Unexpected Variations in Sites of Lithiation of *N*-(2-Methoxybenzyl)-pivalamide

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Abstract: Directed lithiation of *N*-(2-methoxybenzyl)pivalamide with two mole equivalents of *t*-BuLi in anhydrous THF at –78 °C followed by reactions with various electrophiles gave ring substitution, but *ortho* to the methoxy group rather than *ortho* to the pivaloylaminomethyl group, which was unexpected in view of earlier results reported with *n*-BuLi.

Key words: *N*-(2-methoxybenzyl)pivalamide, directed lithiation, synthesis, dilithium intermediate, electrophile

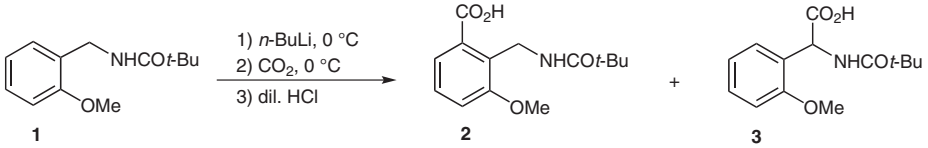
Regioselective synthesis of substituted aromatics is one of the classical problems in synthetic chemistry. Simple electrophilic substitution often leads to various isomers and polysubstituted aromatics and usually takes place under forcing conditions in the presence of a catalyst. In recent years, many efforts have been made to develop clean and environmentally friendly processes for the regioselective production of specific products and it is well recognized that organolithium reagents[1,2] can play an important role in such cases. In particular, lithiation of aromatic compounds often occurs proximal to substituents that possess oxygen or nitrogen atoms.[3] As a result, lithiation of aromatics or heterocycles followed by treatment with an electrophile is one of the most efficient approaches for synthesis of substituted and/or modified derivatives.[4,5] In connection with other work, we were interested in regioselective substitution of substituted benzylamines and wished to employ lithiation techniques for this purpose.

Simig and Schlosser have reported that lithiation of *N*-(4-methoxybenzyl)pivalamide using *n*-BuLi at 0 °C, followed by treatment with carbon dioxide, results in carboxylation at the 2-position, *ortho* to the pivaloylaminomethyl group, rather than *ortho* to the methoxy group. The product was isolated in 64% yield.[6] By contrast, following treatment of *N*-(2-methoxybenzyl)pivalamide (**1**) in the same way two products were reported (Scheme 1).[6] One of these involved carboxylation *ortho* to the pivaloylaminomethyl group (**2**; isolated in 10% yield by fractional crystallization), and the other involved carboxylation at the side chain (**3**; isolated in 14% yield as the methyl ester following treatment of the residue with diazomethane).[6] Again, there was no mention of lithiation *ortho* to the methoxy group. Furthermore, the poor regioselectivity and low yields achieved in the latter reaction render the process unattractive as a synthetic method.

Based on our own experience in the use of lithium reagents in organic synthesis and in directed lithiation reactions,[7] we felt that it might be possible to develop a more regioselective lithiation procedure for *N*-(2-methoxybenzyl)pivalamide. Therefore, we decided to undertake a wider investigation of the directed lithiation of this compound. The results, which we now report, show unexpected variations in the site of lithiation under different conditions. As a result, we have been able to establish conditions for a high-yielding and general ring substitution, but at the position *ortho* to the methoxy group rather than *ortho* to the pivaloylaminomethyl group. Lithiation at this site was not reported at all under the conditions used by Simig and Schlosser.[6]

Initially, *N*-(2-methoxybenzyl)pivalamide (**1**) was lithiated, followed by reaction with carbon dioxide, under conditions similar to those used by Schlosser. The crude product was crystallized from ethyl acetate to give pure white crystals of 3-methoxy-2-(pivaloylaminomethyl)benzoic acid (**2**)[8] in 11% yield, while the ^{1}H NMR spectrum of the mother liquor showed the presence of additional **2** (19%), along with **3** (40%), residual **1** (17%), and another compound, subsequently identified as 2-methoxy-3-(pivaloylaminomethyl)benzoic acid (**4**; 8%).[9]

Our initial variation of the procedure involved attempting the use of alternative lithiating agents, namely *s*-BuLi and *t*-BuLi. The reactions were carried out under the same



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Scheme 1 Lithiation of **1** followed by reaction with CO_2 as reported by Schlosser[6]

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conditions as used with *n*-BuLi. Crystallization of the crude product after use of *s*-BuLi gave **2** in 25% yield, while crystallization of the crude product from the *t*-BuLi reaction allowed isolation of two components, **2** (5% yield) and **4** (40%), the structure of which was confirmed by X-ray crystallography (Figure 1). Inspection of the ^{1}H NMR spectra of the residual mother liquors allowed the overall yields of all components obtained in the reactions to be analyzed, and the results are presented in Table 1.

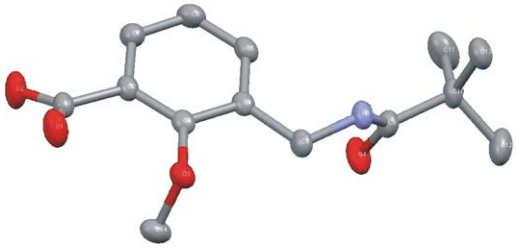


Figure 1 X-ray crystal structure of **4**

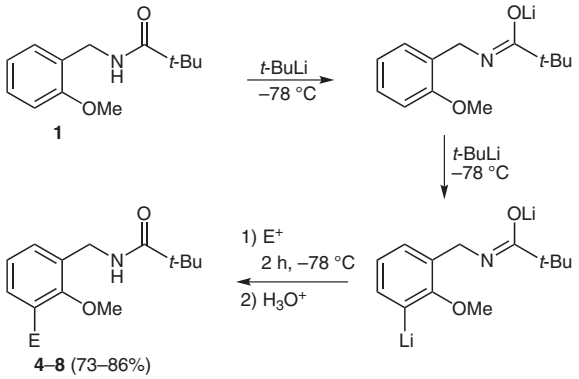
Table 1 Yields of Components from Lithiation of **1** with RLi at 0 °C Followed by Reactions with Carbon Dioxide

RLi	Approximate yields of the components of the total product (%)[a]			
	1	**2**	**3**	**4**
n-BuLi	17	30	40	8
s-BuLi	9	48	38	–
t-BuLi	–	19	26	49

[a] By combination of weights of the crystallized materials and the quantities estimated by ^{1}H NMR to be present in the mother liquors.

The results in Table 1 showed interesting variations in product proportions. In an attempt to increase the selectivity, the reactions were each carried out at –78 °C. Lithiation was conducted over four hours, the cooling bath was then removed, and solid carbon dioxide was then added to the reaction mixture. The reaction mixture was stirred for a further 30 minutes while warming to room temperature, and the products were worked up as before. The *n*-BuLi reaction resulted in quantitative recovery of **1**, suggesting that lithiation with *n*-BuLi did not take place under these conditions. The reaction with *s*-BuLi gave **2** and **3** in lower yields than at 0 °C, along with residual **1**. However, the reaction with *t*-BuLi was extremely interesting.

In this case it was possible to isolate pure **4** in 80% yield following crystallization of the crude product. The mother liquor showed the presence of additional **4** along with a small quantity of **3** and traces of **1**. The reaction clearly had potential as a synthetic method, and therefore, the same lithiation procedure was used for reactions with a range of different electrophiles (Scheme 2). Following workup of the reaction mixtures the crude products were purified by column chromatography (silica gel; Et_2O–hexane, 1:3) or direct crystallization from ethyl acetate to give the corresponding *N*-(3-substituted 2-methoxybenzyl)pivalamides **4-8** in high yields (Table 2).



Scheme 2 Lithiation of **1** with *t*-BuLi at –78 °C followed by reactions with electrophiles

Table 2 Synthesis of Products **4**–**8** According to Scheme 2

Product	Electrophile	E	Yield (%)[a]
4[b]	CO_2	CO_2H	80
5[c]	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	76[d]
6	PhCHO	PhCH(OH)	75
7	Ph_2CO	$Ph_2C(OH)$	73[e]
8	D_2O	D	86

[a] Yield of isolated product after purification by column chromatography unless otherwise indicated.
[b] Compound **4** was purified by crystallization from EtOAc.
[c] The structure of compound **5** was confirmed by X-ray crystallography.
[d] Compound **9** (Figure 2) was obtained as a byproduct in 2% yield.
[e] Compound **10** (Figure 2) was obtained as a byproduct in 3% yield.

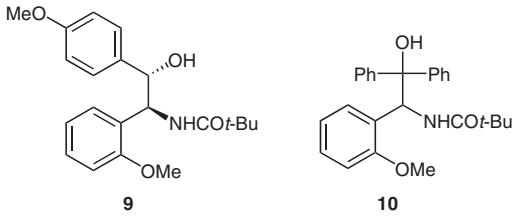


Figure 2 Structures of compounds **9** and **10**

The ^{1}H NMR spectra of **5** and **6** showed the CH_2 hydrogens as two separated double doublets, verifying that they are diastereotopic.

The side-chain-substituted byproduct formed in the reaction with 4-anisaldehyde would be expected to be formed as a mixture of diastereoisomers; however, its NMR spectra showed what appeared to be a single set of signals, indicating that the isolated product was probably a single diastereomer. Its structure was established as **9** (Figure 2) by X-ray crystallography. However, since this byproduct was isolated in only 2% yield, it is possible that a small

amount of the other diastereoisomer was formed but not isolated.

Clearly, the procedure outlined in Scheme 2 represents a simple, efficient, and high yielding route for substitution of *N*-(2-methoxybenzyl)pivalamide (**1**) *ortho* to the methoxy group. It is not clear why lithiation of **1** with *t*-BuLi in THF at –78 °C gives substitution *ortho* to the methoxy group while *n*-BuLi and *s*-BuLi give mixtures containing two main substitution products, neither of which involves lithiation *ortho* to this group. It could have something to do with the way the reagents aggregate, their ability to chelate the two substituents, or the relative bulk of the alkyl groups, but without further information it is not easy to decide. However, whatever the explanation, the method has practical significance.

In summary, *N*-(2-methoxybenzyl)pivalamide (**1**) undergoes lithiation with *t*-BuLi at –78 °C, followed by treatment with electrophiles, to give high yields of the corresponding substituted products **4**–**8** having the substituent *ortho* to the methoxy group. This contrasts with earlier results using other lithiating agents.

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(8) **Analytical Data for Compound 2:** Mp 170–171 °C (lit.[6] 168–169 °C). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.43 (t, *J* = 6 Hz, exch., 1 H, NH), 7.34 (app. t, *J* = 8 Hz, 1 H, H-5), 7.27 (dd, *J* = 2, 8 Hz, 1 H, H-6), 7.19 (br d, *J* = 8 Hz, 1 H, H-4), 4.47 (d, *J* = 6 Hz, 2 H, CH_2), 3.82 (s, 3 H, OCH_3), 1.05 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 177.5 (s, C=O), 169.7 (s, CO_2H), 158.4 (s, C-3), 134.3 (s, C-2), 128.7 (d, C-5), 126.7 (s, C-1), 121.6 (d, C-6), 114.6 (d, C-4), 56.5 (q, OCH_3), 38.4 [s, $C(CH_3)_3$], 35.7 (t, CH_2), 27.8 [q, $C(CH_3)_3$] ppm. MS (ES$^+$): *m/z* (%) = 553 (34) [2 M + Na]$^+$, 531 (42) [2 M + H]$^+$, 329 (32) [M + MeCNNa]$^+$, 304 (3) [M + K]$^+$, 266 (100) [MH]$^+$. HRMS (ES$^+$): *m/z* calcd for $C_{14}H_{20}NO_4$ [MH]$^+$: 266.1392; found: 266.1392. FT-IR: ν_{max} = 3401, 2965, 1698, 1611, 1539, 1467, 1385, 1219 cm^{-1}.

(9) **Analytical Data for Compound 4:** Mp 156–157 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.03 (t, *J* = 6 Hz, exch., 1 H, NH), 7.57 (dd, *J* = 2, 8 Hz, 1 H, H-6), 7.32 (dd, *J* = 2, 8 Hz, 1 H, H-4), 7.16 (app. t, *J* = 8 Hz, 1 H, H-5), 4.32 (d, *J* = 6 Hz, 2 H, CH_2), 3.79 (s, 3 H, OCH_3), 1.15 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (500 MHz, DMSO-d_6): δ = 178.1 (s, C=O), 167.8 (s, CO_2H), 157.1 (s, C-2), 134.6 (s, C-3), 131.5 (d, C-4), 129.6 (d, C-6), 126.1 (s, C-1), 123.9 (d, C-5), 62.1 (q, OCH_3), 38.6 [s, $C(CH_3)_3$], 37.3 (t, CH_2), 27.9 [q, $C(CH_3)_3$] ppm. MS (ES$^+$): *m/z* (%) = 569 (12) [2 M + K]$^+$, 553 (100) [2 M + Na]$^+$, 548 (32) [2 M + NH_4]$^+$, 329 (25) [M + MeCNNa]$^+$, 304 (27) [M + K]$^+$, 288 (70) [M + Na]$^+$, 266 (71) [MH]$^+$. HRMS (ES$^+$): *m/z* calcd for $C_{14}H_{20}NO_4$ [MH]$^+$: 266.1392; found: 266.1386. FT-IR: ν_{max} = 3377, 2972, 1698, 1610, 1540, 1427, 1368, 1247 cm^{-1}.