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FLUORIDE ION INDUCED REACTION OF PHENYLTHIOMETHYLTRIMETHYLSILANE (1) WITH ALDEHYDES AND KETONES: A SIMPLE PROCEDURE FOR THE FORMATION OF ß-HYDROXYPHENYLSULPHIDES

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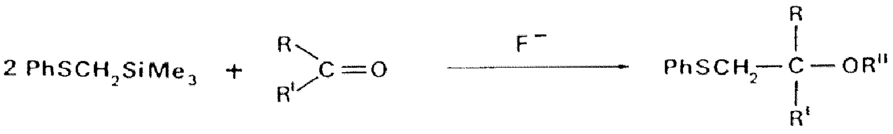
Summary: The tetra n-butylammonium fluoride (TBAF) initiated reaction of phenylthiomethyltrimethylsilane (1) with aldehydes and ketones is reported. ß-Hydroxy-phenylsulphides are formed in good yields even with ketones that contain enolisable protons. In contrast, the reaction of the organosilane (1) with pyridine N-oxide failed to give any 2-phenylthiomethylpyridine. Methylthiomethyltrimethylsilane (4) was found to be less reactive than (1) with aldehydes and ketones and also failed to react with pyridine N-oxide. The effect of free radical scavengers on the fluoride initiated reaction of benzyltrimethylsilane with benzophenone and pyridine N-oxide has been examined.

A number of trialkylsilyl compounds bearing an additional carbon substitutent have been reported recently as precursors to anionic species. On addition of a catalytic amount of fluoride, or by the use of another silylophile, the carbon substituent can be transferred to a suitable electrophilic acceptor. Thus, for example, allyl,[1] and benzyl,[2] and more recently (benzothiazol-2-ylthio)-methyl[3] groups have been added to a limited number of electrophiles using this approach. However, the full scope of this methodology has not been explored. Of particular interest to us was the isolated report of the regioselective preparation of 2-substituted pyridines by the fluoride catalysed reaction of benzyl and allyltrimethylsilane with pyridine N-oxide.[4] We examined the scope of this reaction in an attempt to find a novel method for the preparation of 2-(heteroarylthiomethyl)-pyridines, and other intermediates useful in the preparation of compounds which are known to reduce gastric acid secretion.[5] Initially we investigated the reaction of phenylthiomethyltrimethylsilane (1)[6] with pyridine N-oxide. Unfortunately, despite considerable efforts using a wide variety of reaction conditions we were unable to detect the formation of the desired product. In contrast, the reported reaction using benzyltrimethylsilane was found to be a very efficient method for the preparation of 2-benzylpyridine.

Furthermore, the fluoride initiated reaction of phenylthiomethyltrimethylsilane (1) with a variety of aldehydes and ketones was found to give ß-hydroxyphenylsulphides in excellent yields.(7) Even ketones that enolise under basic conditions gave addition products in reasonable yields (Table).



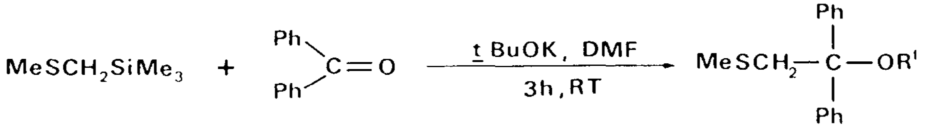
(1) (2) (3)

Table Isolated yields of addition products (3) from TBAF initiated reactions of phenylthiomethyltrimethylsilane (1) with aldehydes and ketones.

Aldehyde or Ketone (2)		Isolated Yield of Addition Product, % (3)	
R	R'	R''	
Ph	H	H	96
Ph	Ph	H	96
Ph	Ph	SiMe$_3$	96
Ph	Me	H	49
Ph	Me	SiMe$_3$	45
Me	Me	H	61
PhCH=CH	H	H	88*

* No product resulting from conjugate addition was detected.

In an attempt to find a thiomethylsilane that reacted with pyridine N-oxide we investigated the use of methylthiomethyltrimethylsilane (4).[8] Again, under a variety of reaction conditions were were unable to detect the formation of the desired 2-substituted pyridine. Interestingly, the fluoride initiated reaction of this organosilane with benzophenone (5) gave only trace amounts of addition products (6) and (7), suggesting that the reactivity of the organosilane had been decreased. However, the use of one equivalent of potassium t-butoxide in DMF gave a mixture of addition products (6) and (7) in 62% yield. Although potassium t-butoxide also initiated the reaction of phenylthiomethyltrimethylsilane (1) with aldehydes and ketones to give the products as mixtures of the silyl ether and hydroxy compounds, the best results were obtained using a 1.0 M solution of TBAF in THF.[9] Using this reagent the product could be isolated either as the silyl ether or the hydroxy compound.



(4) (5) (6) R'=H (7) R'=SiMe$_3$ 62%

In an attempt to explain the lack of reactivity between phenylthiomethyltrimethylsilane (1) and pyridine N-oxide we examined the possibility that a single electron transfer process was in operation in the reaction of benzyltrimethylsilane with pyridine N-oxide.[10] The radical scavengers galvinoxyl, sulphur and 2,2-diphenyl-1-picrylhydrazyl all inhibited the reaction and the yield of 2-benzylpyridine was <1%. However, the use of two nitrosyl derivatives di-t-butylnitroxyl and TEMPO,[11] failed to inhibit the reaction significantly.[12] Exactly the same observations were made when the effects of all of the above radical scavengers on the reaction of benzyltrimethylsilane with benzophenone was examined, and where inhibition was observed benzophenone was recovered in good yield. This suggests that the galvinoxyl, sulphur and the picrylhydrazyl may inhibit these reactions by some pathway other than by interfering with a single electron process. Further work is planned to investigate the reaction mechanism in greater detail.

The mild conditions[13] described above for the formation of β-hydroxysulphides (3), which can be readily converted into a variety of compounds including epoxides[14] and olefins,[15] make this an excellent procedure for the formation of this versatile class of synthetic intermediates.[16]

In a typical reaction, TBAF (1.0 M solution in THF, 0.2 ml, 0.2 mmol) was added to a stirred solution of benzophenone (0.364 g, 4.0 mmol) and phenylthiomethyltrimethylsilane (0.784 g, 8.0 mmol) in freshly distilled THF (5 ml) at 5°C and under an atmosphere of dry nitrogen. The reaction mixture was stirred at 5°C for 30 min and at room temperature for 1.5 h before being separated between ether (25 ml) and water (20 ml). The silylated product (3, R,R'=Ph, $R''=SiMe_3$) (0.72 g, 96%) was obtained by chromatography on silica gel (30 g) with light petroleum as eluent. The hydroxy compound (3, R,R'=Ph_3, R"=H) was prepared in a similar way except that TBAF (1.8 ml) was added prior to aqueous work-up and the reaction mixture was stirred for a further 10 min.

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5. For example Omeprazole, see U K Junggren and S E Sjoestrand, European Patent Application No. 79850022.9, 3 April 1979; Chem. Abstr., 1983, 98, 16689.

6. The use of this reagent as a formyl anion synthon has been reported. P J Kocienski, Tetrahedron Lett., 21, 1559 (1980).

7. For other methods of preparing ß-hydroxyphenylsulphides, see
    a) E J Corey and M Chaykovsky, J. Am. Chem. Soc., 87, 1353 (1965), and
    b) S Nakatsukasa, K Takai and K Utimoto, J. Org. Chem., 51, 5045 (1986).

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9. Available from Aldrich Chemical Co. Ltd. This reagent contains water, which probably accounts for the formation of a small amount of thioanisole in the reaction. An extra equivalent of organosilane was used to compensate for loss by this competing protodesilylation reaction.

10. An SET process has been implicated in the fluoride ion initiated reduction of certain carbonyl compounds with phenyldimethylsilane. D Yang and D D Tanner, J. Org. Chem., 51, 2267 (1986).

11. TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxyl is available from Aldrich Chemical Co. Ltd.

12. 0.2 equiv of scavenger was included in these reactions, which were routinely initiated by 0.1 equiv of TBAF.

13. The formation of the phenylthiomethyl anion from the reaction of thioanisole with n-butyllithium in the presence of DABCO has been reported. See ref 7a.

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