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# ortho-SELECTIVE METALATION AND ELECTROPHILIC SUBSTITUTION OF BENZYLAMINE DERIVATIVES

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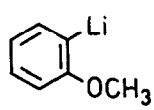
Summary : *N*-Pivaloylbenzylamines and derivatives thereof undergo smooth ortho-metalation when treated with two equivalents of an organolithium reagent. Subsequent carboxylation or hydroxylation lead to a variety of new products.

The metalation of benzene, naphthalene or other simple arenes requires "superbasic" reagents [1]. Donor substituents, however, may considerably facilitate the hydrogen/metal exchange and at the same time orient the attack of the metalating reagent towards the *ortho*-positions. [2] Thus, butyllithium rapidly converts anisol [3] and *N,N*-dimethylaniline to *o*-anisyllithium (1) and *o*-dimethylaminophenyllithium (2), respectively.

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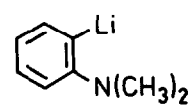
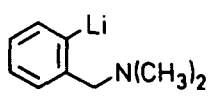



2

The dimethylamino function continues to exert neighboring group assistance even when separated from the reaction center by one additional carbon unit. *N,N*-Dimethylbenzylamine undergoes smooth *ortho*-metalation (to give 3) when treated with butyllithium in tetrahydrofuran [5]. The lithium amide derived from *N*-(*mono*)methylbenzylamine behaves similarly although the metalation product 4 is formed with less satisfactory yield despite more severe reaction conditions [6]. So far, however, no ring-lithiated derivative 5 of benzylamine itself has ever been reported. Consequently, electrophilically substituted derivatives of primary arylmethyl-amines are not yet accessible by the organometallic route.

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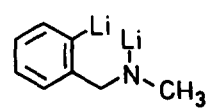


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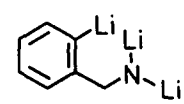
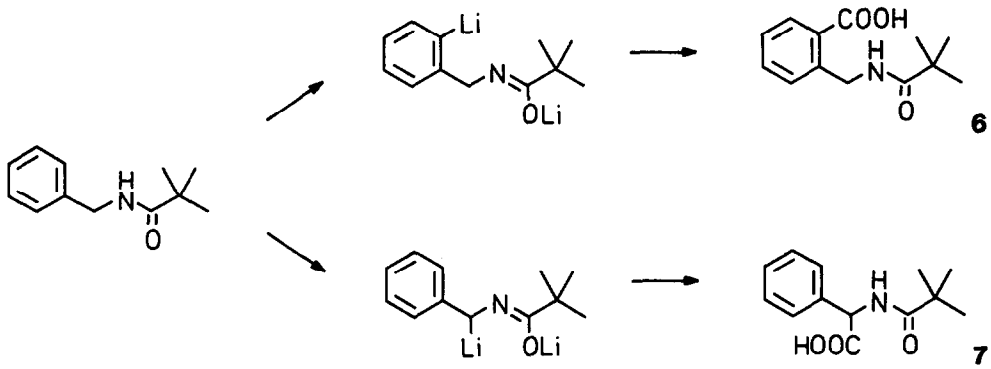


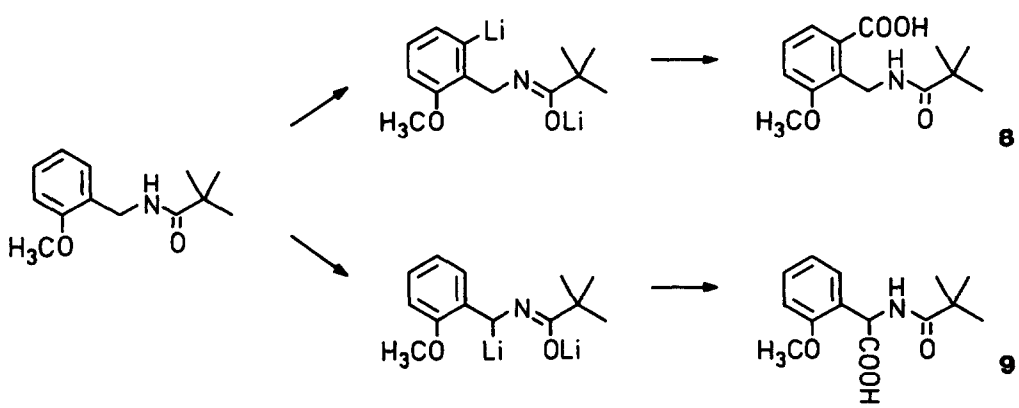

5

We wondered whether this gap could not be closed if the primary amino function were protected by an acyl group. Of course, acetyl- and benzoyl-type groups had to be excluded because of their well known propensity for α-deprotonation or *ortho*-metalation [7]. On the other hand, a pivaloyl moiety should be inert towards organometallic reagents once the adjacent imino group is deprotonated [8].

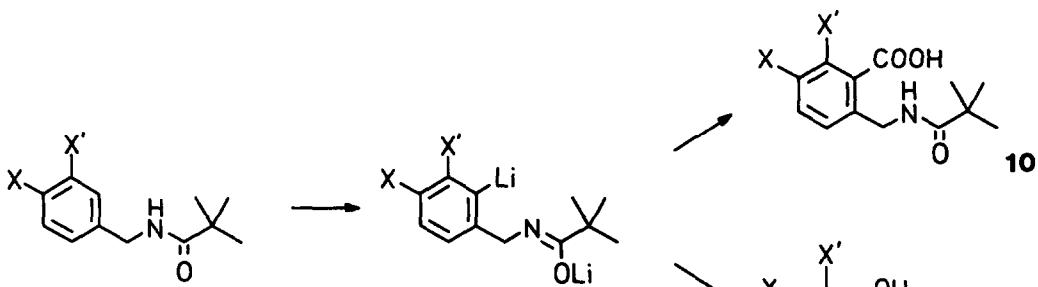
Nevertheless, the outcome of a first reaction [9] between *N*-pivaloylbenzylamine and two equivalents of butyllithium was disappointing. The desired *ortho*-metalation occurred only in competition with an α-metalation; thus two organometallic intermediates and were generated side by side. After quenching with carbon dioxide, acidification and fractional crystallization from ethyl acetate the regioisomeric acids **6** (mp 175 - 176°C) and **7** (mp 142 - 143°C; after treatment with diazomethane : methyl ester, mp 148 - 149°C from ethyl acetate or dichloromethane and diethyl ether) were isolated in 36% and 20% yield, respectively. In the presence of *N,N,N',N'*-tetramethylethylenediamine or potassium *tert*-butoxide [1] the α-position was attacked exclusively [10].




Concomitant *ortho*- and α-metalation also occured with *N*-pivaloyl-*o*-anisylmethylamine as the substrate. Again the two resulting acids, **8** (10%, mp 168 - 169°C) and **9** (14%, isolated after treatment with diazomethane as the methyl ester, mp 68 - 69°C), had to be separated by fractional crystallization and column chromatography.



Of course, a method giving rise to product mixtures is not very attractive. Fortunately most substituted *N*-pivaloyl benzylamines were found to react selectively at *ortho*-positions. Thus, lithiation, carboxylation and acidification of the *m*-anisyl, *p*-anisyl and piperonyl derivatives afforded the pure acids **10a** (61%, mp 167 - 168°C), **10b** (64%, mp 125 - 126°C) and **10c** (65%, mp 182 - 183°C), while consecutive borylation [11] and oxidation produced the phenols **11a** (62%, mp 138 - 139°C), **11b** (80%, mp 101 - 102°C) and **11c** (65%, mp 197 - 198°C) [12]. Evidently *N*-pivaloylamidomethyl is a superior *ortho*-directing group when compared to alkoxy. On the other hand, if these two substituents occupy *meta*-positions they will conjointly activate the CH bond in between and deprotonation of this site occurs with particular ease. *N*-Pivaloylbenzylamines carrying electron-withdrawing groups such as a *m*-trifluoromethyl [10] or a *p*-chloro substituent behave similarly compared with those having alkoxy substituents. The *p*-chlorobenzylamine derivative was converted to the acid **10d** (46%, mp 151 - 152°C) and the phenol **11d** (53%, mp 137 - 138°C) were obtained as the sole isomers.




**a:** X = H, X' = $H_3CO$
**b:** X = $H_3CO$, X' = H
**c:** X + X' = O-$CH_2$-O
**d:** X = Cl, X' = H

Typical working procedure :

At -75°C, a 1.6 N solution (0.15 L) of butyllithium (0.24 mol) in hexane is rapidly added to *N*-pivaloyl-piperonylamine (24 g, 0.10 mol) dissolved in tetrahydrofuran (0.25 L). The suspension is kept 1 h at 0°C before being poured on crushed dry ice. After extraction of the product into water (0.5 L) and upon acidification of the aqueous layer to pH 2 a white material precipitates. Recrystallization from ethyl acetate gives analytically pure 5-pivaloylamidomethyl-4-(1,3-benzodioxolanyl)carboxylic acid, 19.6 g (70%), mp 181 - 182°C.

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[12] The resulting products are versatile building blocks for nitrogen heterocycles in general and alkaloids, such as cotarnine, in particular (G. Simig, M. Schlosser, unpublished).

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