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PHENYLTHIOMETHYLTRIMETHYLSILANE : A NEW FORMYL ANION SYNTHON

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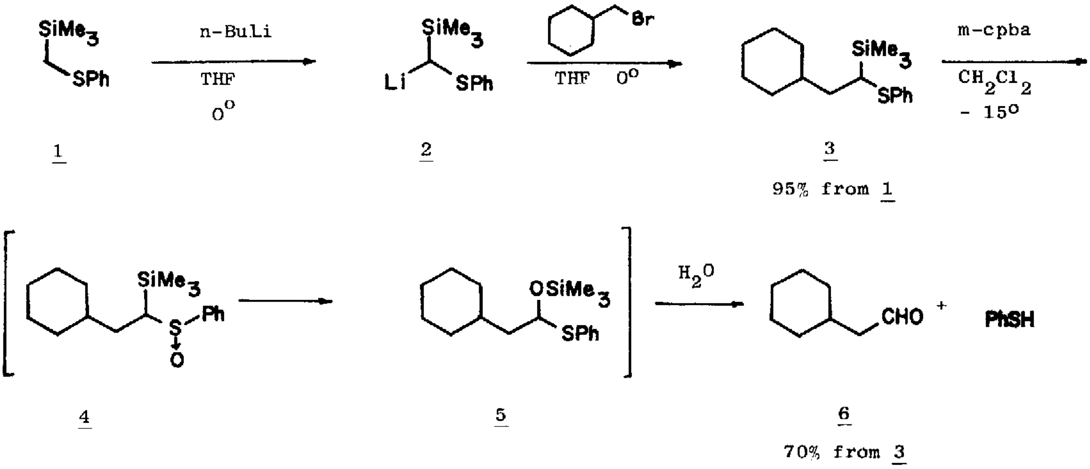
Summary: α-Phenylthioalkyltrimethylsilanes, readily prepared by the alkylation of phenylthiomethyltrimethylsilane with alkyl halides or epoxides, can be converted to O-trimethylsulyl hemithioacetals *via* a Sila-Pummerer Rearrangement of the corresponding sulfoxides. The O-trimethylsilyl hemithioacetals are readily hydrolyzed to aldehydes.

All of the formyl anion synthons reported to date share in varying degrees two principal detractions: they may be poorly nucleophilic - a problem attributable in many cases to limited thermal stability - or the conditions required to expose the latent aldehyde may be deleterious to sensitive functional groups.[1] Since both problems have recently confronted us with insurmountable obstacles to syntheses in progress, we were obliged to seek a new formyl anion synthon having the virtues of at least moderate nucleophilicity, stability to a wide range of reaction conditions, and facile conversion to the unmasked aldehyde. The anion 2 ($PhS\text{-}\overset{\ominus}{C}H\text{-}SiMe_3 \equiv {}^{\ominus}CHO$), derived in quantitative yield from the readily available phenylthiomethyltrimethylsilane[2] (1) by metalation with 1 eq. of n-BuLi in THF for 30 min at 0°, is stable at 18° for at least several hours and rapidly alkylates at 0° with certain halides and epoxides. The resulting α-phenylthioalkyltrimethylsilanes[3] (e.g. 3) are stable toward acid, base, and chromatography and can be distilled without decomposition at bath temperatures of 180°C. The α-phenylthioalkyltrimethylsilanes are distinguished by the extremely mild conditions required for transformation to the free aldehyde.

The sequence is illustrated by the conversion of cyclohexylmethyl bromide to cyclohexylacetaldehyde. Alkylation of a THF solution of **anion 2 with 1 eq of cyclohexylmethyl bromide** at 0° for 1 hr gave a 95% yield of 3 (b.p. 160°(bath)/0.02 mm) after distillation. Oxidation of 3 with 1 eq. of m-chloroperoxy-benzoic acid in CH_2Cl_2 at -15° rapidly gave the thermally unstable sulfoxide 4 which underwent a facile Sila-Pummerer[4] rearrangement (20° overnight or 30 minutes in refluxing THF) to give the hydrolytically unstable O-trimethylsilyl hemithioacetal 5. Addition of water to the THF solution of 5 resulted in rapid hydrolysis at 20° to give cyclohexylacetaldehyde and thiophenol. Thiophenol was simply removed by diluting the reaction mixture with ether and extracting with MNa_2CO_3.[5] Volatile aldehydes were then isolated by distillation of the residue obtained after normal aqueous work-up; non-volatile aldehydes were freed from non-polar sulfur-containing impurities by chromatography.

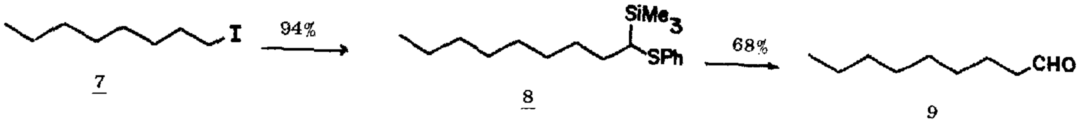


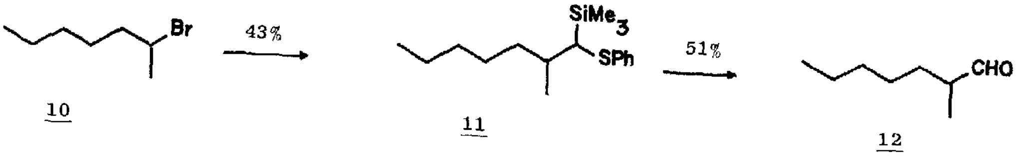
Listed below are some of the transformations which have been achieved using the new formyl anion equivalent.

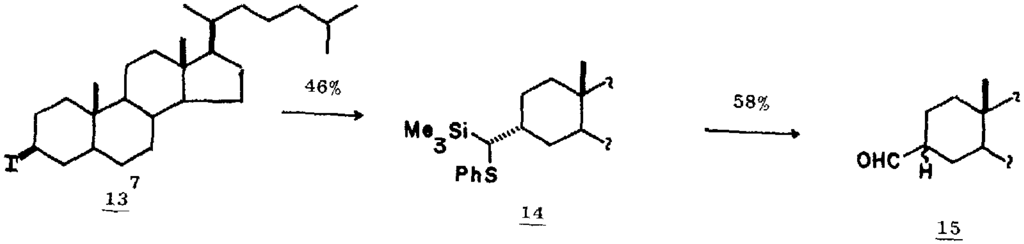
Scope and Limitations: The limitations to the alkylation of 2 are in accord with the usual behaviour expected for anions which are strong bases of moderate nucleophilic strength. Thus, the alkylation proceeds especially well with primary halides and mono- and di-substituted epoxides, whereas with secondary halides such as 2-bromoheptane, only moderate yields of alkylation occurred - the principal course of reaction being elimination. With cyclohexyl bromide elimination was the exclusive mode of reaction; however, the conformationally biased 3β-iodo-5α-cholestane (13) gave 46% of the alkylation product 14 accompanied by 48% cholest-2-ene. Reaction occurred exclusively at sulfur in the case of 3β-cholestanol tosylate. In the case of the tri-substituted epoxide 22 having a hindered reaction terminus, elimination to the known α-methylene carbinol[6] was the preponderant reaction. Addition of HMPA to the reaction mixture gave no improvement.

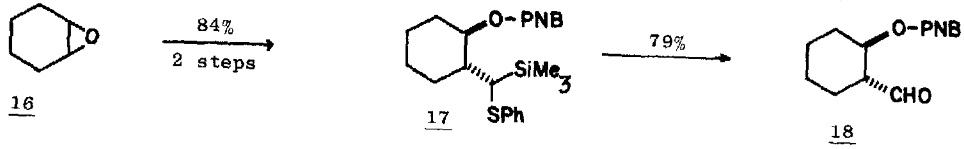
The conversion of the α-phenylthioalkylsilanes to the O-trimethylsilyl hemioacetals also has steric limitations : as the steric crowding about the sulfoxide intermediate increases, the Sila-Pummerer reaction is diverted and enol thioethers become major rather than the usual minor by-product. For example, in the case of 25, the Sila-Pummerer rearrangement was completely suppressed and the isomeric enol thioethers 27 were the major products.

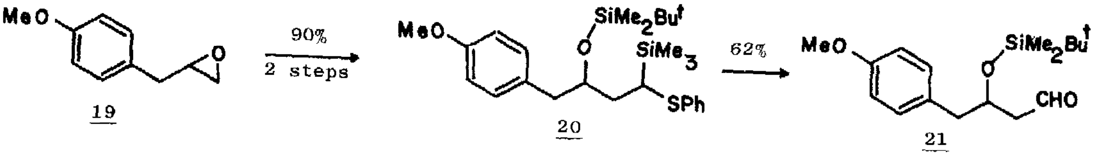
Phenylthiomethyltrimethylsilane appears to be an effective formaldehyde anion synthon[8] within certain steric limitations shared by other related synthons. A distinct advantage to the new synthon, however, is the remarkable facility with which the latent aldehyde can be exposed, thus providing access to particularly acid sensitive aldehydes such as aldols.

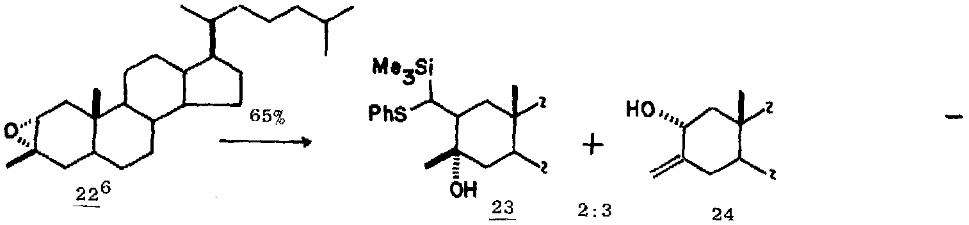


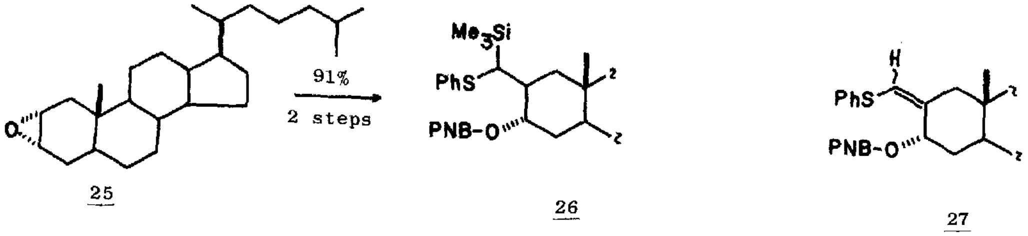












PNB = p-Nitrobenzoyl

References and Notes

1. S.F. Martin, Synthesis, 633 (1979) and references cited therein.
2. G. D. Cooper, J. Amer. Chem. Soc., 76, 3713 (1954). Phenylthiomethyltrimethylsilane can be conveniently prepared on a mole scale in 90% yield by reaction of Phenylthiomethyllithium, prepared by the method of Corey and Seebach [J. Org. Chem., 31, 4097 (1966)], with $ClSiMe_3$ at -20°: ir (film) 1250, 850 and 740 cm^{-1}; δ ($CDCl_3$) 0.05 (9H, s), 2.05 (2H, s), 7.2-7.5 (5H, m). We thank Prof. P.G. Sammes and Dr. B. Bonini for communicating this procedure.
3. The α-Phenylthioalkyltrimethylsilanes 11, 14, 17, 20, 23, and 26 were obtained as mixtures of diastereomers as evidenced by the doubling of the Me_3Si and PhS-CH-$SiMe_3$ signals in the n.m.r. spectra. The chemical shift and coupling constants for the two diastereomers of 17 (separable by fractional crystallization from $CHCl_3$-ligroin) were typical. Major isomer (62%): m.p. 160-161°; δ 0.22 (9H, s, Me_3Si) and 2.93 (1H, d, J = 3 Hz, PhS-CH-$SiMe_3$). Minor isomer (38%) m.p. 131-132°; δ 0.21 (9H, s) and 2.72 (1H, d, J = 2 Hz).
4. A. G. Brook, Accts. Chem. Res., 7, 77 (1974) and E. Vedejs and M. Mullins, Tetrahedron Lett., 2017 (1975).
5. For molecules which are particularly sensitive to base, the hydrolysis and removal of thiophenol as the copper complex could be effected in one step by shaking a THF solution of the o-trimethylsilyl hemithioacetal with aqueous $CuSO_4$.
6. P. J. Kocienski and J. Tideswell, Syn. Comm., 9, 411 (1979).
7. E. J. Corey, M. G. Howell, A. Boston, R. L. Young, and R. A. Sneen, J. Amer. Chem. Soc 78, 5036 (1956).
8. The metalation-alkylation sequence fails with the α-phenylthioalkyltrimethylsilanes; thus higher aldehyde synthons have been inaccessible under the conditions described herein.

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