temp	3	15	69
Ph	Me	(Me)$_2$CH	H	60	13	16	54
Ph	Me	(Me)$_3$C	H	60	13	17	65
Ph	Me	Pr	H	60	13	18	55
Ph	Me	Ph	Me	60	4	19	50
Ph	Me	Ph	Ph	60	15	20	26

a) All the reactions were performed among each 1 mmol of α-alkoxysilanes, cesium fluoride, and 1.5 mmol of carbonyl compounds in 2 ml of dry dimethylformamide. b) As the mixtures of erythro and threo isomers. The isomer ratios were determined on the ^{1}H-NMR spectra and found to be about 1/1 in all cases. c) Isolated yields.

As the adducts 5-20 are the regioselectively mono-protected derivatives of unsymmetrical 1,2-diols, the regioselective chemical conversions may be achieved as a useful process in organic synthesis. Thus, the tetrahydropyranyl ethers 5, 7, and 8 were methylated giving the bis-ethers 23-25 and then the pre-exsistent protecting groups (THP) were removed under mild acidic conditions affording the methyl ethers 6, 26, and 27 (Scheme 2). By this process, the protection of 1,2-diols can be transferred to the adjacent position.

Some of the methyl-protected unsymmetrical 1,2-diols 6, 9, 26, and 27 were heated with methyltriphenoxyphosphonium iodide[17)] in hexamethylphosphoric triamide at 90 °C for 3 h and then hydrolyzed under reflux in methanol-HCl giving the methyl ketones 28-31 in fair yields.

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11) The corresponding α-hydroxysilanes were obtained by the reductive silylations of benzaldehyde (57%), piperonal (53%), and cinnamaldehyde (45%) with lithium tetrakis(trimethylsilyl)aluminate.

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14) The yields of alkylation steps were given as follows: 1 (88%); 2 (57%); 3 (98%); 4 (60%).

15) The adduct 5 was obtained as a 1:1 mixture of erythro and erythro isomers. This is the same to the other cases (see Table 1). All the new compounds reported herein gave the satisfactory spectral and elemental data.

16) An acetyl protecting group could be used as well: When α-(trimethylsilyl)-benzyl acetate was allowed to react with p-anisaldehyde under the similar conditions, the mono-acetate of the corresponding 1,2-diols was obtained in 54% yield. However, it was found that the acetyl protecting group was readily transferred to the adjacent hydroxy moiety.

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