

Naphthalene-Catalysed Lithiation of Dialkyl Sulfates: A New Route for Organolithium Reagents

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Abstract: The lithiation of primary and secondary dialkyl sulfates with an excess of lithium powder in the presence of a catalytic amount of naphthalene at -78°C leads to the corresponding alkyl-lithium reagents (1:2 molar ratio), which react with different electrophiles, mainly carbonyl compounds, to yield the expected coupling products. This methodology represents an indirect way for transforming alcohols into organolithium compounds through the corresponding dialkyl sulfates.

Among the procedures for preparing organolithium reagents the most useful involve either halogen-lithium^{1a} or hydrogen-lithium^{1b} exchanges. Other less common methodologies use, for instance, mercury- or tin-lithium transmetallation^{1c}, reductive cleavage of ethers or thioethers^{1d}, or the Shapiro reaction^{1e}. In general, the way to prepare alkyl-lithium reagents starts from halogen-containing materials -usually alkyl bromides or chlorides- and so the resulting solution of the organolithium derivative contain the corresponding lithium halide^{1a}. We very recently found² that allylic and benzylic mesylates can be transformed into the corresponding organolithium derivatives by a naphthalene-catalysed lithiation with lithium powder³. However, this method does not work for alkylic systems. In this paper we report on the conversion of dialkyl sulfates -easily prepared from the corresponding alcohols- into alkyl-lithium compounds following the same methodology.

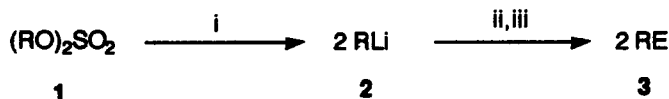
The reaction of different dialkyl sulfates **1** with an excess of lithium powder (1:14 molar ratio) in the presence of a catalytic amount of naphthalene (1:0.16 molar ratio) at -78°C led to a solution of the corresponding organolithium reagent **2** (1:2 molar ratio), which reacted with several electrophiles, mainly carbonyl compounds to yield the expected reaction products **3** (Scheme 1 and Table 1). In the absence of naphthalene the reaction took place with much poorer yield (Table 1, footnote c). On the other hand, it is important to keep the low temperature in order to avoid secondary processes, mainly coupling reactions between the alkyl-lithium formed and the starting dialkyl sulfate; for instance, the above described reaction using diethyl sulfate **1b** as starting material and benzaldehyde as electrophile at room temperature afforded the corresponding product **3ba** in only 14% yield (compare with Table 1, entry 4). The process is general for primary (Table 1, entries 1-6 and 9-11) and

Table 1. Transformation of Dialkyl Sulfates **1** into Alkyl-Lithium Reagents **2** and Reaction with Electrophiles. Obtention of Compounds **3**.

| Entry | Starting sulfate | | Electrophile | Product ^a | | | | |
|-------|---|-----------|------------------------------------|----------------------|-------------------------------------|------------------------|----------------------|------|
| | R | No | | No. | E | Yield (%) ^b | <i>R_f</i> | Lit. |
| 1 | Me | 1a | PhCHO | 3aa | PhCHOH | 52 ^c | 0.34 ^d | 5 |
| 2 | Me | 1a | Ph ₂ CO | 3ab | Ph ₂ COH | 99 | 0.61 ^e | 6 |
| 3 | Me | 1a | (PhCH ₂ S) ₂ | 3ac | PhCH ₂ S | 64 | 0.25 ^f | 7 |
| 4 | Et | 1b | PhCHO | 3ba | PhCHOH | 73 | 0.35 ^g | 5 |
| 5 | Et | 1b | (CH ₂) ₅ CO | 3bb | (CH ₂) ₅ COH | 41 | 0.30 ^e | 8 |
| 6 | Et | 1b | Ph ₂ CO | 3bc | Ph ₂ COH | 70 | 0.47 ^{e,h} | 9 |
| 7 | <i>i</i> -Pr | 1c | PhCHO | 3ca | PhCHOH | 40 | 0.76 ^g | 10 |
| 8 | <i>i</i> -Pr | 1c | Ph ₂ CO | 3cb | Ph ₂ COH | 55 | 0.42 ^e | 11 |
| 9 | <i>n</i> -Bu | 1d | <i>i</i> -PrCHO | 3da | <i>i</i> -PrCHOH | 25 | 0.41 ^e | 12 |
| 10 | <i>n</i> -Bu | 1d | PhCHO | 3db | PhCHOH | 55 | 0.17 ^g | 5 |
| 11 | <i>n</i> -Bu | 1d | Ph ₂ CO | 3dc | Ph ₂ COH | 83 | 0.58 ^e | 13 |
| 12 | <i>n</i> -C ₆ H ₁₃ CHMe | 1e | PhCHO | 3ea | PhCHOH | 31 | 0.83 ^g | 14 |
| 13 | <i>n</i> -C ₆ H ₁₃ CHMe | 1e | Et ₂ CO | 3eb | Et ₂ COH | 23 | 0.85 ^e | - |
| 14 | <i>n</i> -C ₆ H ₁₃ CHMe | 1e | Ph ₂ CO | 3ec | Ph ₂ COH | 48 | 0.65 ⁱ | 15 |

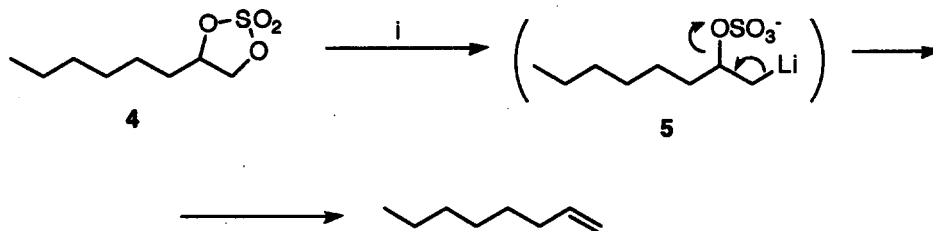
^a All products were >95% pure (GLC) and gave spectroscopic data (IR, ¹H and ¹³C NMR, and MS) according to the proposed structures. ^b Isolated yields after flash chromatography (silica gel, hexane/ethyl acetate) based on the starting dialkyl sulfate **1** for the stoichiometry **1**→**2**. ^c 28% yield in absence of naphthalene under the same reaction conditions. ^d Hexane/ethyl acetate 4/1. ^e Hexane/ethyl acetate 9/1. ^f Hexane. ^g Hexane/ethyl acetate 6/1. ^h Mp 91-92°C. ⁱ Hexane/ethyl acetate 19/1.

secondary (Table 1, entries 7,8 and 12-14) dialkyl sulfates. We were not able to prepare tertiary dialkyl sulfates by the conventional methods, so we could not test the same process for these starting materials. In general the starting dialkyl sulfates were prepared from the corresponding alcohols following the Sharpless procedure⁴.



Scheme 1. *Reagents and conditions:* i, Li powder (excess), naphthalene (4% molar), THF, -78°C; ii, E⁺=PrⁱCHO, PhCHO, Et₂CO, (CH₂)₅CO, Ph₂CO, (PhCH₂S)₂, -78 to 20°C; iii, H₂O-HCl.

We also tried the application of this procedure for the preparation of dilithium compounds starting from cyclic sulfates derived from 1,2-diols. Thus, the lithiation of compound **4** followed by treatment with benzaldehyde as electrophile and under the same reaction conditions as for compounds **1** yielded 1-octene as the only organic reaction product detected by GLC. In this case the first formed monoorganolithium derivative (probably the most stable primary carbanion **5**) suffers spontaneous β-elimination¹⁶ to give the obtained olefin (Scheme 2).



Scheme 2. *Reagents and conditions:* i, Li powder (excess), naphthalene (4% molar), THF, -78°C.

From the results described here we conclude that this methodology represents a new way for obtaining organolithium compounds starting from dialkyl sulfates. If one considers that the dialkyl sulfates precursors are easily accessible starting from the corresponding alcohols⁴, this route is an indirect transformation of alcohols into the corresponding alkyl-lithium derivatives. It is also worthy to note that under the here described reaction conditions the obtained organolithium reagents are not decomposed by the starting dialkyl sulfate through the corresponding coupling reaction.

In a *typical procedure* a suspension of lithium powder (100 mg, 14 mmol) and naphthalene (20 mg,

0.16 mmol) in tetrahydrofuran (5 ml) was stirred under argon until a dark green colour appeared and then it was cooled at -78°C . To the resulting suspension was added a solution of the corresponding dialkyl sulfate 1 (1 mmol) (**CAUTION!**: dialkyl sulfates are harmful chemicals and should be handled with special precautions) in tetrahydrofuran (2 ml) for 15 min. After 1 h of additional stirring at -78°C the corresponding electrophile (2 mmol) was added and the mixture was stirred for *ca.* 5 h allowing the temperature to rise to 20°C . The resulting mixture was then hydrolyzed with water (5 ml), neutralized with 2 N hydrochloric acid and extracted with ether (2x20 ml). The organic layer was dried over anhydrous sodium sulfate and the solvents were evaporated *in vacuo* (15 torr). The resulting residue was purified by flash chromatography (silica gel, hexane/ethyl acetate) affording the corresponding products 3.

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References and Notes

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