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Site Selective Substitution of Carbamate and Carbamoyl Protected Benzylamines

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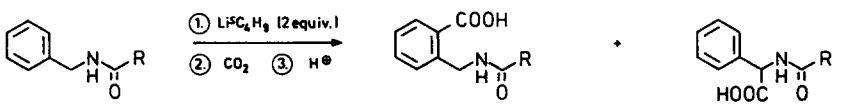
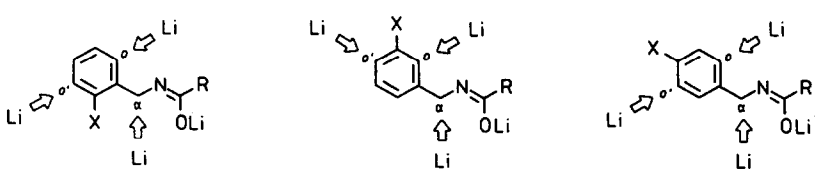
Abstract: *Methoxy and fluoro substituted benzylamines can be metalated optionally at the position adjacent to the nitrogen bearing side chain or adjacent to the hetero substituent as a function of the acyl type protective group.*

Benzylamines are employed as key intermediates in isoquinoline syntheses. The hetereocyclic ring may be constructed either by intramolecular aromatic hydroxyalkylation (Pomeranz-Fritsch method) [1] or by "off-shore cyclization" [2 - 4]. In the latter case, the required carbofunctional module can be most conveniently introduced by electrophilic substitution of an *ortho* metalated intermediate. The practicability of this approach has been demonstrated with *N,N*-dialkyl substituted benzylamines as starting materials [5]. *N*-Acyl protected benzylamines offer a greater synthetic flexibility. However, when *N*-pivaloylbenzylamine was submitted to metalation with butyllithium (2 equiv.) and subsequent carboxylation with dry ice, a 2 : 1 mixture of *o*- and α-substituted products **1** [R = $C(CH_3)_3$] and **2** [R = $C(CH_3)_3$] was isolated [6]. This lack of selectivity has now been overcome by the appropriate choice of the protective group. *N*-(*tert*-Butoxycarbonyl)benzylamine undergoes with *sec*-butyllithium in tetrahydrofuran (4 h - 50 °C) α-metalation and *N*-(dimethylcarbamoyl)benzylamine *o*-metalation exclusively, thus producing the pure acids **2** [R = $OC(CH_3)_3$] and **1** [R = $N(CH_3)_2$].

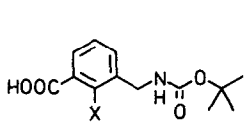


	1	**2**
R = $C(CH_3)_3$	36 %	20 %
R = $OC(CH_3)_3$	-	79 %
R = $N(CH_3)_2$	82 % [7]	-

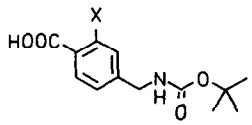
Both, the *tert*-butoxycarbonyl (BOC) and the dimethylcarbamoyl (DMC) moiety can be easily removed by hydrolysis under acidic conditions and hence are particularly advantageous from a preparative point of view. In order to examine their scope of applicability, we have selected benzylamines carrying *methoxy* and *fluoro* substituents as substrates [X = OCH_3 or F]. In such cases, three sites compete for metalation : α-position, the *o*-position (adjacent to the amidomethyl side chain) and the *o'*-position (adjacent to the hetero substituent).



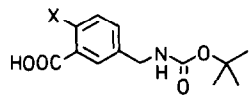
We have prepared the BOC and DMC protected derivatives of 2-, 3- and 4-methoxy- and 2-, 3- and 4-fluorobenzylamines. After lithiation, the reaction mixtures were poured on dry ice and the carboxylic acids formed were isolated by extraction. Only two results were disappointing. *N*-BOC-3-Fluorobenzylamine underwent predominant *ortho*- besides some α-metalation; *N*-DMC-2-methoxybenzylamine gave concomitant *o*- and *o'*-metalation. Except these two cases, perfect optional regiocontrol was achieved : the BOC and DMC moieties were found to direct efficiently the organolithium reagent to the *o'*- and *o*-positions, respectively. The products **3** - **8** thus obtained are shown below; the reagents (LIC-KOR = butyllithium/potassium *tert*-butoxide, $Li^sC_4H_9$ = *sec*-butyllithium) and the reaction conditions are specified (tetrahydrofuran being the only solvent used). The yields indicated refer to isolated, pure compounds. [8]



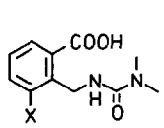
3a: 46% [$Li^sC_4H_9$, 24 h -50°C]
3b: 50% [LIC-KOR, 4 h -75 °C]



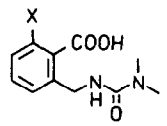
4a: 57% [LIC-KOR, 24 h -50°C]
4b:



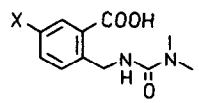
5a: 63% [LIC-KOR, 24 h -50°C]
5b: 63% [LIC-KOR, 4 h -75°C]



6a: -
6b: 81% [$LiC(CH_3)_3$, 4 h -100°C]



7a: 86% [$Li^sC_4H_9$, 4 h -50°C]
7b: 94% [LiC_4H_9, 4 h -75°C]



8a: 85% [$Li^sC_4H_9$, 4 h -50°C]
8b: 87% [$Li^sC_4H_9$, 4 h -50°C]

a: X = H_3CO **b:** X = F

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3 Consecutive treatment of *N-tert*-butoxycarbonyl-*o*-tolylamine with *sec*-butyllithium (2 equiv.) in tetrahydrofuran, *N,N*-dimethylformamide and acid affords *N-tert*-butoxycarbonyl-3-hydroxy-1,2,3,4-tetrahydroisoquinoline with high yield (G. Katsoulos, M. Schlosser, unpublished results, 1989).

4 Other examples : J. von Braun, F. Zobel, *Ber. Dtsch. Chem. Ges.* **56** (1923), 2142; M. Natsume, S. Kumadaki, K. Kiuchi, *Chem. Pharm. Bull.* **20** (1972), 1592; G. Nonaka, Y. Kodera, I. Nishioka, *Chem. Pharm. Bull.* **21** (1973), 1020; D.J. Jakiela, P. Helmquist, L.D. Jones, *Org. Synth.* **62** (1984), 74; B. Wünsch, M. Zott, *Synthesis* **1992**, 927; B.O.T. Kammermeier, U. Lerch, C. Sommer, *Synthesis* **1992**, 1157.

5 G. Simig, M. Schlosser, *Tetrahedron Lett.* **31** (1990), 3125.

6 G. Simig, M. Schlosser, *Tetrahedron Lett.* **29** (1988), 4277.

7 The yield increased to 90% when *tert*-butyllithium was used as the metalation agent.

8 The identity and purity of all new compounds was corraborated by correct combustion analyses and nmr-spectroscopic data.

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