

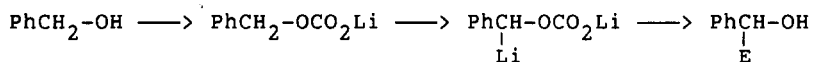
**$\alpha$ -LITHIO TRIMETHYLSILYLMETHYL LITHIUM CARBONATE AS METHANOL DIANION  
SYNTHON.<sup>1</sup> A ONE-POT SYNTHESIS OF  $\alpha$ -HYDROXY KETONES.**

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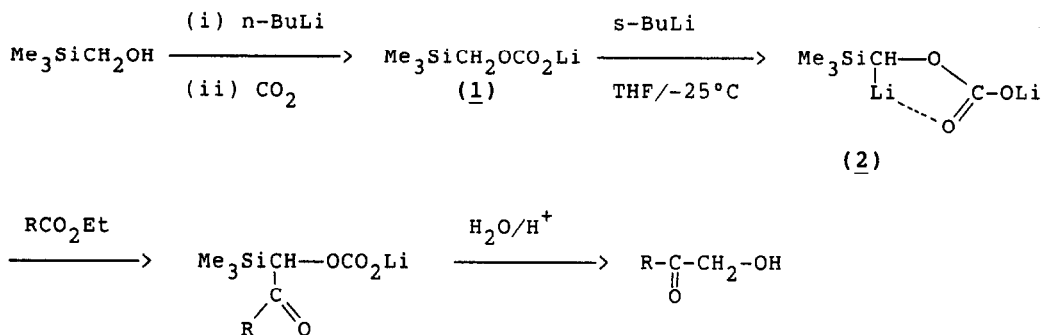
**Abstract:** 1-Trimethylsilylmethanol is used via its lithiated lithium carbonate in a one-pot procedure to hydroxymethylate esters, dimethylamides, acid chlorides and nitriles to give the corresponding hydroxymethyl carbonyl compounds in the synthetic conversion  $\text{RCOX} \rightarrow \text{RCOCH}_2\text{OH}$ .

The potential of nucleophilic hydroxymethylation in organic synthesis was recognised some years ago by Seebach.<sup>2</sup> However, exploration in this field has been severely limited by the high energetics of  $\alpha$ -lithiation in an alcohol. Thus apart from the  $\alpha$ -stannylmethanol / butyllithium system,<sup>3</sup> other reported methods<sup>4</sup> have approached this objective in an indirect fashion, and as a result, are all multistep procedures.

Certain classes of O-alkyl lithium carbonates and N-alkyl lithium carbamates are emerging as useful intermediates which can undergo lithiation alpha to the O- or N-nucleophilic center.<sup>5,6</sup> These intermediates are easily prepared by reaction of a lithium alkoxide or amide anion with  $\text{CO}_2$  and, at the end of the reaction sequence, de-protection is achieved spontaneously during hydrolytic work-up. Recently we described the successful  $\alpha$ -lithiation of benzyl alcohol via its lithium carbonate:<sup>5</sup>



Since methanol could not be  $\alpha$ -lithiated by this method, we searched for a suitable activating auxiliary which could be readily removed subsequently. The trimethylsilyl group appeared to be ideally suited for this purpose for two reasons. First, a silyl group has the proven ability to stabilize an alpha-carbanion<sup>7</sup> and secondly, it can be easily removed when adjacent to a suitable functional group. We now report the application of  $\text{Me}_3\text{SiCH}_2\text{OH}$  via its lithium-carbonate<sup>8</sup> as a novel and an effective nucleophilic hydroxymethylating agent.

Scheme 1

The lithium carbonate (1) of  $\text{Me}_3\text{SiCH}_2\text{OH}$  was prepared easily ( $\text{n-BuLi} / \text{CO}_2$ ).  $\alpha$ -Lithiation on this lithium carbonate was achieved with  $\text{s-BuLi}$  in THF at  $-25^\circ\text{C}$  (Scheme 1). Use of  $\text{n-BuLi}$  or  $\text{t-BuLi}$  gave somewhat inferior yields. Reaction of this  $\alpha$ -lithio species (2) with different electrophiles followed by hydrolytic work-up directly afforded the products of nucleophilic hydroxymethylation. Fair to good yields of the  $\alpha$ -hydroxymethyl carbonyl products were obtained using esters, a dimethylamide, or a nitrile as electrophile.

Representative examples are shown in Table 1. The low yield with benzoyl chloride is probably due to an undesired lithium-halogen exchange process. The  $\alpha,\beta$ -Unsaturated esters significantly gave solely the carbonyl-addition products; no trace of any 1,4-addition was detected. However, enolizable electrophiles such as cyclohexanone and aliphatic esters gave none of the desired products. Use of benzophenone resulted mainly in ketyl formation.

Table 1. Reaction of  $\text{Me}_3\text{SiCH}(\text{Li})\text{OCO}_2\text{Li}$  with Electrophiles.

Electrophile	Product	Yield(%)	m.p. ( $^\circ\text{C}$ ) <sup>a</sup>
$p\text{-Me-C}_6\text{H}_4\text{CO}_2\text{Et}$	$p\text{-Me-C}_6\text{H}_4\text{COCH}_2\text{OH}$	68	87-88(89-90) <sup>9a</sup>
PhCN	PhCOCH <sub>2</sub> OH	65	86-88(89-90) <sup>9b</sup>
PhCONMe <sub>2</sub>	PhCOCH <sub>2</sub> OH	60	86-88(89-90) <sup>9b</sup>
PhCOCl	PhCOCH <sub>2</sub> OH	23	86-88(89-90) <sup>9b</sup>
Me <sub>2</sub> C=CHCO <sub>2</sub> Et	Me <sub>2</sub> C=CHCOCH <sub>2</sub> OH	63	oil <sup>9c</sup>
$\underline{t}$ -PhCH=CHCO <sub>2</sub> Et	$\underline{t}$ -PhCH=CHCOCH <sub>2</sub> OH	42	66-68(69-70) <sup>12f</sup>

<sup>a</sup> literature melting points in parentheses.

The above, results however, do not differentiate between (2) and the lithiomethyl lithium carbonate (3)<sup>10</sup> as the reacting species. This was settled decisively in the favor of the former by using benzaldehyde as the electrophile (Scheme 2) which produced only phenylacetaldehyde (4) (70%) and not the diol (5). For this reason, we believe that with the other electrophiles above, the initial adducts are desilylated during the work-up stage.<sup>11</sup>



### Scheme 2

$\alpha$ -Hydroxy ketones are traditionally prepared via electrophilic hydroxylation of ketone enolates,<sup>12</sup> a procedure not without complications. Thus direct oxygenation often results in complex products of over-oxidation.<sup>12a-c</sup> Methyl ketone enolates are hydroxylated by the MoO<sub>5</sub>.Py.HMPA complex but the products undergo condensation with the starting material, resulting in very low yields.<sup>12d</sup> On the other hand, Rubottom's<sup>12e</sup> mCPBA oxidation of silyl enol ethers and Moriarty's<sup>12f</sup> hyper-valent iodine oxidation are quite effective. Our approach to hydroxymethyl ketones utilises a novel "methanol dianion synthon" in a sequence which is conceptually opposite to the existing ones. Additionally, the transformation shown in Scheme 2 (PhCHO  $\longrightarrow$  PhCH<sub>2</sub>CHO) could provide a potentially attractive route for the homologation of aldehydes.<sup>13</sup>

A typical experimental procedure is as follows : n-BuLi (1 ml, 2.5 M) was added, at -78°C to a THF solution (25 ml) of 1-trimethylsilylmechanol (0.25g , 2.5 mmole) in a Schlenk reactor (200 ml). It was warmed to 25°C and after 5 min dry CO<sub>2</sub> gas was bubbled through this solution for 5 min. All volatile contents were evacuated under 0.5 mm leaving a white residue of the lithium carbonate (1). The reactor was purged with argon and the residue was dissolved in THF (30 ml). s-BuLi (2.1 ml , 1.3 M) was slowly added to this solution at -78°C. The solution was warmed to -25°C and held there for 2 hrs. It was then cooled down to -78°C followed by the addition of the appropriate electrophile (2.5 mmole) in THF (10 ml). After stirring for 30 min at 25°C, it was acidified with 2N HCl. Extractive work-up with ether followed by silica-gel chromatography gave the hydroxymethyl ketones.<sup>9</sup>

Finally, Me<sub>3</sub>SiCH<sub>2</sub>OH is commercially available<sup>14</sup> and the convenient "one-pot" sequence described above makes it an efficient <sup>-</sup>CH<sub>2</sub>OH synthon. Possible further extentions of this methodology are being studied.

References and Notes :

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Part 5: Katritzky, A.R. and Akutagawa, K. J. Am. Chem. Soc. 1986, 108, 6808.  
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8. Unlike  $\text{Bu}_3\text{SnCH}_2\text{OH}$  (ref. 3),  $\text{Me}_3\text{SiCH}_2\text{OH}$  gave no C-alkylation when treated with 2 equivalents of BuLi followed by benzaldehyde. Lack of formation of an "ate" complex (which occurs for the tin analogue) is presumed to be responsible for this failure.
9. (a) von Auwers, K. Chem. Ber. 1906, 39, 3757. (b) Wolff, L. Liebig. Annal. 1912, 394, 23. (c) Novel compound :  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 200MHz) 5.9 (1H, s), 4.2 (2H, s), 2.3 (1H, br, OH), 2.2 (3H, s) and 1.9 (3H, s);  $\delta_{\text{C}}$  ( $\text{CDCl}_3$ , 50MHz) 198.0 ( $\text{C}=\text{O}$ ), 158.9 ( $\beta\text{-C}$ ), 119.0 ( $\alpha\text{-CH}$ ), 68.6 ( $\text{CH}_2$ ), 27.8 ( $\text{CH}_3$ ), 21.4 ( $\text{CH}_3$ );  $\text{M}^+$  (HRMS) found 114.0728,  $\text{C}_6\text{H}_{10}\text{O}_2$  requires 114.0681.
10. There is evidence that  $\text{Me}_3\text{Si-C}$  bonds are occasionally cleaved with BuLi (c.f. ref. 7) which in our hand could give rise to (3).
11. The silyl group in  $\alpha$ -silyl carbonyl compounds are readily protodesilylated in the presence of acid or base; see e.g. (a) Brook, A.G. in Advances in Organometallic Chemistry, Stone, F.G.A. and West, R. ed., Academic Press, New York, 1968, 7, p. 96; (b) Brook, A.G. Accts. Chem. Res. 1974, 7, 77.
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13. Detailed procedures for the homologation of aldehydes will be reported in due course.
14.  $\text{Me}_3\text{SiCH}_2\text{OH}$  was purchased from Petrarch Systems, Inc. and is now available also from Aldrich.

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