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BASE INDUCED REACTION AT THE BENZYL POSITION OF N-BENZYLBENZAMIDE

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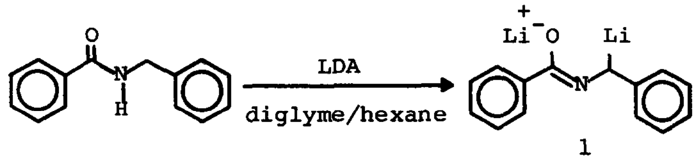
Mono- and disubstituted benzamides, as well as benzylamines, are well known to undergo ortho-metalation when treated with appropriate strong bases.[1-5] More recently, it has been reported that lithiation alpha to nitrogen is observed for certain N,N-disubstituted benzamides.[6-9] We wish to report that treatment of N-benzylbenzamide with an excess of lithium diisopropylamide (LDA) results in lithiation exclusively at the benzyl position. No ortho-lithiation at either phenyl group is observed. Moreover, under the established reaction conditions this dibasic intermediate is stable and can be readily reacted with a variety of electrophiles in good yield. We believe that this is the first report of a metalation alpha to nitrogen of a monosubstituted amide.

The general reaction is outlined below:



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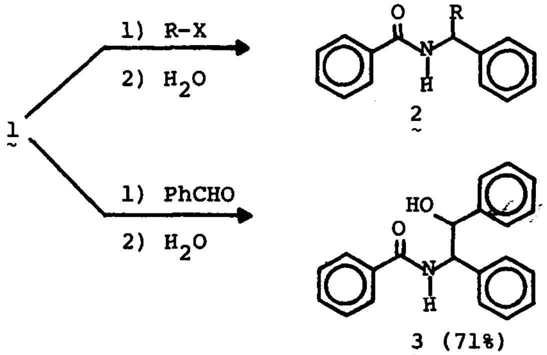

2a, R = nBu, X = I (95%)
2b, R = Me, X = I (79%)
2c, R = CH_2Ph, X = Cl (79%)

3 (71%)

The organolithium intermediate, 1, can also be generated with n-butyllithium or lithium 2,2,6,6-tetramethylpiperidide. In a typical reaction, a flask fitted with a serum cap and stir bar is charged with N-benzylbenzamide (1.90 mmoles) and diisopropylamine (2.85 mmoles) in diglyme (4 ml freshly distilled from

$LiAlH_4$ at reduced pressure). The solution is purged with dry argon and stirred in a dry ice-isopropanol bath. A solution of approximately 1.5 M butyllithium in hexane (4.75 mmoles) is then added over a period of 2 minutes. With the addition of the second equivalent of butyllithium the solution takes on an intense blue color indicative of **1**. A solution containing the electrophile (2.85 mmoles) in diglyme (1 ml) is added and the reaction is allowed to warm to room temperature. The reaction mixture is then neutralized with dilute hydrochloric acid which results in the precipitation of the product. The products were identified by nmr, ir, reported melting point, and by mixed melting point with material synthesized by conventional methods.

The conversions of N-benzylbenzamide to products as determined by nmr and/or glpc were found to be 95% or greater in each case. The reported yields represent isolated and recrystallized products. Except for **2a**, the yields have not been optimized.

Since N-benzylbenzamide is readily prepared from and hydrolyzed to benzylamine, the synthetic utility presented here can be considered as substitutions at the alpha position of benzylamine.[10] Considering that the reaction forms carbon-to-carbon bonds between the alpha and beta positions, many new structures and new pathways to known structures may be possible. The reactions with benzyl halides and benzaldehydes may be of particular interest as they represent a novel route to the synthesis of phenethylamine derivatives. Work toward the determination of the scope of this and other related reactions is currently in progress.

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