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LITHIUM THIOMETHOXIDE: A CONVENIENT MERCAPTIDE REAGENT

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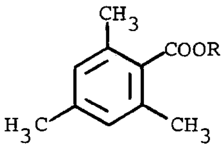
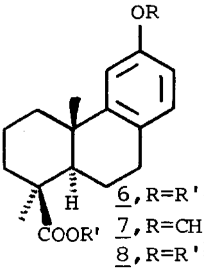
In recent years lithium thiopropoxide (1)[2] and sodium thioethoxide (2)[3,4] have been shown to be effective reagents for the cleavage of hindered esters[2,3,5] and the demethylation of methyl aryl ethers.[2-4] During the course of other studies we had occasion to investigate the possibility of using lithium thiomethoxide (3) in place of these more complex analogs. We now wish to report that CH_3SLi (3) possesses a number of properties which render it an attractive alternative to 1 and 2. Preeminent among these properties are ease of preparation, stability, and shelf life.

Both lithium thiopropoxide (1) and sodium thioethoxide (2) are prepared *in situ* under an inert atmosphere and used directly.[2-5] There is no evidence available to indicate whether solutions of 1 or 2 have long-term stability. We have found that lithium thiomethoxide (3) can be prepared conveniently in bulk and isolated as a stable, free-flowing, off-white solid which can be stored for prolonged periods (>1 year at room temperature) without apparent deterioration in either appearance or reactivity. Although we have stored and utilized 3 under a nitrogen atmosphere, it is unaffected by brief exposure to air (i.e. weighing).

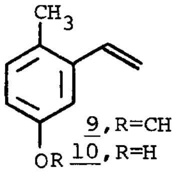
The reactivity of 3 is similar to that of 1 and 2. Thus, treatment[6,7] of esters 4 and 6 with 3 at 25° for 2 hrs affords the corresponding acids 5 and 7, each in 98% yield.[6] When 6 is reacted with 3 under more vigorous conditions (120°,36 hrs), ether cleavage also occurs[2] and 8 is obtained in 95% yield.



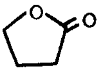
4, $R=CH_3$
5, $R=H$



6, $R=R'=CH_3$
7, $R=CH_3$, $R'=H$
8, $R=R'=H$



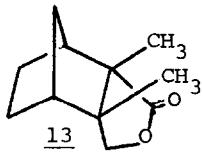
9, $R=CH_3$
10, $R=H$



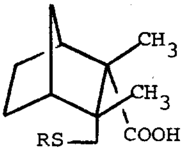
11

$CH_3SCH_2CH_2CH_2COOH$

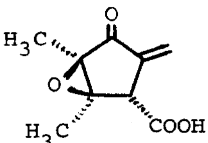
12



13



14, $R=CH_3$
15, $R=C_6H_5$



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Reaction of the aryl ether 9[9] with 3 (160°,2 hr) affords 10 as an oil in 80% yield. The sensitive styrene double bond is unaffected.

Lactones 11 and 13[11] are opened by 3 (25°,36 hrs) to the methylthio acids 12 and 14 (mp 127-29°) in 69 and 75% yields, respectively (it should be noted that the conversion of 13 to 14 presumably involves S_N2 displacement at a neopentyl-like carbon). In contrast to the facile reaction of 13 with 3, opening of 13 with lithium thiophenoxide in HMPA requires reaction temperatures of ~200° and affords 15 in mediocre yield.

Lithium thiomethoxide has also been used to advantage in the synthesis of (±)-methylenomycin A (16) by Scarborough and Smith.[12]

Lithium thiomethoxide. A two-necked, round-bottomed flask fitted with a magnetic stirrer and rubber septum and maintained under a nitrogen atmosphere is cooled to 0° in an icebath. Liquid methanethiol (~100g) is added followed by approximately 200cc of ice-cold anhydrous ether. Commercial ethereal methyllithium (~.5 mol) is then introduced *via* syringe with continued cooling at a rate such that gas (CH_4) evolution does not become excessively violent. During the course of the addition of CH_3Li a white solid separates. When addition of CH_3Li is complete the resulting slurry is placed on a rotary evaporator and the ether and unreacted CH_3SH are removed *in vacuo* (aspirator). Residual volatile material is removed under high vacuum. The product is obtained as a free-flowing solid which is used without further purification; it can be stored under nitrogen in a stoppered flask at room temperature. Protection from light does not appear to be necessary.

References and Notes

1. Receipt of a Research Career Development Award (1975-80) from the National Institutes of Health is gratefully acknowledged.
2. P.A. Bartlett and W.S. Johnson, *Tetrahedron Letters*, 4459 (1970).
3. G.I. Feutrill and R.N. Mirrington, *Aust. J. Chem.*, *25*, 1731 (1972).
4. *Idem.*, *ibid*, *25*, 1719 (1972); *Tetrahedron Letters*, 1327 (1970). For a recent report of the use of 2 to demethylate aryl ethers see S.C. Welch and A.S.C.P. Rao, *ibid*, 505 (1977).
5. For a review see J.E. McMurry, *Org. Reactions*, *24*, 187 (1976).
6. All reactions were conducted by combining the substrate with 3 in hexamethylphosphoric triamide in a ratio of ~1:1:7 (g:g:ml). All yields refer to isolated products.
7. To our knowledge the cleavage of esters or ethers with 3 has not been previously reported. Two brief reports of its use in other reactions have appeared,[8] but neither indicates how it was prepared. A preparation of CH_3SLi from methanethiol and lithium in liquid ammonia has been reported: H. Pleininger, *Ber.*, *83*, 265 (1950).
8. R.S. Matthews and T.E. Meteyer, *Chem. Comm.*, 1576 (1971); E. Vilsmaier and G. Becker, *Synthesis*, 55 (1975).
9. Prepared in the course of another study from 2-methyl-5-methoxybenzaldehyde[10] by reaction with methylenetriphenylphosphorane in ether.
10. 2-Methyl-5-methoxybenzaldehyde was prepared by the procedure of C. Huynh, S. Julia, R. Lorne and D. Michelot, *Bull. Soc. chim. Fr.*, 4057 (1972). See also J.-P. Gesson and J.-C. Jacquesy, *J.C.S. Chem. Comm.*, 652 (1976). We are grateful to Dr. Julia for a preprint of their full paper [*Bull. Soc. chim. Fr.*, 1482 (1976)] and additional experimental details. We also thank Prof. Jacquesy for helpful information.
11. The preparation of 13 will reported elsewhere.
12. R.M. Scarborough and A.B. Smith, III, submitted for publication. We thank Professor Smith for a preprint.