

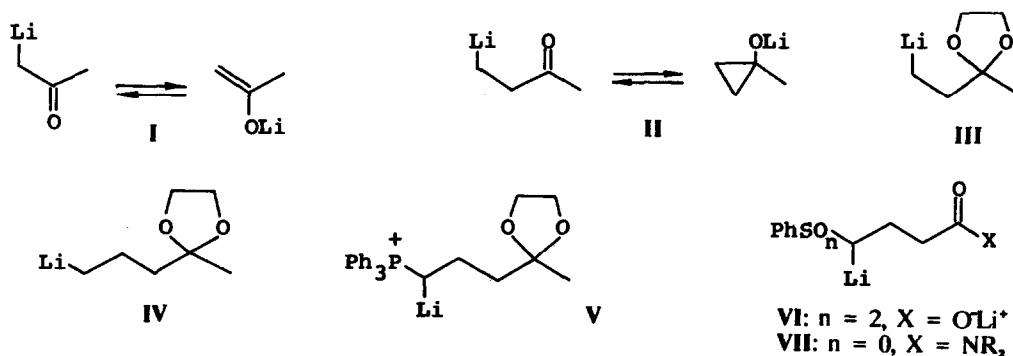
## 2-(3-LITHIOPROPYL)- AND 2-(3-LITHIOPROPYL)-2-METHYL-1,3-DIOXOLANE: NEW MASKED LITHIUM BISHOMOENOLATES IN THE SYNTHESIS OF BIFUNCTIONALIZED COMPOUNDS <sup>+1</sup>

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**Summary:** 2-(3-Lithiopropyl)- and 2-(3-lithiopropyl)-2-methyl-1,3-dioxolane (**2**) are prepared by lithiation of the corresponding chlorinated precursors with lithium naphthalenide at  $-78^{\circ}\text{C}$ . The reaction of these masked bishomoenolates with different electrophiles yields the expected monoprotected functional carbonyl compounds (**3-12**), which can be easily deprotected under acid conditions.

Functionalized organometallic compounds present great interest in organic synthesis because they can react with electrophilic reagents yielding directly polyfunctionalized molecules.<sup>2</sup> When the functionality is a carbonyl group and the metal atom is lithium<sup>3</sup> the stability of these species depends strongly on the relative position of the metal atom and the carbon-oxygen double bond.<sup>4</sup> Thus, since enolate intermediates<sup>5</sup> of the type **I** and stable species which give C-coupling reactions,<sup>6</sup> the corresponding homoenolate intermediates of the type **II** behave as typical alcoholate.<sup>7</sup> This problem has been overcome using two different strategies: (a) forming homoenolates derivatives from less electropositive metals<sup>8</sup> or (b) protecting the carbonyl group as a ketal of the type **III**.<sup>9</sup> In relation to the corresponding masked lithium bishomoenolates of the type **IV**,<sup>10</sup> the only examples described in the literature are stabilized species of the type **V**,<sup>14</sup> **VI**,<sup>15</sup> and **VII**.<sup>16</sup> However, to our knowledge, the masked non-stabilized simplest intermediate of the type **IV** is still unknown. This paper describes the preparation of such lithium masked bishomoenolates, which represent convenient synthons<sup>17</sup> for the unit  $\text{C-C-C-C=O}$  and can be also consider as  $d^+$  reagents.<sup>18</sup>



<sup>+1</sup>Dedicated to Prof. G. Wilke on occasion of his 65th birthday.

Table. Reaction of bishomoenolates **2** with electrophiles

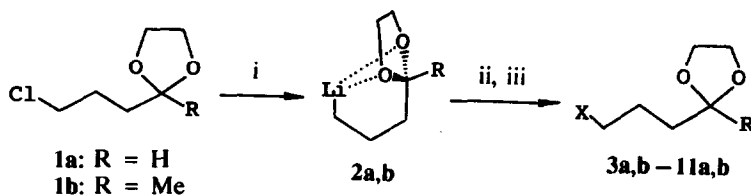
Entry	Inter.	Electrophile	Products <sup>a</sup>			
			No	X	Yield(%) <sup>b</sup>	R <sub>f</sub> <sup>c</sup>
1	<b>2a</b>	H <sub>2</sub> O	<b>3a</b>	H	85	0.72
2	<b>2a</b>	<i>i</i> -PrCHO	<b>4a</b>	<i>i</i> -PrCH(OH)	61	0.43 <sup>d</sup>
3	<b>2a</b>	PhCHO	<b>5a</b>	PhCH(OH)	60	0.27 <sup>d</sup>
4	<b>2a</b>	<i>c</i> -C <sub>3</sub> H <sub>5</sub> COPh	<b>6a</b>	<i>c</i> -C <sub>3</sub> H <sub>5</sub> C(OH)Ph	57	0.61 <sup>d</sup>
5	<b>2a</b>	( $\overline{\text{CH}_2}$ ) <sub>3</sub> CO	<b>7a</b>	( $\overline{\text{CH}_2}$ ) <sub>3</sub> C(OH)	52	0.42 <sup>d</sup>
6	<b>2a</b>	PhCN	<b>8a</b>	PhCO	56	0.43
7	<b>2a</b>	PhCON( $\overline{\text{CH}_2}$ ) <sub>4</sub>	<b>8a</b>	PhCO	57	0.43
8	<b>2a</b>	PhNCS	<b>9a</b>	PhNHCS	65	0.41 <sup>d</sup>
9	<b>2a</b>	PhNCHPh	<b>10a</b>	PhCH(PhNH)	61	0.43
10	<b>2a</b>	(PhCH <sub>2</sub> S) <sub>2</sub>	<b>11a</b>	PhCH <sub>2</sub> S	85	0.58
11	<b>2b</b>	H <sub>2</sub> O	<b>3b</b>	H	90	0.69
12	<b>2b</b>	D <sub>2</sub> O	<b>3'b</b>	D	80 <sup>e</sup>	0.69
13	<b>2b</b>	<i>i</i> -PrCHO	<b>4b</b>	<i>i</i> -PrCH(OH)	52	0.60 <sup>d</sup>
14	<b>2b</b>	PhCHO	<b>5b</b>	PhCH(OH)	51	0.35 <sup>d</sup>
15	<b>2b</b>	<i>c</i> -C <sub>3</sub> H <sub>5</sub> COPh	<b>6b</b>	<i>c</i> -C <sub>3</sub> H <sub>5</sub> C(OH)Ph	78	0.33
16	<b>2b</b>	( $\overline{\text{CH}_2}$ ) <sub>3</sub> CO	<b>7b</b>	( $\overline{\text{CH}_2}$ ) <sub>3</sub> C(OH)	61	0.23 <sup>d</sup>
17	<b>2b</b>	PhCN	<b>8b</b>	PhCO	62	0.46
18	<b>2b</b>	PhCON( $\overline{\text{CH}_2}$ ) <sub>4</sub>	<b>8b</b>	PhCO	55	0.46
19	<b>2b</b>	PhNCS	<b>9b</b>	PhNHCS	73	0.22
20	<b>2b</b>	PhCHNPh	<b>10b</b>	PhCH(PhNH)	82	0.52
21	<b>2b</b>	(PhCH <sub>2</sub> S) <sub>2</sub>	<b>11b</b>	PhCH <sub>2</sub> S	62	0.67

<sup>a</sup>All products were >95% pure (g.l.c. and n.m.r.) and gave satisfactory spectral data (i.r., <sup>1</sup>H n.m.r., and mass spectra). <sup>b</sup>Based on the starting material **1**. Yields after flash chromatography (silica gel, hexane/ethyl acetate) have not been optimized. <sup>c</sup>Silica gel, hexane/ethyl acetate: 4/1. <sup>d</sup>Silica gel, hexane/ethyl acetate: 3/2. <sup>e</sup>>95% deuterium from mass spectrometry.

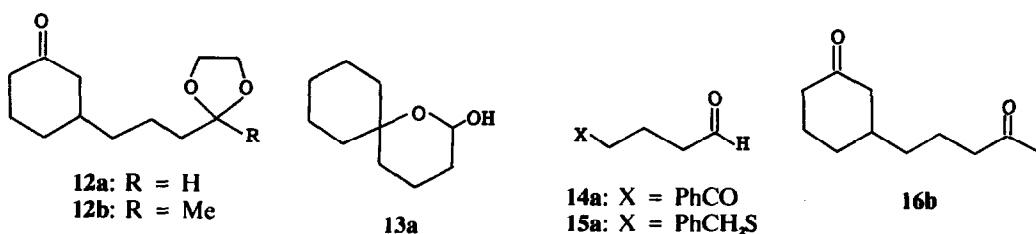
The reaction of the chloroacetals **1** with lithium naphthalenide<sup>19</sup> in tetrahydrofuran at -78°C led to the corresponding masked lithium bishomoenolates **2**, which were stable at this temperature, and reacted with different electrophilic reagents (-78°C to room temperature) to give, after hydrolysis, the expected products **3-11** (Scheme and Table). Intermediates **2** have to be manipulated at low temperature in order to avoid their partial or total decomposition mainly by abstraction of a proton from the solvent.<sup>20</sup>

We have also investigated the reaction of the intermediates **2** with  $\alpha,\beta$ -unsaturated ketones in the presence of a catalytic amount (1:0.25 molar ratio) of the complex copper (I) bromide-dimethyl sulphide.<sup>21</sup> Thus, starting from **2a** or **2b** and cyclohexenone the corresponding products **12a** (61%;

$R_f=0.30^{2a,c}$ ) and **12b** (63%;  $R_f=0.55^{2a,c}$ ) were obtained, respectively.



**Scheme.** Reagents: i,  $\text{Li}^+\text{C}_{10}\text{H}_8^-$ ,  $-78^\circ\text{C}$ ; ii,  $\text{E}^+$ ,  $-78$  to  $20^\circ\text{C}$ ; iii,  $\text{H}_2\text{O}$ .



We think that products **4-12** may have interest from a synthetic point of view because they contain, in general, two functional groups, one of them -the masked carbonyl group arisen from **2-** in a protected form, so they are regioselectively protected bifunctional compounds. However, the acid hydrolysis of these products yields the expected functionalized carbonyl compound in almost quantitative isolated yields. Thus, for instance, the treatment of compounds **7a**, **8a**, **11a**, and **12b** with 2 N hydrochloric acid in tetrahydrofuran yielded products **13a** (99%<sup>2a,c</sup>), **14a** (93%;  $R_f=0.35^{2a,c}$ ), **15a** (95%;  $R_f=0.53^{2a,c}$ ), and **16b** (94%;  $R_f=0.45^{2a,c}$ ), respectively. Compounds of the type **13a** can be used as precursors of substituted tetrahydropyrans by reduction<sup>23</sup> or alkylation,<sup>24</sup> or transformed into the corresponding  $\delta$ -lactones by oxidation.<sup>25</sup> On the other hand, compounds of the type **16b** have been successfully employed in annulation reactions.<sup>24</sup> In conclusion, we think that intermediates of the type **2** are useful synthons for the four-carbons unit  $^-\text{C}-\text{C}-\text{C}-\text{C}=\text{O}$ , that can be adequate for the synthesis of biologically active compounds of the brevicomins type.<sup>26</sup>

In a *typical reaction*, to a solution of the corresponding dioxolane **1** (2.5 mmol) in THF (5 ml) was added a solution of lithium naphthalenide (6.0 mmol) in THF at  $-78^\circ\text{C}$  under an argon atmosphere and the mixture was stirred for 7 h at the same temperature. Then the corresponding electrophile (2.5 mmol)<sup>27</sup> was added and the resulting solution were stirred overnight allowing the temperature to rise to  $20^\circ\text{C}$ . Then the resulting mixture was hydrolyzed with water (5 ml), neutralized with 2N hydrochloric acid, extracted with ether (2x5 ml), and the organic layer dried over anhydrous sodium sulphate. Solvents were removed (15 torr) and the resulting residue were chromatographed (silica gel; hexane/ethyl acetate) to give the corresponding products **3-11**. In the case of obtaining products **12**, copper (I) bromide-dimethyl sulphide complex (0.6 mmol) was added after formation of intermediate **2** and the mixture stirred for 30 min before adding cyclohexenone (2.5 mmol); in this case the final hydrolysis was carried out with a saturated aqueous solution of ammonium chloride.<sup>28</sup>

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