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

Keith Smith,* Gamal A. El-Hiti,*¹ Mohammed B. Alshammari

School of Chemistry, Cardiff University, Main Building, Park Place, Cardiff, CF10 3AT, UK
Fax +44(29)20870600; E-mail: smithk13@cardiff.ac.uk; E-mail: el-hitiga@cardiff.ac.uk

Received: 07.11.2012; Accepted after revision: 19.11.2012

Abstract: Lithiation of *N*-[2-(4-methoxyphenyl)ethyl]pivalamide at –20 to 0 °C with three 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 those 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 academia, 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 DMG 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 the 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 pivaloylaminoethyl 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 °C 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.

Initially, **1** was lithiated with *t*-BuLi (3 mol equiv) under conditions similar to those used by Schlosser,¹² followed by reaction with benzophenone (1.4 mol equiv). 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

A reaction carried out with *n*-BuLi under the same conditions as were used with *t*-BuLi resulted in the starting ma-

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

SYNLETT 2013, 24, 0117–0119

Advanced online publication: 11.12.2012

DOI: 10.1055/s-0032-1317859; Art ID: ST-2012-D0962-L

© Georg Thieme Verlag Stuttgart · New York

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

terial **1** being recovered quantitatively, indicating that no C-lithiation had taken place, but lithiation of **1** with *n*-BuLi (3.0 mol equiv) at $-20\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$ over two hours, 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 workup of the reaction mixtures

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.

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

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).

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 $-75\text{ }^{\circ}\text{C}$ to $-50\text{ }^{\circ}\text{C}$ gave side-chain substitution, while lithiation with *n*-BuLi at $-20\text{ }^{\circ}\text{C}$ to $0\text{ }^{\circ}\text{C}$ 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 $-75\text{ }^{\circ}\text{C}$ to $-50\text{ }^{\circ}\text{C}$ with *t*-BuLi (3.0 mol equiv) for three hours (conditions previously shown to produce **4**), and the mixture was then warmed to $0\text{ }^{\circ}\text{C}$ and maintained for a further two hours, after which benzophenone (1.4 mol equiv) was added. The cooling bath was removed, and the mixture was stirred for two hours while warming to room temperature. Purification of the crude product by column chromatography gave **7** in 82% yield along with 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 $0\text{ }^{\circ}\text{C}$, 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 isomerizes at $0\text{ }^{\circ}\text{C}$.

Acknowledgment

We thank Cardiff University and the Saudi Government for financial support.

References and Notes

- (1) Permanent address: G. A. El-Hiti, Department of Chemistry, Faculty of Science, Tanta University, Tanta 31527, Egypt.

- (2) See, for example: (a) Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon: Oxford, **2002**. (b) Schlosser, M. *Organometallics in Synthesis*, 2nd ed.; Wiley: Chichester, **2002**, 1–352. (c) Capriati, V.; Florio, S.; Salomone, A. *Top. Stereochem.* **2010**, *26*, 135. (d) Coldham, I.; Sheikh, N. S. *Top. Stereochem.* **2010**, *26*, 253.
- (3) See, for example: (a) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (b) Nájera, C.; Sansano, J. M.; Yus, M. *Tetrahedron* **2003**, *59*, 9255. (c) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206. (d) Chadwick, S. T.; Ramirez, A.; Gupta, L.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 2259. (e) Dyke, A. M.; Gill, D. M.; Harvey, J. N.; Hester, A. J.; Lloyd-Jones, G. C.; Muñoz, M. P.; Shepperson, I. R. *Angew. Chem. Int. Ed.* **2008**, *47*, 5067. (f) Coldham, I.; Raimbault, S.; Chovatia, P. T.; Patel, J. J.; Leonori, D.; Sheikh, N. S.; Whittaker, D. T. E. *Chem. Commun.* **2008**, 4174. (g) Coldham, I.; Leonori, D.; Beng, T. K.; Gawley, R. E. *Chem. Commun.* **2009**, 5239. (h) Coldham, I.; Raimbault, S.; Whittaker, D. T. E.; Chovatia, P. T.; Leonori, D.; Patel, J. J.; Sheikh, N. S. *Chem. Eur. J.* **2010**, *16*, 4082. (i) Robinson, S. P.; Sheikh, N. S.; Baxter Carl, A.; Coldham, I. *Tetrahedron Lett.* **2010**, *51*, 3642. (j) Guerrand, H. D. S.; Adams, H.; Coldham, I. *Org. Biomol. Chem.* **2011**, *9*, 7921. (k) Thompson, M. J.; Louth, J. C.; Little, S. M.; Jackson, M. P.; Boursereau, Y.; Chen, B.; Coldham, I. *ChemMedChem* **2012**, *7*, 578. (l) Sheikh, N. S.; Leonori, D.; Barker, G.; Firth, J. D.; Campos, K. R.; Meijer, A. J. H. M.; O'Brien, P.; Coldham, I. *J. Am. Chem. Soc.* **2012**, *134*, 5300.
- (4) See, for example: (a) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) El-Hiti, G. A. *Heterocycles* **2000**, *53*, 1839. (d) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489. (e) Ancil, E. J.-G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150. (f) Smith, K.; El-Hiti, G. A. *Curr. Org. Synth.* **2004**, *1*, 253. (g) Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667. (h) Schlosser, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 376. (i) Foubelo, F.; Yus, M. *Curr. Org. Chem.* **2005**, *9*, 459. (j) Rathman, T. L.; Bailey, W. F. *Org. Process Res. Dev.* **2009**, *13*, 144. (k) Houlden, C. E.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Org. Lett.* **2010**, *12*, 3090. (l) Page, A.; Clayden, J. *Beilstein J. Org. Chem.* **2011**, *7*, 1327. (m) El-Hiti, G. A.; Hegazy, A. S.; Alotaibi, M. H.; Ajarim, M. D. *ARKIVOC* **2012**, (vii), 35.
- (5) Examples for substituted benzenes: (a) Clayden, J.; Turner, H.; Pickworth, M.; Adler, T. *Org. Lett.* **2005**, *7*, 3147. (b) Clayden, J.; Dufour, J. *Tetrahedron Lett.* **2006**, *47*, 6945. (c) Burgos, P. O.; Fernández, I.; Iglesias, M. J.; García-Granda, S.; Ortiz, F. L. *Org. Lett.* **2008**, *10*, 537. (d) Castanet, A.-S.; Tilly, D.; Véron, J.-B.; Samanta, S. S.; De, A.; Ganguly, T.; Mortier, J. *Tetrahedron* **2008**, *64*, 3331. (e) Michon, C.; Murai, M.; Nakatsu, M.; Uenishi, J.; Uemura, M. *Tetrahedron* **2009**, *65*, 752. (f) Tilly, D.; Fu, J.-M.; Zhao, B.-P.; Alessi, M.; Catanet, A.-S.; Snieckus, V.; Mortier, J. *Org. Lett.* **2010**, *12*, 68. (g) Slocum, D. W.; Wang, S.; White, C. B.; Whitley, P. E. *Tetrahedron* **2010**, *66*, 4939. (h) Cho, I.; Meimetis, L.; Belding, L.; Katz, M. J.; Dudding, T.; Britton, R. *Beilstein J. Org. Chem.* **2011**, *7*, 1315. (i) Schmid, M.; Waldner, B.; Schnürch, M.; Mihovilovic, M. D.; Stanetty, P. *Tetrahedron* **2011**, *67*, 2895. (j) Volz, N.; Clayden, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 12148.
- (6) Examples for substituted heterocycles: (a) Robert, N.; Bonneau, A.-L.; Hoarau, C.; Marsais, F. *Org. Lett.* **2006**, *8*, 6071. (b) Comoy, C.; Banaszak, E.; Fort, Y. *Tetrahedron* **2006**, *62*, 6036. (c) Luisi, R.; Capriati, V.; Florio, S.; Musio, B. *Org. Lett.* **2007**, *9*, 1263. (d) Clayden, J.; Hennecke, U. *Org. Lett.* **2008**, *10*, 3567. (e) McLaughlin, M.; Marcantonio, K.; Chen, C.; Davies, I. W. *J. Org. Chem.* **2008**, *73*, 4309. (f) Capriati, V.; Florio, S.; Luisi, R.; Mazzanti, A.; Musio, B. *J. Org. Chem.* **2008**, *73*, 3197. (g) Affortunato, F.; Florio, S.; Luisi, R.; Musio, B. *J. Org. Chem.* **2008**, *73*, 9214. (h) Musio, B.; Clarkson, G. J.; Shipman, M.; Florio, S.; Luisi, R. *Org. Lett.* **2009**, *11*, 325. (i) Clayton, J.; Clayden, J. *Tetrahedron Lett.* **2011**, *52*, 2436. (j) Ibrahim, N.; Chevot, F.; Legraverend, M. *Tetrahedron Lett.* **2011**, *52*, 305.
- (7) See, for example: (a) Smith, K.; El-Hiti, G. A.; Abdo, M. A.; Abdel-Megeed, M. F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1029. (b) Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F.; Abdo, M. A. *J. Org. Chem.* **1996**, *61*, 647. (c) Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F.; Abdo, M. A. *J. Org. Chem.* **1996**, *61*, 656. (d) Smith, K.; El-Hiti, G. A.; Pritchard, G. J.; Hamilton, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2299. (e) Smith, K.; El-Hiti, G. A.; Shukla, A. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2305. (f) Smith, K.; El-Hiti, G. A.; Hawes, A. C. *Synthesis* **2003**, 2047. (g) Smith, K.; El-Hiti, G. A.; Mahgoub, S. A. *Synthesis* **2003**, 2345. (h) El-Hiti, G. A. *Synthesis* **2003**, 2799. (i) Smith, K.; El-Hiti, G. A.; Abdel-Megeed, M. F. *Synthesis* **2004**, 2121. (j) El-Hiti, G. A. *Synthesis* **2004**, 363. (k) Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Synthesis* **2005**, 2951. (l) Smith, K.; Barratt, M. L. *J. Org. Chem.* **2007**, *72*, 1031.
- (8) (a) Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Synlett* **2009**, 2242. (b) Smith, K.; El-Hiti, G. A.; Hegazy, A. S.; Fekri, A.; Kariuki, B. M. *ARKIVOC* **2009**, (xiv), 266.
- (9) (a) Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Chem. Commun.* **2010**, 46, 2790. (b) Smith, K.; El-Hiti, G. A.; Hegazy, A. S.; Fekri, A. *Heterocycles* **2010**, *80*, 941. (c) Smith, K.; El-Hiti, G. A.; Hegazy, A. S. *Synthesis* **2010**, 1371. (d) Smith, K.; El-Hiti, G. A.; Hegazy, A. S.; Kariuki, B. *Beilstein J. Org. Chem.* **2011**, *7*, 1219.
- (10) Simig, G.; Schlosser, M. *Tetrahedron Lett.* **1988**, *29*, 4277.
- (11) Smith, K.; El-Hiti, G. A.; Alshammari, M. B. *Synthesis* **2012**, *44*, 2013.
- (12) Simig, G.; Schlosser, M. *Tetrahedron Lett.* **1991**, *32*, 1963.
- (13) Assignments of signals are based on integration values, coupling patterns, and expected chemical shifts and have not been rigorously confirmed. Signals with similar characteristics might be interchanged.
- (14) **Analytical Data for 7**
White solid (0.32 g, 92%); mp 179–181 °C. FTIR: $\nu_{\max}$ = 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 $_6\text{H}_3$), 6.79 (dd, J = 2.8, 8.3 Hz, 1 H, H-5 of 4-MeOC $_6\text{H}_3$), 6.24 (d, J = 2.8 Hz, 1 H, H-3 of 4-MeOC $_6\text{H}_3$), 6.15 (br, exch., 1 H, NH), 3.63 (s, 3 H, OCH $_3$), 3.37 (app q, J = 7 Hz, 2 H, CH_2NH), 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 $_6\text{H}_3$), 147.1 (s, C-1 of 2 C_6H_5), 146.6 (s, C-2 of 4-MeOC $_6\text{H}_3$), 132.8 (d, C-6 of 4-MeOC $_6\text{H}_3$), 130.7 (s, C-1 of 4-MeOC $_6\text{H}_3$), 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 $_6\text{H}_3$), 111.9 (d, C-5 of 4-MeOC $_6\text{H}_3$), 83.0 (s, COH), 55.0 (q, OCH $_3$), 41.1 (t, CH_2NH), 38.4 [s, C(CH $_3$) $_3$], 32.5 (t, ArCH $_2$), 27.5 [q, C(CH $_3$) $_3$] ppm. MS (EI): m/z (%) = 399 (77) [$\text{M} - \text{H}_2\text{O}$] $^+$, 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 $\text{C}_{27}\text{H}_{29}\text{NO}_2$ [$\text{M} - \text{H}_2\text{O}$] $^+$: 399.2198; found: 399.2187.