

Variations in Site of Lithiation of *N*-(2-(4-Methoxyphenyl)ethyl)pivalamide; Use in Ring Substitution

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Abstract: Lithiation of *N*-(2-(4-methoxyphenyl)ethyl)pivalamide at –20 to 0 °C with three mole equivalents of *n*-BuLi in anhydrous THF, followed by reactions with various electrophiles, gives high yields of products involving ring substitution *ortho*- to the pivaloylaminoethyl group, which was unexpected in view of earlier results reported with *t*-BuLi.

Key words: *N*-(2-(4-methoxyphenyl)ethyl)pivalamide, directed lithiation, synthesis, electrophile, dilithium intermediate

Phenylethylamine derivatives, especially ones containing oxygen substituents on the phenyl ring (which includes many biologically active compounds such as dopamine, adrenaline and mescaline), represent a hugely important class of chemicals of interest to both industry and academe, and selective methods for their synthesis are of considerable interest. Organolithium reagents play an important role in the development of clean and environmentally friendly processes for the regioselective production of specific products.^{2,3} For example, lithiation of aromatic compounds often takes place proximal to a directing metalating group (DMG), which typically possess an oxygen or nitrogen atom.⁴ Use of such

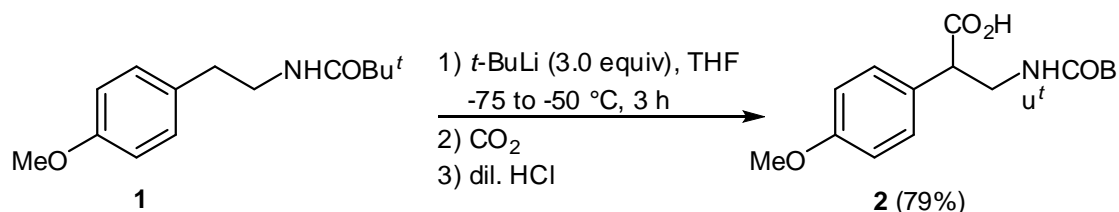
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DMGs to facilitate lithiation, followed by reactions of the organolithium intermediates obtained *in-situ* with electrophiles, has found wide application in a variety of synthetic transformations to produce substituted aromatics or heterocycles.^{5,6} This approach is one of the most efficient for synthesis of substituted and/or modified derivatives, which sometimes might be difficult to produce by other routes.^{5,6}

In connection with other work on the use of lithium reagents in organic synthesis,⁷ we have recently reported a detailed study for the regioselective lithiation and substitution of various substituted benzylamines.^{8,9} Sometimes different products were formed, depending on the nature of the lithiating agent or reaction conditions. We found, for example, that treatment of *N*-(2-methoxybenzyl)pivalamide with *t*-BuLi in THF at -78 °C, followed by reaction with an electrophile, gave substitution *ortho*- to the methoxy group selectively,⁸ in sharp contrast with results reported by Simig and Schlosser, who showed that lithiation of this substrate using *n*-BuLi at 0 °C, followed by treatment with carbon dioxide, resulted in carboxylation *ortho*- to the pivaloylaminomethyl group in 64% yield.¹⁰

Recently, we have been interested in regioselective lithiation and substitution of phenethylamine derivatives and found that direct lithiation of ring-unsubstituted acyl derivatives occurred at the α -position.¹¹ Simig and Schlosser also reported that lithiation of *N*-2-((4-methoxyphenyl)ethyl)pivalamide (**1**) using *t*-BuLi at -75 to -50 °C, followed by treatment with carbon dioxide, resulted in carboxylation at the CH₂ next to the 4-methoxyphenyl ring (α -lithiation) to give **2** in 79% yield (Scheme 1).¹² We wished to investigate the possibility of ring lithiation of *N*-(2-(4-methoxyphenyl)ethyl)pivalamide (**1**), notwithstanding that lithiation at this site was not reported at all under the conditions used by Simig and Schlosser.¹² We have therefore investigated lithiation under other conditions and

now report that we have been able to establish conditions for a high-yielding and general ring-substitution process.



Scheme 1. Lithiation of **1** followed by reaction with CO₂ as reported by Schlosser¹²

Initially, **1** was lithiated with *t*-BuLi (three molar equivalents) under conditions similar to those used by Schlosser,¹² followed by reaction with benzophenone (1.4 molar equivalents). The crude product was purified by column chromatography to give residual **1** (30%) and a new product, *N*-(3-hydroxy-2-(4-methoxyphenyl)-3,3-diphenylpropyl)pivalamide (**3**; Figure 1), obtained in 58% yield. Compound **3** was clearly obtained *via* the intermediacy of dilithium species **4** (Figure 1), which was in accord with the results reported by Schlosser.¹²

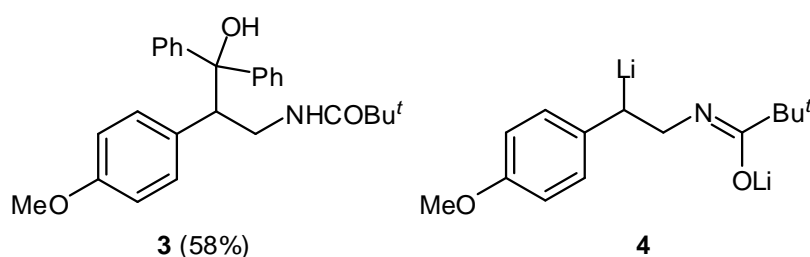
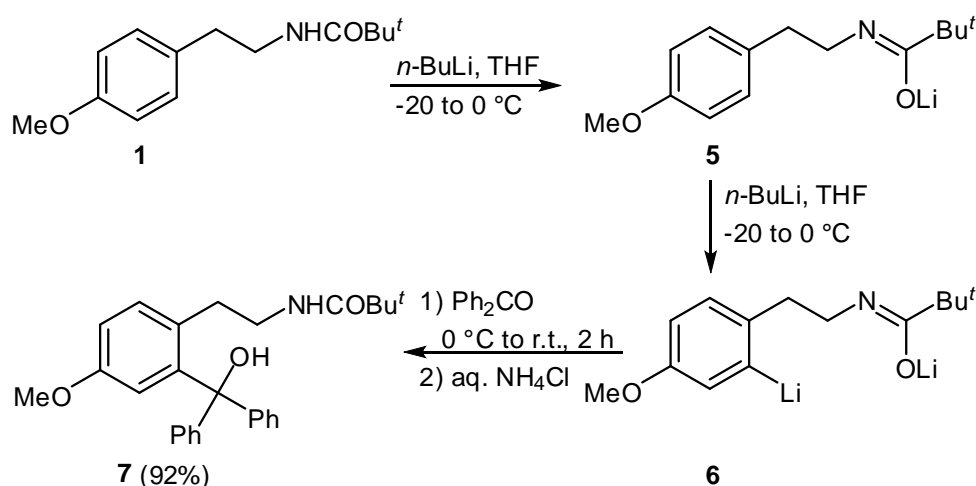


Figure 1 Structures of compound **3** and dilithium intermediate **4**

A reaction carried out with *n*-BuLi under the same conditions as were used with *t*-BuLi resulted in the starting material **1** being recovered quantitatively, indicating that no *C*-lithiation had taken place, but lithiation of **1** with *n*-BuLi (3.0 molar equivalents) at -20 to 0

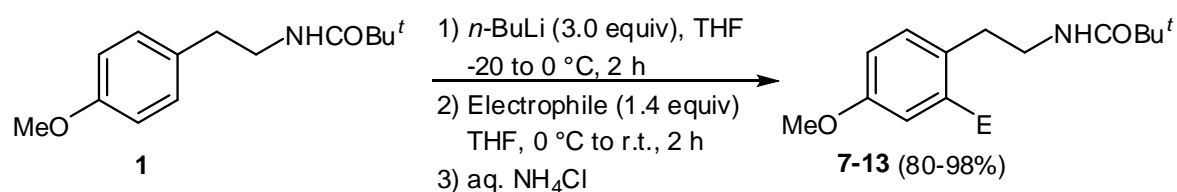
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°C over 2 h, followed by treatment with benzophenone gave a new compound, shown by its spectral properties^{13,14} to be **7** (Scheme 2), isolated in 92% yield. This suggested that lithiation took place on the ring and that lithium reagents **5** and **6** were produced *in-situ* (Scheme 2).



Scheme 2 Lithiation of **1** with *n*-BuLi followed by reactions with benzophenone

The latter 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 3). Following work-up of the reaction mixtures the crude products were purified by column chromatography (silica gel; Et₂O–hexane, 1:1) to give the corresponding substituted products **7–13** in 80–98% yields (Table 1).



Scheme 3 Lithiation of **1** with *n*-BuLi followed by reactions with electrophiles

Table 1 Synthesis of Products **7–13** According to Scheme 3

Product	Electrophile	E	Yield (%) ^a
7	Ph ₂ CO	Ph ₂ C(OH)	92
8	(CH ₂) ₅ CO	(CH ₂) ₅ C(OH)	88
9	EtCOMe	EtC(OH)Me	95
10	4-MeOC ₆ H ₄ CHO	4-MeOC ₆ H ₄ CH(OH)	80
11	4-Me ₂ NC ₆ H ₄ CHO	4-Me ₂ NC ₆ H ₄ CH(OH)	90
12	Me ₂ NCHO	CHO	98
13	I ₂	I	89

^a Yield of isolated product after purification by flash column chromatography.

Clearly, the procedure outlined in Scheme 3 represents a simple, efficient and high yielding route for substitution of *N*-(2-(4-methoxyphenyl)ethyl)pivalamide (**1**) *ortho*- to the pivaloylaminoethyl group. However, it was not clear why lithiation of **1** with *t*-BuLi at -75 to -50 °C gave side-chain substitution, while lithiation with *n*-BuLi at -20 to 0 °C gave ring substitution. One possibility was that at low temperature the lithiation step was under kinetic control, leading to the intermediate **4**, with only the *t*-BuLi sufficiently reactive to effect the lithiation under such conditions, but that at higher temperature the organolithium intermediate **4** was capable of isomerization to **6**, so that reactions conducted at the higher temperature were under thermodynamic control. In order to test this possibility, the reaction of **1** was initially carried out at -75 to -50 °C with *t*-BuLi (3.0 molar equivalents) for 3 h (conditions previously shown to produce **4**), and the mixture was then warmed to 0 °C and maintained for a further 2 h, after which benzophenone (1.4 molar equivalents) was added. The cooling bath was removed and the mixture was stirred for 2 h while warming to room temperature. Purification of the crude product by column chromatography gave **7** in 82% yield along with

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residual **1** (14%). This finding clearly indicated that the dilithium reagent **6** (Scheme 2) is thermodynamically more stable than the dilithium reagent **4** (Figure 1) at higher temperature.

In conclusion, *N*-(2-(4-methoxyphenyl)ethyl)pivalamide (**1**) undergoes lithiation with *n*-BuLi at 0 °C, followed by treatment with various electrophiles, to give high yields of the corresponding substituted products having the substituent *ortho*- to the pivaloylaminoethyl group. This contrasts sharply with earlier results using *t*-BuLi at lower temperature, which gave α -substitution. The variation arises because the dilithium reagent **4**, formed at low temperature with *t*-BuLi, is less stable than dilithium reagent **6**, to which it isomerises at 0 °C.

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(14) Analytical data for **7**: white solid (0.32 g, 92%); mp 179–181 °C. IR (FT): ν_{\max} = 3321, 2958, 1627, 1575, 1292, 1243 cm^{-1} . ^1H NMR (500 MHz, CDCl_3) δ = 7.35–7.26 (m, 11 H, OH and 2 C_6H_5), 7.16 (d, J = 8.3 Hz, 1 H, H-6 of 4-MeOC $_6$ H $_3$), 6.79 (dd, J = 2.8, 8.3 Hz, 1 H, H-5 of 4-MeOC $_6$ H $_3$), 6.24 (d, J = 2.8 Hz, 1 H, H-3 of 4-MeOC $_6$ H $_3$), 6.15 (br, exch., 1 H, NH), 3.63 (s, 3 H, OCH $_3$), 3.37 (app. q, J = 7 Hz, 2 H, CH $_2$ NH), 2.60 (t, J = 7.2 Hz, 2 H, CH $_2$), 1.11 [s, 9 H, C(CH $_3$) $_3$] ppm. ^{13}C NMR (125 MHz, CDCl_3) δ = 178.8 (s, C=O), 156.9 (s, C-4 of 4-MeOC $_6$ H $_3$), 147.1 (s, C-1 of 2 C_6H_5), 146.6 (s, C-2 of 4-MeOC $_6$ H $_3$), 132.8 (d, C-6 of 4-MeOC $_6$ H $_3$), 130.7 (s, C-1 of 4-MeOC $_6$ H $_3$), 127.9 (d, C-3/C-5 of 2 C_6H_5), 127.7 (d, C-2/C-6 of 2 C_6H_5), 127.2 (d, C-4 of 2 C_6H_5), 117.1 (d, C-3 of 4-MeOC $_6$ H $_3$), 111.9 (d, C-5 of 4-MeOC $_6$ H $_3$), 83.0 (s, C–OH), 55.0 (q, OCH $_3$), 41.1 (t, CH $_2$ NH), 38.4 [s, C(CH $_3$) $_3$], 32.5 (t,

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ArCH₂), 27.5 [q, C(CH₃)₃] ppm. MS (EI): m/z (%) = 399 (77, [M - H₂O]⁺), 298 (99), 285 (90), 261 (33), 239 (10), 222 (26), 209 (31), 193 (73), 165 (53), 152 (13), 105 (48), 83 (100).

HRMS (EI): m/z calcd for C₂₇H₂₉NO₂ ([M - H₂O]⁺): 399.2198; found: 399.2187.