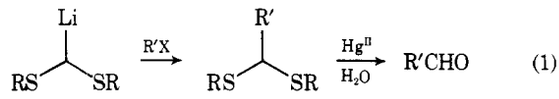
Methylthioformaldine. A New Formaldehyde Anion Equivalent

Summary: Lithium methylthioformaldine, a new formaldehyde anion equivalent, is easily generated and reacts rapidly with primary and secondary halides as well as carbonyl compounds; its hydrolysis to an aldehyde occurs under extremely mild conditions and in high yield.

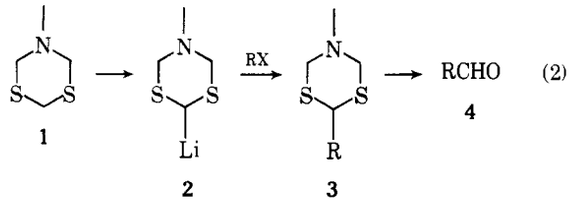
Sir: The alkylation of metalated mercaptal compounds and subsequent hydrolysis of the resulting products has become a standard method of aldehyde synthesis[1] (eq 1). Although



(1)

most reported examples give high yields in both the alkylation and subsequent hydrolysis steps,[1] we have encountered a number of examples in which either or both steps are sluggish. The long reaction times resulted in a number of side reactions which reduced both the yield and purity of the final isolated aldehyde. Frequently tedious chromatographic procedures were required to isolate pure materials.

Speculating that a nitrogen heteroatom in the 5 position of a 1,3-dithiane system might enhance the rate of both the alkylation and hydrolysis steps via intramolecular chelation,[2] we have examined the reactions of several typical alkylating agents with 4,5-dihydro-5-methyl-1,3,5-dithiazin-2-yllithium [lithium methylthioformaldine (LiMTF), **2**][3,4] (eq 2). The



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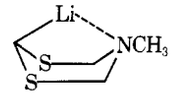


MTF anion is easily generated in tetrahydrofuran (THF) at −78 °C with 1.05 equiv of *n*-butyllithium. As Table I indicates, the alkylation proceeds quickly between −78 and 0 °C to give high yields of pure dithioacetals **3**. Whereas primary alkyl halides gave no detectable traces of elimination products, moderate amounts of olefin (13–20%) were observed with secondary halides. Unfortunately, the reactions of **2** with mesylates and tosylates gave highly colored mixtures containing only trace amounts of the desired products.[5] In contrast to the more vigorous hydrolysis conditions of the 1,3-dithiane adduct[1] (i.e., 4 h at 50 °C in wet acetonitrile), **3** was easily cleaved[6] in 2 h at room temperature in 90% isolated yield (98% NMR yield) with $HgCl_2$/HgO in wet methylene chloride. In a competitive hydrolysis reaction, a mixture of 1 mmol of 2-pentyl-MTF [**3**, R = $(CH_2)_4CH_3$] and 1 mmol of 2-heptyl-1,3-dithiane was treated with 4 equiv of $HgCl_2$ and 4 equiv of $CdCO_3$ at room temperature in methylene chloride. After 2 h **3** was selectively cleaved to hexanal leaving the 1,3-dithiane untouched. This high reactivity would allow the selective hydrolysis of a specific aldehyde in a multifunctional (i.e., multiprotected) compound. Although there have been methods developed which allow removal of dithianes by mild oxidation,[6] this new group's removal is selective, mild, and totally nonoxidative thus allowing reaction with even the most delicate of compounds. The yield of hydrolysis of the MTF grouping to an aldehyde is considerably higher than for the corresponding 1,3-dithiane (i.e., 90% vs. 65–80%).[6,7]

Table I

Alkylating agent	Alkylation product(s), % yield (mp, °C)[a]	Reaction temp, °C (time, h)
n-Hexyl iodide	Quant	−78 (1)
n-Hexyl bromide	95	−30 (1)
n-Hexyl chloride	40	25 (1)
n-Hexyl mesylate	0	−30 (1)
n-Hexyl tosylate	10	−30 (1)
n-Decyl iodide	95 (37)	−78 (1)
Isopropyl iodide	87	−30 (1)
2-Bromooctane	50	0 (2)
2-Iodooctane	80	0 (2)
Benzaldehyde	quant (113)	−30 (1)
p-Dimethylaminobenzaldehyde	quant (155)	−30 (1)
Butanal	85	−20 (0.5)
Acetophenone	90	−20 (0.5)
4-*tert*-Butylcyclohexanone	85, 3:2 mixture	−20 (1)

[a] Satisfactory analytical and spectral data were obtained for all new compounds.

The extension of this method to a ketone synthesis was unfortunately unsuccessful. When **3** (R = *n*-hexyl or *n*-decyl) was treated in THF with any of the following, no significant amount of metalation was observed (as followed by D_2O quenching): *n*-butyllithium, *n*-butyllithium/HMPA, *sec*-butyllithium, *tert*-butyllithium, lithium diisopropylamide, *n*-butyllithium/TMEDA, or KH. Although this is a drawback for the extensive use of this reagent as a general carbonyl anion, this result does allow for the selective formation of a 1,3-dithiane anion in the presence of a MTF-protected aldehyde.

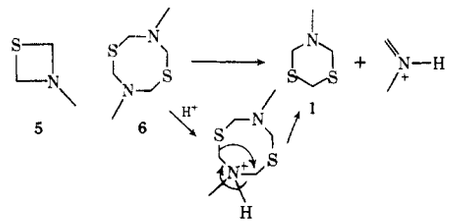
In a representative aldehyde synthesis hendecanal was produced in 86% overall yield as follows. Freshly sublimed (1 mmHg at 70 °C)[3] **1** [10 mmol (1.34 g)] was dissolved in 20 ml of dry THF (distilled from potassium benzophenone ketyl) under argon. After the solution was cooled to −78 °C, 1.05 equiv of *n*-butyllithium in hexane was added dropwise via syringe. After the mixture was stirred for 1 h, a white precipitate had formed. *n*-Decyl iodide (10 mmol, 2.0 ml, stored over 4 Å molecular sieves and Cu powder) was then added dropwise. The solution was stirred at −78 °C for 1 h and then allowed to warm to 0 °C. Upon reaching 0 °C the solution quickly became homogenous. Water was added and the solution was extracted with ether or methylene chloride. The organic phase was dried over $MgSO_4$, and the solvent removed in vacuo to yield 2.7 g (9.6 mmol, 95% yield) of **3** (R = *n* − $C_{10}H_{21}$) as an oil which crystallized upon standing (mp 37 °C).[8] This material was dissolved in 25 ml of wet methylene chloride under argon and treated with 2.2 equiv of $HgCl_2$ and 2.2 equiv of HgO or $CdCO_3$. The reaction was stirred at room temperature until TLC (silica gel, ether–hexane 1:1) indicated the complete conversion (~2 h) of **3** (R_f 0.6) to the aldehyde **4** (R_f 0.75). Anhydrous $MgSO_4$ was added to aid filtration of the precipitated mercury salts. Water was added to the filtrate and the solution extracted with methylene chloride. After drying over $MgSO_4$, the solvent was removed in vacuo giving 1.5 g of a crude oil. This material was distilled bulb to bulb

giving 1.46 g of pure hendecanal (86% overall yield from the iodide).

Acknowledgment. The authors wish to express appreciation to Jenny Adams and Alice Fukushima for technical assistance.

References and Notes

(1) For leading references, see T. Nakai, M. Okawara, *Chem Lett.*, **7**, 731–732 (1974), and D. Seebach, *Synthesis*, 17 (1969).
(2) For leading references, see D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, **7**, 147 (1974).
(3) Preparation of **1**: J. Graymore, *J. Chem. Soc.*, 865 (1935); British Patent 943 273 [*Chem. Abstr.*, **60**, 5528a (1964)].
(4) The literature preparation of **1** indicates that cyclobutane **5** is formed by



reaction of formaldehyde, methylamine, and hydrogen sulfide.[3] On close examination by NMR and mass spectroscopy, this intermediate was shown to be cyclooctane **6**. This explains the facile conversion of **6** to **1**.
(5) A. I. Meyers and co-workers have noted similar problems in the alkylation of α-lithio imino esters; cf. *J. Am. Chem. Soc.*, **91**, 763 (1969).
(6) Very low yields of aldehydes were obtained using the following dithiane hydrolysis procedures: refluxing in 20% sulfuric acid [D. Collins and J. Graymore, *J. Chem. Soc.*, 9 (1957)]; Cu(I) triflate [T. Cohen et al., *J. Org. Chem.*, **40**, 812 (1975)]; and CuCl/CuO [K. Narasaka et al., *Bull. Soc. Chem. Jpn.*, **45**, 3724 (1972)].
(7) (a) E. J. Corey and B. W. Erickson, *J. Org. Chem.*, **36**, 3553 (1971); (b) E. Vedejs and P. L. Fuchs, *ibid.*, **36**, 366 (1971).
(8) Crystalline methiodides of **3** are easily obtained by reaction with a molar excess of clean methyl iodide in peroxide free ether.

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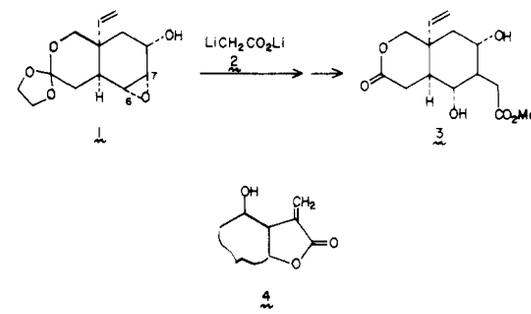
Specific Directing Effects in the Opening of Vicinal Hydroxy Epoxides

Summary: Important directing effects in the ring opening of α-hydroxy epoxides and α-trimethylsilyloxy epoxides are observed in their reactions with dilithioacetate. In reactions of the same substrates with diethylethoxyethynylalane, the key factor determining the sense of ring opening is the stereochemical relationship of the oxy function with the epoxide.

Sir: The decisive step in our recent syntheses of vernolepin and vernomenin involved the reaction of hydroxy epoxide **1** with dilithioacetate (**2**), to give, after suitable treatment, the crucial methyl ester **3**.[1-3] Within the limits of our detection, we were unable to find any product arising from attack at C_6. We thought this result to be surprising since compound **1** would be expected to exist in a preferred conformation, wherein trans diaxial opening would dictate reaction at C_6. We considered the possibility that the ortho ester linkage in **1** effectively shields axial entry at C_6, clearing the way for unencumbered attack at C_7 through a higher energy conformer (Curtin–Hammett principle).[4] Another interesting feature of the process is that the O tetrahydropyranyl derivative of **1** is not attacked by **2**, even under relatively forcing conditions.

In view of the rather wide occurrence of systems such as **4** in both cis- and trans-lactonic arrangements in natural products,[5] many of which have antitumor properties of varying degrees of promise, it was of interest to investigate a potentially straightforward method of synthesis, involving the opening of vicinal, oxygen-substituted epoxides with **2**. Surprisingly, there has been no recorded study, using compound **2**,[6] which is addressed to the attractive possibility of synthesizing systems such as **4** by a direct method of this sort.[7]



As substrates for this investigation, we have studied compounds **5**, **6**, **7**, and **8**. Compound **5** was, of course, well known from the work of Henbest.[8] Silylation of **5** with trimethylchlorosilane–triethylamine–ether at room temperature gives **6** in 81% yield.

The entry to the trans-oxy epoxide series was much facilitated by a recent disclosure of Heathcock, wherein epoxidation of 3-trimethylsilyloxycyclohexene affords **8** as virtually the sole product.[9] Cleavage of **8** with ammonium chloride gives **7**.[9] The reactions of **5**–**8** with **2** are described below.

Lithium diisopropylamide (from 20 mequiv of *n*-butyllithium and an equivalent amount of diisopropylamine) in dimethoxyethane reacted with 10 mequiv of dry acetic acid at −40 °C to generate a solution of **2**. To this solution, was added 1 mequiv of **5**. The system was heated at 55 °C for 15 h. The reaction was quenched with water. After separation of the neutral fraction (starting material) by extraction, the acids were isolated by acidification and extraction. The total acid fraction was heated with *p*-TsOH in benzene and the resultant lactones were readily purified by chromatography on silica gel, using 1:1 ethyl acetate–hexane for elution. There was thus obtained, in 66% combined yield,[10] the homogeneous lactones **9** and **10** in a 3:1 ratio (Scheme I).

When the same reaction was conducted on silyl ether **6**, compounds **9** and **10** were obtained in a ratio of 1:3.2. The structures of the lactones were supported by C and H analysis and infrared and mass spectra: for **9** $\bar{\nu}$ ($CHCl_3$) 1770 cm^{-1}, *m/e* 156 (parent); for **10** $\bar{\nu}$ ($CHCl_3$) 1795 cm^{-1}, *m/e* 156 (parent). Each compound gave a monoacetate (*m/e* 198) with pyridine–acetic anhydride. The NMR spectra ($CHCl_3$) of the two acetates, **9a** and **10a**, readily allowed for their decisive differentiation.[11] In **9a**, both the acetoxy and *O*-lactonic methine protons give rise to a doublet of triplets [δ 3.85 (lactonic methine, J_d = 4.0 Hz, J_t = 11.0 Hz), 4.75 (acetoxymethine J_d = 3.8 Hz, J_t = 11.5 Hz)]. This reflects two virtually equal axial–axial couplings and one axial–equatorial coupling for each proton. Accordingly, the three hydrogens at the asymmetric carbons must be axial—a situation embraced in **9a**. In the isomeric acetoxylactone, the lactonic methine (δ 3.88) is seen as a doublet of doublets (J_1 = 2.8 Hz, J_2 = 11.0 Hz) while the acetoxy-bound methine proton gives rise to a multiplet ($h_{1/2} \sim 7$ Hz). It may be safely concluded that his proton is predominantly equatorially disposed, while the lactonic methine hydrogen is axial. Thus, compounds **9** and **10** both arise from inversion of configuration of the epoxide by anion