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## Metalation of Arylmethyl Methyl Ethers and Connection with Their Reductive Electrophilic Substitution

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Abstract: Stable  $\alpha$ -methoxy arylmethyl carbanions can be generated by metalation of arylmethyl methyl ethers, 1, with *n*-BuLi in THF at -40 °C, avoiding Wittig rearrangement to the corresponding alkoxides 2. Reaction of these carbanions with various electrophiles afforded the expected products 3 in satisfactory yields. Connection between the metalation procedure and the reductive electrophilic substitution of arylmethyl methyl ethers allowed the transformation of compounds 1 into 2-arylpropanoic acids, 5.

 $\alpha$ -Alkoxy-substituted arylmethyl carbanions generated by the metalation reaction of arylmethyl alkyl ethers with butyl lithium (*n*-BuLi) in THF or in THF-containing solvent mixtures are reported to be unstable, even at low temperatures. Under these conditions, rearrangement of such carbanions to the corresponding alkoxides (Wittig rearrangement) is expected.<sup>1</sup> More elaborated synthetic procedures were therefore developed to generate synthetic analogues of these carbanions.<sup>2-4</sup> At variance with these reports, we have recently reported the generation of stable  $\alpha$ -methoxy arylmethyl carbanions by the reductive cleavage of aromatic dimethyl acetals with Li metal in tetrahydrofuran (THF) at -40 °C.<sup>5</sup>



Scheme 1: 1a, 2a: Ar = C<sub>6</sub>H<sub>5</sub>, R = CH<sub>3</sub>; 1b, 2b: Ar = C<sub>6</sub>H<sub>5</sub>, R = C<sub>2</sub>H<sub>5</sub>; 1c, 2c: Ar = 2-(CH<sub>3</sub>O)C<sub>6</sub>H<sub>4</sub>, R = CH<sub>3</sub>; 1d, 2d: Ar = 4-(CH<sub>3</sub>)C<sub>6</sub>H<sub>4</sub>, R = CH<sub>3</sub>; 3a: Ar = C<sub>6</sub>H<sub>5</sub>, R = CH<sub>3</sub>, E = CH<sub>3</sub>; 3b: Ar = C<sub>6</sub>H<sub>5</sub>, R = CH<sub>3</sub>, E = CH<sub>4</sub>; 3c: Ar = C<sub>6</sub>H<sub>5</sub>, R = CH<sub>3</sub>, E = CH<sub>2</sub>CH<sub>2</sub>OH; 3d: Ar = C<sub>6</sub>H<sub>5</sub>, R = CH<sub>3</sub>, E = (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>COH; 3e: Ar = 2-(CH<sub>3</sub>O)C<sub>6</sub>H<sub>4</sub>, R = CH<sub>3</sub>, E = D; 3f: Ar = 2-(CH<sub>3</sub>O)C<sub>6</sub>H<sub>4</sub>, R = CH<sub>3</sub>, E = C, CH<sub>3</sub>O)C<sub>6</sub>H<sub>4</sub>, R = CH<sub>3</sub>, E = C<sub>4</sub>H<sub>9</sub>; 3g: Ar = 4-(CH<sub>3</sub>)C<sub>6</sub>H<sub>4</sub>, R = CH<sub>3</sub>, E = D; 3h: Ar = 4-(CH<sub>3</sub>)C<sub>6</sub>H<sub>4</sub>, R = CH<sub>3</sub>, E = C<sub>4</sub>H<sub>9</sub>

To make this matter clear, we have reinvestigated the metalation reaction of arylmethyl alkyl ethers, 1, in THF and wish now to report that, contrary to literature's expectations, the  $\alpha$ -methoxy arylmethyl carbanions generated at low temperature according to this procedure are sufficiently stable to be trapped with electrophiles (Scheme 1).

The reactivity of arylmethyl methyl ether, 1a, and of arylmethyl ethyl ether, 1b, taken as model compounds, was investigated under various metalation conditions. Selected results are reported in Table 1. The results of D<sub>2</sub>O quenching experiments, carried out to check the formation of the  $\alpha$ -alkoxy-substituted methylphenyl carbanions, are also reported in Table 1.<sup>6</sup>

Metalation of **1a** was performed by the action of *n*-BuLi (1 to 2 equiv of a 1.6 M solution in hexane) in anhydrous THF. Quenching of the reaction mixtures with H<sub>2</sub>O afforded the product of Wittig rearrangement, *i.e.*, 1-phenylethanol, **2a**, and/or starting material, both at room temperature and at -20 °C (entries 1 and 2). D<sub>2</sub>O quenching experiments showed that quantitative metalation of compound **1a** can be achieved by the action of *n*-BuLi in THF at -40 °C during 1 h (entries 3 and 4); under these conditions, Wittig rearrangement of the intermediate  $\alpha$ -methoxy methylphenyl carbanion is almost completely suppressed, whilst a significant amount of **2a** was recovered after 6 h reaction time (entry 5). These results show that a proper choice of reaction temperature and time is essential to avoid rearrangement of the  $\alpha$ -methoxy methylphenyl carbanion.

Entry	Compound	Equiv of <i>n</i> -BuLi	T(°C)	t(h)	Product Distribution (%) <sup>a</sup>	
					1(%D) <sup>b</sup>	2
1	1a	2	25	1	-	71c
2	la	2	-20	1	76 (>95)	24
3	1a	2	-40	1	>95 (>95)	<5
4	1a	1.2	-40	1	>95 (>95)	<5
5	1a	2	-40	6	92 (92)	8
6	1 b	1.2	-40	1	30 (n.d.) <sup>d</sup>	13
7	1 b	1.2	-80	3	46 (28) <sup>e</sup>	-
8	1 b	1.2f	-80	3	28 (36)g	-

Table 1. Products Distribution in the Metalation Reaction of Compounds 1a and 1b

<sup>a</sup>Yields were determined by <sup>1</sup>H NMR analyses of the crude reaction mixtures, unless otherwise indicated. <sup>b</sup>As determined by <sup>1</sup>H-NMR by monitoring the percentage of deuterium incorporation in the benzylic position after D<sub>2</sub>O quenching; n.d. means not determined. <sup>c</sup>Isolated yield. <sup>d</sup>Compound **4** formed in 57% yields. <sup>e</sup>Compound **4** formed in 26% yields. <sup>f</sup>In the presence of 1.2 equiv of TMEDA. <sup>g</sup>Compound **4** formed in 36% yields.

Somewhat different results were obtained with compound 1b. As above, metalation of 1b was accomplished by the action of 1.2 equiv of *n*-BuLi at -40 °C for 1 h. Under these conditions a significant amount of the rearranged product (1-phenyl-1-propanol, 2b) was recovered (entry 6). This is in agreement with the finding of Schöllkopf and co-workers,<sup>7</sup> which reported that the ethyl group undergoes the Wittig rearrangement more easily than the methyl group. The main reaction product (57%) was however benzyl alcohol, 4, *i.e.*, the

product of a  $\beta$ -elimination reaction occurring on the intermediate  $\alpha$ -ethoxy methylphenyl carbanion.<sup>7,8</sup> Formation of compound **2b** can be avoided by lowering the temperature to -80 °C. Under these conditions, however, the intermediate carbanion formed in a relatively low amount, as evidenced by D<sub>2</sub>O quenching, whilst 4 still formed in 26% yield (entry 7). Addition of TMEDA to the reaction mixture did not improve this result (entry 8).

These findings prompted us to investigate the alkyllithium promoted electrophilic substitution of arylmethyl methyl ethers. The results are reported in Table 2.6

Trapping of the carbanion generated by the action of *n*-BuLi or *sec*-BuLi on **1a** at -40 °C with different electrophiles (CH<sub>3</sub>I, C<sub>4</sub>H<sub>9</sub>Br, (CH<sub>2</sub>CH<sub>2</sub>)<sub>2</sub>O, (C<sub>6</sub>H<sub>5</sub>)<sub>2</sub>CO) was successful, affording compounds **3a-d** in satisfactory yields. The metalation reaction was extended to the substituted compounds **1c** and **1d**; interestingly, quenching of the intermediate  $\alpha$ -methoxy arylmethyl carbanions with D<sub>2</sub>O afforded regioselectively compounds **3e** and **3g**, respectively, whilst quenching with C<sub>4</sub>H<sub>9</sub>Br afforded compounds **3f** and **3h**, respectively, as the only electrophilic substitution products.

Entry	Compound	t(h)	EX	Product, E =	Yield (%) <sup>b</sup>
1	1a	1	CH <sub>3</sub> I	<b>3a</b> , CH <sub>3</sub>	86 <sup>c</sup>
2	1a	1	CH <sub>3</sub> I	<b>3a</b> , CH <sub>3</sub>	>95 <sup>d</sup>
3	1a	1	C4H9Br	3b, C4H9	68 <sup>e</sup>
4	1a	0.25	(CH <sub>2</sub> CH <sub>2</sub> )O <sup>f</sup>	3c, CH <sub>2</sub> CH <sub>2</sub> OH	45e
5	1a	3	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> CO	3d, (C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> COH	76 <sup>e</sup>
6	1 c	0.5	D <sub>2</sub> O	<b>3e</b> , D	85
7	1 c	1	C4H9Br	<b>3f</b> , C4H9	76
8	1 d	0.5	D <sub>2</sub> O	<b>3</b> g, D	90
9	1 d	1	C <sub>4</sub> H <sub>9</sub> Br	<b>3h</b> , C <sub>4</sub> H <sub>9</sub>	80

Table 2. Electrophilic Substitution of Compounds 1a, 1c and 1d<sup>a</sup>

<sup>a</sup>Metalation reactions were run at -40 °C for 1 h with 1.2 equiv of *n*-BuLi, unless otherwise indicated; see note 6. <sup>b</sup>Yields were determined by <sup>1</sup>H NMR analyses of the crude reaction mixtures, unless otherwise indicated. <sup>c</sup>14% of **3b** was also recovered. <sup>d</sup>The metalation was run with 1.2 equiv of *sec*-BuLi. <sup>c</sup>Yields determined on isolated products after flash chromatography. <sup>f</sup>Gaseous (CH<sub>2</sub>CH<sub>2</sub>)O was bubbled into the reaction mixture for 5 min.

To further improve the usefulness of the above reported results, we have investigated a connection between the metalation procedure and the reductive electrophilic substitution of arylmethyl methyl ethers.<sup>9</sup> Such an approach should allow the synthesis of disubstituted arylmethyl derivatives like, *e.g.*, 2-arylpropanoic acids, a class of compounds endowed with interesting pharmacological properties. Accordingly, **1a** was metalated with 1 equiv of *sec*-BuLi in THF at -40 °C and the intermediate carbanion quenched with 1 equiv of CH<sub>3</sub>I. After 1 h stirring, the mixture was warmed to 0 °C and added to a suspension of 2.2 equiv of Li metal and 4 mol % of

naphthalene<sup>10</sup> in THF at 0 °C. After 1 h stirring, the mixture was chilled again to -40 °C and quenched with gaseous CO<sub>2</sub>. Work-up and flash chromatography afforded 2-phenylpropanoic acid, **5a**, in 53% overall yield. Starting from **1c**, a similar procedure afforded the 2-arylpropanoic acid **5b** in 48% yield (Scheme 2).

 $ArCH_2OCH_3$  i - v  $ArCH(CH_3)COOH$ 
 $Ia: Ar = C_6H_5$   $5a: Ar = C_6H_5, 53\%$  yield

  $Ic: Ar = 4 - (CH_3O)C_6H_4$   $5b: Ar = 4 - (CH_3O)C_6H_4, 48\%$  yield

**Scheme 2**: i, *sec*-BuLi, -40 °C, THF/cyclohexane; ii, CH<sub>3</sub>I, -40 °C; iii, Li, naphthalene (cat.), 0 °C; iv, gaseous CO<sub>2</sub>, -40 °C; v, H<sub>3</sub>O<sup>+</sup>

Our results show the potential synthetic usefulness of the metalation procedure in the generation and trapping with electrophiles of  $\alpha$ -methoxy-substituted arylmethyl carbanions. Connection with the reductive electrophilic substitution reaction allows the use of arylmethyl methyl ethers as synthetic equivalents of arylmethyne dianions, leading to the introduction of two different substituents onto the arylmethyl carbon. Further work is in progress to extend this methodology to other pharmacologically active disubstituted arylmethyl derivatives.<sup>11,12</sup>

## **References and Notes**

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- 6. The substrate (5 -10 mmol) was dissolved under Ar in dry THF (10 20 ml) and chilled to the reported temperature. To this mixture 1 to 2 equiv of a 1.6 M solution of *n*-BuLi in hexane (or of a 1.3 M solution of *sec*-BuLi in cyclohexane) were added and the mixture was stirred for the reported time (Table 1). The reaction was quenched by slow dropwise addition of H<sub>2</sub>O, the cold bath removed, and the resulting mixture extracted with Et<sub>2</sub>O. D<sub>2</sub>O quenching was performed by slow dropwise addition of 2-3 ml of D<sub>2</sub>O to the reaction mixture, followed by stirring for 0.5 h and work-up as above. Quenching with electrophiles was performed at -40 °C by slow dropwise addition of 1.2 equiv of the appropriate electrophile dissolved in a minimum amount of THF, followed by stirring at -40 °C for the time reported in Table 2 and work-up as above. The crude products were purified by flash chromatography.
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- 11. All compounds gave analytical and spectral (<sup>1</sup>H and <sup>13</sup>C NMR, IR) data in agreement with the assigned structures.
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