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A General Preparative Method for α-Lithioethers and Its Application to a Concise, Practical Synthesis of Brevicomin

Sir:

Until recently, α-lithioethers were nearly always prepared by deprotonation of an α-carbon atom of an ether which has a special anion-stabilizing feature. Examples of the latter are substituents such as carbonyl,[1] cyano,[2] phenylthio,[3] or most commonly carbon–carbon unsaturation;[4] in addition, sp^2 hybridization of the ether carbon atom allows ready deprotonation by alkyllithiums even when anion-stabilizing substituents are absent.[5] Schöllkopf,[6] and later Peterson,[7] showed that α-lithiomethyl methyl ether can be prepared from α-stannylmethyl methyl ether precursors by exchange with an alkyllithium, and Still[8] has demonstrated how this principal can be applied to the preparation of α-lithioethers of types **1** and **2**, species which do not possess special anion-stabilizing features.

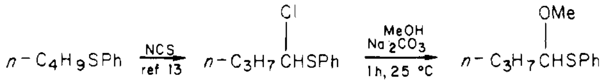
$ROCH_2Li$

1

$RCH(OR')Li$

2

We now report that a variety of types of unstabilized and stabilized α-lithioethers can be rapidly prepared in tetrahydrofuran at −63 or −78 °C from α-(phenylthio)ethers by reductive lithiation with lithium 1-(dimethylamino)naphthalenide (LDMAN)[9] or lithium naphthalenide (LN). What makes this method one of considerable generality is the ready availability of various types of α-(phenylthio)ether substrates or their vinylogues as demonstrated by eq 1–7.

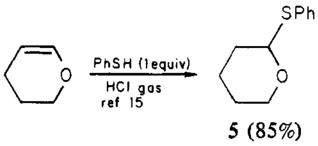


$$n\text{-}C_4H_9SPh \xrightarrow[\text{ref 13}]{\text{NCS}} n\text{-}C_3H_7CH(Cl)SPh \xrightarrow[\text{1h, 25 °C}]{\text{MeOH, Na}_2\text{CO}_3} n\text{-}C_3H_7CH(OMe)SPh \quad (1)$$

3 (92%)

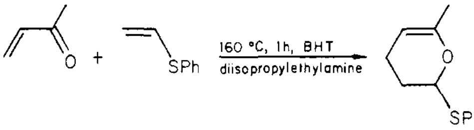
$$Me_2C(OMe)_2 \xrightarrow[\text{BF}_3\cdot\text{OEt}_2,\ -45\ °\text{C; ref 14}]{\text{PhSH (1equiv)}} Me_2C(OMe)SPh \quad (2)$$

4 (61%)



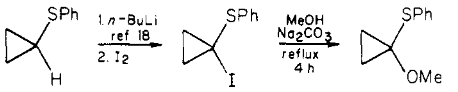
(3)

5 (85%)



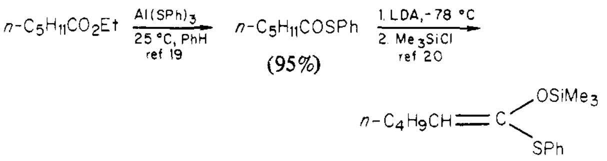
(4)

6 (73%[17])



(5)

7 (83%)



(6)

(95%)

8 (100%) (mixture of *E* and *Z*)

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(7) Peterson, D. J. *Organomet. Chem. Rev., Sect. A* **1972**, *7*, 295.

(8) (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (b) Still, W. C.; Mitra, A. *Ibid.* **1978**, *100*, 1927. Still, W. C.; Sreekumar, C. *Ibid.* **1980**, *102*, 1201. See also: Seebach, D.; Meyer, N. *Angew Chem., Int. Ed. Engl.* **1976**, *15*, 438.

(9) We have recently introduced this reagent for the preparation of certain sulfur-stabilized anions by reductive lithiation of the appropriate bis(phenylthio)acetals.[10] While this reagent must be prepared and used below −45 °C, it has a major advantage with respect to lithium naphthalenide, which has also been used to prepare such anions,[11] in that the byproduct, 1-(dimethylamino)naphthalene, can be easily separated from the desired product by acid extraction.[10] Certain reductions have been performed previously by Bank and Platz[12] by using the sodium analogue.

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(18) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Rigby, J. H.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1977**, *99*, 3080.

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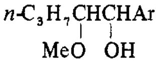
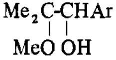
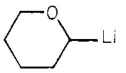
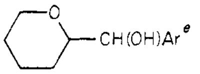
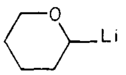
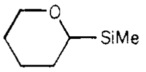
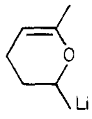
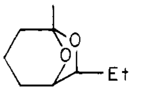
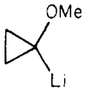
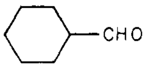
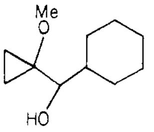
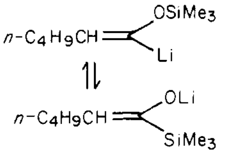
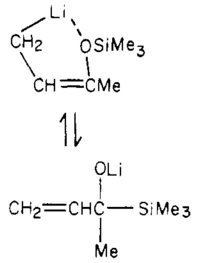
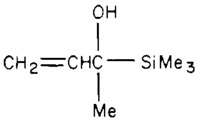
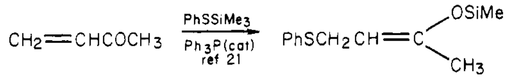
Table I. Reductive Lithiations of α-(Phenylthio)ethers in THF[a]

substrate	α-lithioether	electrophile[b]	product[b]	yield, %[c]
3	n-$C_3H_7CH(OMe)Li$,[d] **10**	ArCHO	 $n\text{-}C_3H_7\underset{MeO}{CH}\underset{OH}{CH}Ar$[e]	85
3	n-$C_3H_7CH(OMe)Li$, **10**	Me_3SiCl	n-$C_3H_7CH(OMe)SiMe_3$	68
4	$Me_2C(OMe)Li$, **11**	ArCHO	 $\underset{MeO}{Me_2C}\text{-}\underset{OH}{CHAr}$	69
5	 **12**[d]	ArCHO		65
5	 **12**	Me_3SiCl		64
6	 **13**	EtCHO	 **14**[e]	40
7	 **15**		 **16**	90
8	 **17**	H_2O	n-$C_5H_{11}COSiMe_3$	88
9	 **18**	H_2O		79

[a] Except where noted, lithium 1-(dimethylamino)naphthalenide was used for 30 min at -63 °C or for 45 min at -78 °C. [b] Ar = *p*-anisyl. [c] Yields not optimized. [d] Lithium naphthalenide used at -78 °C for 45 min. [e] Mixture of two diastereomers.



(7)

9 (94%) (mixture of *E* and *Z*)

The results of the reductive lithiations of **3**–**9** followed by reaction of the resulting α-lithioethers with various electrophiles are shown in Table I.[22] The initial product (**18**) of reductive lithiation of **9** can be written as an α-lithioether, but the more likely structure is the vinylogous α-lithioether shown;[4e] such compounds are known to be in rapid equilibrium with the corresponding lithium alkoxide,[4e,23,24] and it is reasonable to suggest a similar reverse Brook[25] rearrangement for **17**.

We are unaware of successful deprotonation procedures for the preparation of any of the types of α-lithioethers or their vinylogues listed in the table.[26] It appears likely that **10** would be available by Still's stannylation–destannylation technique.[8] An (unchelated) analogue of **18** has been prepared[24] by tin–lithium exchange on a compound prepared by silylating the adduct of lithiotrimethyltin and cyclohex-2-en-1-one, but it is questionable whether this procedure would be successful for the far more easily polymerized methyl vinyl ketone. It should be mentioned that the sodio analogue of **17** is probably an intermediate in the reductive silylation of **8** with sodium in the presence of trimethylsilyl chloride.[20]

It is particularly noteworthy that attempts to prepare **12** by lithium–selenium exchange[15b] and tertiary lithio compounds such as **11** by lithium–tin exchange[8a] were unsuccessful. This highlights the probable fundamental difference between the present method of producing anions and the usual methods such as deprotonation and metal–metal exchange. In the latter methods, it is likely that the rate-determining step is anion formation, and there is a direct relationship between the stability of the anion and its ease of formation. Reductive lithiation via radical anions is believed to involve an electron transfer to the substrate followed by homolytic cleavage of a carbon–heteroatom bond, resulting in the formation of an anionic leaving group (in this case thiophenoxide) and a carbon radical; reduction of the latter yields the carbanion.[11c] Because of the excellent correlation between the mildness of the conditions used and the expected stability of the carbon radical produced,[27] we think that it is likely that the first electron transfer is rapid and reversible and that the rate-determining step is the formation of the carbon radical. Thus, this procedure is ideal for preparing anions such as α-lithioethers since the ether linkage,

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(22) New compounds have been characterized by ^1H NMR, IR, and mass spectroscopy and either by their exact masses, as determined by high-resolution mass spectroscopy, or by combustion analyses.

(23) Hosomi, A.; Hashimoto, H.; Sakurai, H. *J. Organomet. Chem.* **1979**, *175*, C1. Kuwajima, I.; Kato, M. *J. Chem. Soc., Chem. Commun.* **1979**, 708.

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(26) Attempts to prepare close analogues of **18** by deprotonation of the corresponding allyl silyl ether were unsatisfactory.[4e,f]

(27) For example, α-(phenylthio)ethers and bis(phenylthio)ketals are readily cleaved at -78 °C whereas phenyl alkyl sulfides appear to require temperatures at least 30 °C higher,[11c] and phenyl vinyl sulfides are not reduced below 0 °C.[28]

(28) Rattigan, D.; Hutchins, R., unpublished results.

while only weakly stabilizing the anionic product,[4c,29] markedly stabilizes the radical[30] produced in the rate-determining step.

A simple application of this technology is illustrated by the two-flask synthesis of brevicomin (**14**), comprising (1) the Diels–Alder addition of commercially available phenyl vinyl sulfide[31] and methyl vinyl ketone (eq 4) and (2) treatment of the adduct (**6**) with LDMAN followed by trapping of the anion (**13**) with propionaldehyde. Acidic workup removes the (dimethylamino)naphthalene and causes the ring closure to an acetal. The product (**14**), a mixture of endo (57%) and exo (43%) isomers, was characterized by the ^{1}H NMR spectrum of the mixture,[32] the relative retention times of the two isomers on a Carbowax 20M GLC column,[33] and the mass spectrum of each isomer[32] obtained by combined gas chromatography–mass spectrometry. Both isomers are exuded by the female Western Pine beetle, the exo isomer being a key component of its aggregation pheromone;[33,34] the endo isomer is a potent inhibitor of the aggregation behavior of the very destructive Southern Pine beetle.[35] The attractive features of the present synthesis compared to other reported syntheses[33,36] include brevity, the use of nonpoisonous and relatively inexpensive reagents, and the probable ease of scale up due to the fact that no chromatographic separations are required; the product is isolated in pure form directly by distillation. No attempt has yet been made to influence the stereoselectivity of the reaction of the anion **13** with propionaldehyde and thus the endo/exo ratio of **14**.

We shall report at a later date on the utility of α-lithiocyclopropyl methyl ethers of the type **15** for the production of cyclobutanones via their aldehyde adducts such as **16**.

α-Lithioethers should be interesting synthetic intermediates not only because of their nucleophilic reactivity as illustrated in this paper but also because of their ability to undergo the Wittig and related rearrangements.[4a] These uses are now under study.

Acknowledgment. We thank Dr. Alvin Marcus for recording the mass spectra and the National Institutes of Health for support of this work (GM 22760 and BRSG Grant S07 RR07084-13).

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Received July 8, 1980

Aziridine-2,3-diones

Sir:

The study of strained molecules allows chemists to explore the limits of stability in organic chemistry, and permits calibration of theory and experiments in extreme cases.[1] Three-membered rings possessing carbonyl groups are usually unstable and quite reactive because of the large strain energies. α-Lactones have been generated at very low temperatures and observed spectroscopically,[2] and α-lactams are also unstable unless they possess bulky substituents.[3] Introduction of one more carbonyl group to these three-membered rings should further increase the strain energies of the rings. Thus, three-membered rings bearing two carbonyl groups are hitherto unknown. In view of these facts, aziridine-2,3-diones are experimentally as well as theoretically intriguing and challenging molecules. Treatment of oxanilic acid with thionyl chloride does not give *N*-phenylaziridine-2,3-dione but leads instead to a dimeric product, 2,3,5,6-tetraoxo-1,4-diphenylpiperazine.[4] In this communication, we report the formation of these unstable compounds in the low-temperature photolysis of ozonides of diphenylmaleylimides.

An ozonide usually undergoes homolysis of the oxygen–oxygen bond followed by a double β scission on irradiation to give an acid anhydride and a radical pair (or a biradical). Photolysis of ozonides has been utilized for the synthesis of three-membered rings such as cyclopropanes[5] and for the generation of unstable compounds such as cyclobutadienes[6] and Dewar benzenes.[7] Therefore, photolysis of ozonides of maleylimides is a quite promising method for the generation of aziridine-2,3-diones.

Ozonides of diphenylmaleylimides (**1a**–**1d**) were obtained as stable crystalline compounds by ozonolysis of the corresponding imides in acetone at −78 °C. The structures of the ozonides were confirmed by elemental analyses, spectral data,[8] and the fact that reduction of the ozonides with dimethyl sulfide gives the corresponding bis(phenylglyoxalyl)imides quantitatively.

When **1b** in benzene was irradiated with a high-pressure mercury lamp at room temperature, benzoic anhydride and methyl isocyanate were obtained almost quantitatively. The formation of carbon monoxide was also confirmed by both hemoglobin and palladium chloride tests,[9] though the yield was not determined. Photolysis of other ozonides gave similar results. The fact that benzoic anhydride is formed efficiently in the photolysis clearly shows that these ozonides undergo the expected reaction to give 1,3-biradicals (**2**). The isocyanates and carbon monoxide formed in these reaction conditions are presumed to be produced by decomposition of aziridine-2,3-diones (**3**) and/or cleavage of the biradicals (Scheme I).

Next, the low-temperature photolysis of **1** was carried out in order to examine the intermediacy of **3**. The ozonide (**1b**) in a KBr pellet was photolyzed at 77 K for 1 h, and the reaction was

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(8) **1b**: mp 137–138 °C; IR (KBr) 1765 (w), 1705 cm^{-1}; NMR (CDCl$_3$) δ 3.23 (s, 3 H), 7.4–7.8 (m, 10 H). Anal. Calcd for $C_{17}H_{13}O_5N$: C, 65.69; H, 4.20; N, 4.49. Found: C, 65.41; H, 4.08; N, 4.53.

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