

tert-Butylmethoxyphenylsilyl Ether - A New Selective, Stable Alcohol Protecting Group with Remarkable Lability to Fluoride.

Yvan Guindon*, Réjean Fortin, Christiane Yoakim and John W. Gillard
Merck Frosst Canada Inc., P.O. Box 1005, Pointe Claire/Dorval, Quebec, Canada H9R 4P8

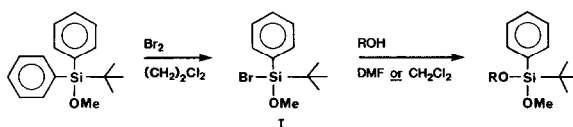
Abstract - tert-Butylmethoxyphenylsilyl ethers, which can be formed from primary, secondary or tertiary alcohols and tert-butylmethoxyphenylsilyl bromide, are selectively cleaved by fluoride in the presence of other silyl ethers.

In the vast repertoire of protecting groups¹ available to organic chemists, the silyl ethers have emerged as one of the most useful for the protection of alcohols. The widely used tert-butyldimethylsilyl ethers (t-BDMSi) developed by Corey and Venkateswarlu² possess an excellent profile if one considers their stability to base, mild acid and a variety of chemical reactions. Improved stability to acid hydrolysis, selectivity for primary hydroxyl groups and the presence of a chromophore were the added advantages offered by the tert-butyldiphenylsilyl ethers (t-BDPSi) developed by Hanessian and Lavallée³.

Some limitation is imposed in the concurrent use of these excellent protecting groups. The gain in primary selectivity achieved in the case of tert-butyldiphenylsilyl chloride is accomplished through a dramatic increase in steric bulk, a factor which expresses itself in the considerable hydrolytic stability of the derived silyl ether. Thus, a tert-butyldiphenylsilyl ether cannot be cleaved in the presence of other silyl ethers hydrolytically or through the use of fluoride.

Due to such limitations, a valuable addition to silicon-based protecting groups would be a silyl derivative which could be removed selectively in the presence of t-BDMSi and t-BDPSi ethers through a non-hydrolytic process. The following properties would also be desirable: hydrolytic stability between t-BDMSi and t-BDPSi ethers; selectivity towards primary hydroxyl groups; reactivity towards tertiary alcohols.

In order to achieve these objectives, we have considered silyl acetal derivatives⁴ based on the premise that an added hetero-atom will modify the electronic nature of the silicon, increasing its sensitivity to nucleophilic reagents such as fluoride. We report herein on the tert-butylmethoxyphenylsilyl ether group (t-BMPSi), a new and versatile protecting group for alcohols which meets the above criteria, and which is readily prepared from tert-butylmethoxyphenylsilyl bromide **I**.

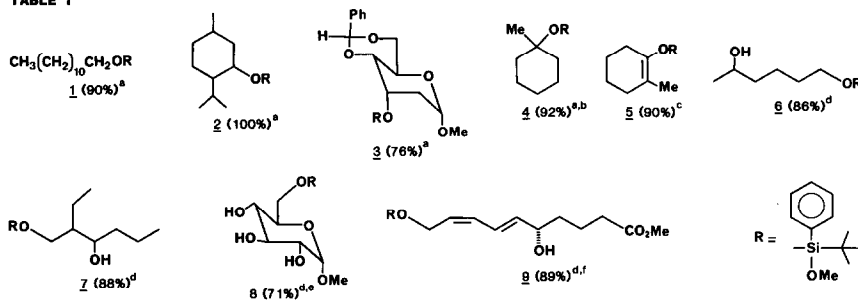


This latter reagent was synthesized by treating the tert-butyldiphenylsilyl ether of MeOH with bromine.

Reactivity and Selectivity - Table 1 summarizes the results with a variety of substrates. The tert-butylmethoxyphenylsilyl bromide **1** reacts in DMF in the presence of Et₃N with primary, secondary and tertiary alcohols to give the corresponding silyl ethers in good yield (Table 1, **1-4**). Under the same conditions enolizable ketones may be converted to enol silyl acetals (e.g. **5**, Table 1) which possess useful hydrolytic stabilities. The silylation of the tertiary alcohol 1-methylcyclohexanol **4** in good yield is notable. In contrast, the treatment of this substrate with tert-butyldimethylsilyl chloride, imidazole and DMF was reported⁵ to give 10% of the corresponding silyl ether after 3 days.

Particularly interesting and useful is the ability to achieve selective silylation of primary hydroxyl groups by the simple expedient of changing the solvent from DMF to CH₂Cl₂. As examples **6-9** in Table 1 show, exclusive primary protection was achieved for 1,3 diols, 1,5 diols and polyols.⁶ We suggest that, in the case of CH₂Cl₂ as solvent, a primary alcohol may undergo a nucleophilic displacement on a tetrahedral silicon species, such an attack being sterically unfavored for secondary or tertiary alcohols. However, the addition of DMF⁶ to the reaction mixture could induce the formation of a hexacoordinated silicon species⁷ whose geometry permits reactivity with secondary and tertiary alcohols.

TABLE 1



^a 1.1 equiv. of t-BMPSi-Br in DMF (0.3 M) in the presence of 1.3 equiv. of Et₃N at R.T. for 1 hr. ^b Reaction time was 12 hours. ^c To the ketone was added 1 equiv. t-BMPSi-Br and 1 equiv. of Et₃N in DMF (1 M), reaction time was 12 hours, 7% of the kinetic enol was isolated as well. ^d 1.2 equiv. of t-BMPSi-Br in CH₂Cl₂ (0.1 M) and 1.3 equiv. Et₃N at R.T. for 1-2 hours. ^e Due to lack of solubility of the substrate, the reaction was left with vigorous stirring at R.T. for 36 hours. NMR data supports this structure (see ref. 8). ^f The starting material was prepared as described in ref. 9.

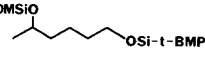
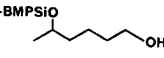
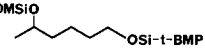
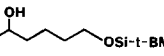
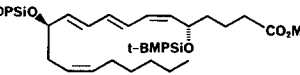
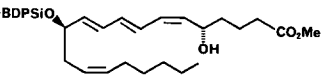
Stability - To evaluate the potential scope of this new silyl ether as a protecting group, different chemical transformations were made on polyfunctional substrates bearing a tert-butylmethoxyphenylsilyl ether. t-BMPSi ethers were found to be compatible¹⁰ with reactions such as acylation, tosylation, PCC oxidation, NaBH₄ reduction, benzylation, hydrogenolysis and addition to carbonyl functions of either Grignard reagents or n-BuLi. Hydrolytic stability

towards acids and bases was also studied. Under acid conditions (HCl, 0.1N in MeOH) a secondary or primary tert-butylmethoxyphenylsilyl ether is more stable than its tert-butyldimethylsilyl counterpart and can also be removed more readily than a tert-butyldiphenylsilyl derivative.

Sodium hydroxide (0.1 N in MeOH-H₂O, 9/1) cleaved a t-BMPSi derivative, after 16 hours, but base hydrolysis of benzoates and acetates was easily affected prior to removal of the silyl acetal.

Deprotection - One of the most striking and useful features of the tert-butylmethoxyphenylsilyl ether group is its sensitivity to fluoride. tert-Butylmethoxyphenylsilyl ethers can be cleaved in dichloroethane, by tetrabutylammonium fluoride in THF, in the presence of either a primary or secondary tert-butyldimethylsilyl ether or a tert-butyldiphenylsilyl ether, as illustrated in Table 2. The difference of reactivity toward fluoride is such that a close monitoring of the reaction is not necessary, since a tert-butyldimethylsilyl ether reacts very slowly in ClCH₂CH₂Cl with nBu₄N⁺F⁻ provided the THF concentration is less than 10%, and a tert-butyldiphenylsilyl ether is practically inert under these conditions. This has interesting synthetic potential. One can, for example, use the tert-butylmethoxyphenylsilyl bromide in CH₂Cl₂ to protect a primary hydroxyl group and subsequently, introduce a t-BDPSi or t-BDMSi ether on a secondary hydroxyl group and then treat with fluoride to selectively unmask the primary hydroxy group, as exemplified in entry 4, Table 2. On the other hand, the selective cleavage of a tert-butyldimethylsilyl ether in the presence of a tert-butylmethoxyphenylsilyl ether is possible under acidic conditions as illustrated in entries 2 and 5 (Table 2). This is of significant interest since one can selectively differentiate, depending on the conditions chosen, one silyl ether from another (t-BMPSi ether from a t-BDMSi) as one goes from protic acid conditions to fluoride treatment.

TABLE 2

ENTRY	SUBSTRATE (t-BMPSIOR)	SOLVENT	REAGENT	PRODUCT ^a (ROH)	YIELD ^b (%)
1	t-BDMSiO(CH ₂) ₃ OSi-t-BMP	(CH ₂) ₂ Cl ₂	n-Bu ₄ NF ^c	t-BDMSiO(CH ₂) ₃ OH	80
2	"	MeOH	HCl ^d	HO(CH ₂) ₃ OSi-t-BMP	84
3	t-BDPSiO(CH ₂) ₃ OSi-t-BMP	(CH ₂) ₂ Cl ₂	n-Bu ₄ NF ^c	t-BDPSiO(CH ₂) ₃ OH	88
4		(CH ₂) ₂ Cl ₂	n-Bu ₄ NF ^c		94
5		MeOH	HCl ^d		87
6		(CH ₂) ₂ Cl ₂	n-Bu ₄ NF ^c		78

^a All products were identified by comparison with authentic samples. ^b Isolated yields. ^c The reaction was carried out at 0.02 M, using a 10% (V/V) solution of Bu₄NF (1M in THF) in (CH₂)₂Cl₂. ^d The reaction was carried out at R.T. at a concentration of 0.1M using a 10% (V/V) solution of aqueous HCl (0.1N) in MeOH.

In summary, this new hydroxyl protecting group, the tert-butylmethoxyphenylsilyl ether possesses the following properties: hydrolytic stability (a t-BMPSi ether is more stable under acidic conditions than its t-BDMSi ether counterpart); selective fluoride cleavage in the presence of t-BDMSi and t-BDPSi ethers. The tert-butylmethoxyphenylsilyl bromide has the following characteristics: highly selective for primary hydroxyl groups when the reaction is done in dichloromethane; very potent silylating agent when DMF is present in the reaction mixture (which permits reaction with tertiary hydroxyl group).

The reagent therefore has unique properties either when used alone or when used to complement other silyl protecting groups.

Synthesis of tert-butylmethoxyphenylbromosilane

To a solution of 34.4 g tert-butyldiphenylmethoxysilane in 600 mL dry dichloroethane cooled to 0°C was added a solution of 8 mL Br₂ (1.2 eq.) in 8 mL 1,2 dichloroethane. The reaction mixture was warmed to R.T. and stirred for 16 hr. The solution was distilled, excess Br₂ and solvent being initially removed, followed by tert-butylmethoxyphenylbromosilane (B.P. 97-102°C, 1 mm Hg) 22.2 g, (65%). ¹H NMR(CDCl₃) 1.02 (s, 9H), δ3.60 (s, 3H), δ7.45,(m, 2H) and 7.75 (m, 3H).

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4. Cyclic silyl "acetals" such as di-tert-butylsilylene, diisopropylsilylene and diphenylsilylene have been previously reported as diol protecting groups:
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5.
 - a) T.J. Barton and C.R. Tulley, J. Org. Chem., **43**, 3649 (1978).
 - b) tert-Butyldimethylsilyl perchlorate (see ref. 5a) has been reported to react with 1-methylcyclohexanol to give the corresponding silyl ether.
6. Secondary alcohols react very slowly (T 1/2 >24 hrs) with our reagent in CH₂Cl₂. Addition to the reaction mixture of .02 equiv. of DMF accelerates the reaction significantly (T 1/2 = 90 min).
7.
 - a) R.J.P. Corriu, G. Dabosi and M. Martineau, J. Organometal. Chem., **186**, 25 (1980).
 - b) R.J.P. Corriu and C. Guerin, J. Organometal. Chem., **198**, 231 (1980).
 - c) The possibility of transfer silylation of DMF may also explain this augmented reactivity.
8. The diastereotopic nature of this silyl acetal was evidenced by the appearance of doubled NMR signals in certain cases. The anomeric and certain ring protons of the methyl-6-O-tert-butylmethoxyphenylsilyl- α -D glucopyranoside were doubled. Homonuclear decoupling proved their diastereomeric origin.
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10. In each of these reactions, the obtained yields were over 80% (without optimization) with no evidence of cleavage of the t-BMPSi ether.

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