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Tetrahedron Letters
Tetrahedron Letters 48 (2007) 6434–6436

New stabilising groups for lateral lithiation of *ortho*-cresol derivatives

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Received 1 June 2007; revised 2 July 2007; accepted 11 July 2007
Available online 17 July 2007

Abstract—1-(2-Methoxyethoxy)-2-methylbenzene and 1-(2-dimethylaminoethoxy)-2-methylbenzene have been lithiated using *sec*-BuLi under a variety of conditions and the laterally lithiated species trapped with electrophiles.

The methoxyethoxy substituent has been reported as being an effective stabiliser for *ortho*-lithiation.[1] In our previous work on compound **1** it gave very efficient lateral lithiation.[2] We were intrigued to know whether the stabilisation of laterally lithiated species by this group and the related dimethylaminoethoxy group was general.

Here we report lithiations of compounds **2** and **3**.[3] The two outcomes felt to be most probable: lateral and *ortho*-lithiation, are shown (Fig. 1). In the literature, 2-methoxytoluene has been deprotonated with *n*-BuLi/KO-*t*-Bu leading to lateral deprotonation products including products arising from migration of the methyl from oxygen to carbon, while the methoxymethyl analogue of **3** gives exclusive *ortho*-lithiation when treated with *sec*-BuLi.[4]

The results of reactions of **2** are shown in Table 1. Deuteration could be carried out cleanly and with good conversion (72:26 product to starting material) in diethyl ether by generating the lithio species at −30 °C for 2 h using 1.3 equiv of *sec*-BuLi before quenching with D_2O. Only a small amount of the *ortho*-deuterated product **5a** was observed.[5] Generating the lithio species at −78 °C for 2 h led to isolation of starting material only. Methylation could be carried out cleanly with 76% conversion to compound **4b**. Keeping the concentrations of all reagents low was important with the formation of *ortho*-cresol (as well as *ortho*-methylation product **5b**) accompanying product formation above 0.05 M in **2**. Use of *tert*-butyl methyl ether as a solvent led to increased methylation at the *ortho*-position. Use of TMEDA as an additive, common in the preparation of organolithium compounds, shifted the reaction from lateral to *ortho*-lithiation products completely, again accompanied by some of the deprotected compound **6**. Allylation gave a clean reaction at the lateral position but with only 25% conversion to product. This could be improved to 50% by the addition of tetrabutylammonium iodide. Silylation with TMSCl was also clean and gave somewhat better conversion to product. Generation of the lithio species over longer time periods and/or at higher temperatures in diethyl ether and TBME tended to result in lower conversion to **4** and more recovered starting material, suggesting that the lithio species may be quenched by the solvent in these cases. The wide variations in product distribution with solvent, concentration and electrophile suggest that the degree of aggregation is the most important factor in these systems. The complete change of regioselectivitiy when TMEDA was added would seem to confirm this.

Removal of the methoxyethyl group was carried out on compounds **4b** and **4c** using aluminium triiodide in toluene giving the known compounds **7** and **8** in 62% and 65% yields, respectively (Scheme 1).[6]

A similar range of electrophiles was investigated with compound **3** (Table 2). More than 2 equiv of *sec*-BuLi

Keywords: Lateral lithiation; Alkylation; Cresol.
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doi:10.1016/j.tetlet.2007.07.070

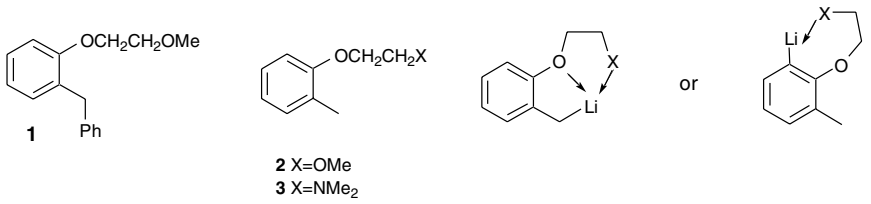
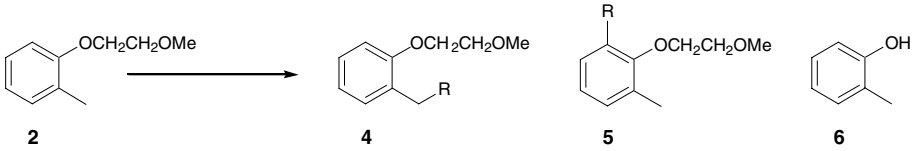


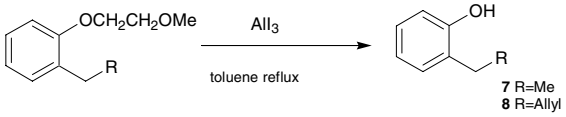
Figure 1.

Table 1. Reactions of **2**



Entry	R–X	Solvent, concn, additive	Prod.	4	5	6	2
1	D_2O	Diethyl ether, 0.03 M	**a**	72	2	0	26
2	D_2O	TBME	**a**	26	2	0	72
3	Me-I	Diethyl ether, 0.06 M	**b**	71	15	14	0
4	Me-I	Diethyl ether, 0.03 M	**b**	76	4	0	20
5	Me-I	TBME	**b**	77	23	0	0
6	Me-I	Diethyl ether, 0.03 M, TMEDA	**b**	0	65	15	20
7	Allyl-Br	Diethyl ether, 0.03 M	**c**	25	0	0	75
8	Allyl-Br	Diethyl ether, 0.03 M, Bu_4NI	**c**	50	0	0	50
9	TMS-Cl	Diethyl ether, 0.03 M	**d**	74	0	0	26

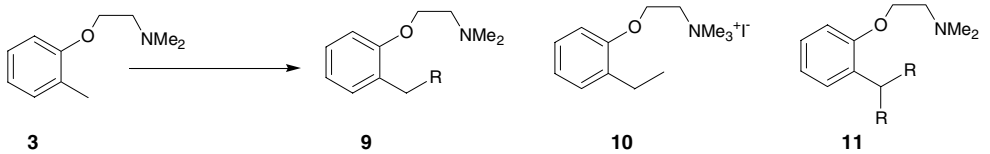
Conditions: Solution of **2** and *sec*-BuLi (1.3 equiv) in ether stirred at −30 °C for 2 h followed by addition of electrophile (1.5 equiv) and warming to rt.



Scheme 1. Conditions: AlI_3, toluene, reflux, 12 h.

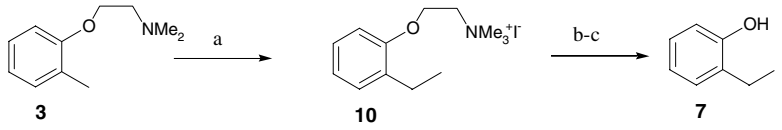
were needed for all reactions of **3**. The reason for this stoichiometry is unclear but no lithiation took place at less than 2 equiv. Deuteration in ether was clean and gave better conversion to product than that observed with **2**. One problem with compound **3** was the tendency for the amine nitrogen to react with excess electrophile which could make recovery of the product difficult. When the lithio species was reacted with a large excess of iodomethane (2.5 equiv of iodomethane led to 100% recovery of starting material) the major product was the dimethylated quaternary salt **10**. This could be avoided with allyl electrophiles and TMS-Cl, though TMS-Cl gave rise to a di-substituted product **11**.[7] Generally, reactions of **3** gave cleaner conversion to lateral lithiation products than those of **2**. Neither deprotection to *ortho*-cresol nor products of *ortho*-lithiation were observed in any of the reactions.

Table 2. Reactions of **3**



Entry	R–X, equiv	Solvent, additive	Prod.	9	10	3	11
1	D_2O, 2.5	Diethyl ether	**a**	83	0	17	0
2	D_2O, 2.5	TBME	**a**	73	0	27	0
3	Me-I, 10.0	Diethyl ether	**b**	0	80	20	0
4	Me-I	TBME	**b**	31	63	6	0
5	Allyl-Br, 2.5	Diethyl ether	**c**	75	0	25	0
6	TMS-Cl, 2.5	Diethyl ether	**d**	0	0	14	86
7	Benzophenone	Diethyl ether	**e**	72	0	28	0

Conditions: Solution of **3** and *sec*-BuLi (2.3 equiv) in ether stirred at −30 °C for 2 h followed by addition of electrophile and warming to rt.



3 10 7

Scheme 2. Reagents and conditions: (a) solution of **3** and *sec*-BuLi (2.3 equiv) in ether stirred at −30 °C for 2 h followed by addition of MeI (10.0 equiv) and warming to rt; (b) KO^{t}Bu, DMSO, rt, 2 h; (c) acidic work-up.

A method was developed for removal of the dimethylaminoethoxy group which involved quaternisation of the nitrogen using iodomethane in the same pot as the alkylation reaction, treatment with KO^{t}Bu in DMSO to eliminate trimethylammonium iodide and acidic work-up to cleave the vinyl ether to the cresol derivative. This was used to prepare compound **7** from **3** in 64% overall yield (Scheme 2).

The efficient removal of the stabilising group combined with high conversions to the products of lateral lithiation may render this group highly useful in synthesis. These possibilities will be investigated in future work.

Acknowledgement

We thank the EPSRC for mass spectrometry services.

References and notes

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