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A USEFUL METHOD TO INTRODUCE ORTHO AMINO GROUPS IN AROMATIC COMPOUNDS

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Abstract : Aromatic lithio compounds were reacted with tosyl azide and the resulting triazenes, in situ, were reduced with Ni-Al alloy to give primary aromatic amines.

In connection with the synthesis of a natural product, we needed 3-methoxyanthranilic acid. A simple synthesis, by nitration of m-methoxy benzoic acid, reported[1] in 1912 did not yield good results. Other methods[2] involved elaborate sequences.

The work on organo lithiation reactions from this laboratory[3] and elsewhere[4], indicated that N-methyl amide derivative of m-methoxy benzoic acid could be lithiated at 2-position in excellent yield. If the organolithium compound could be converted to the amino compound, that would lead to a simple synthesis of 3-methoxyanthranilic acid.

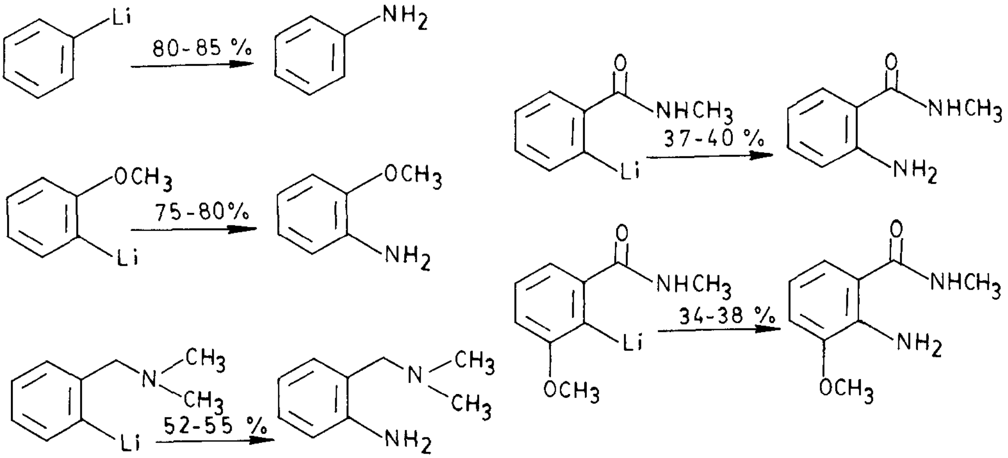
There are three methods reported for the conversion of an aromatic lithio compound to an amine. The earliest one, due to Gilman[5], involves reaction with methoxyamine. Another one, due to Trost[6], involves conversion of the lithio compound, in situ, to the Grignard reagent and further reaction with $PhSCH_2N_3$ followed by hydrolysis with KOH. The latest method, due to Hassner[7], involves the treatment of an organolithium compound with a vinyl azide followed by hydrolysis with KOH or dilute acid.

All the reagents mentioned above, for the conversion of the organolithium compounds to an amine i.e. CH_3ONH_2, $PhSCH_2N_3$ and vinyl azide, are not commonly available. The possibility of using tosyl azide, a stable readily available reagent, was then considered. However, it is reported that the tosyl azide in its reactions with carbanions[8], after hydrolytic work-up, furnishes only tosyl amine and diazo compounds.

There are reports that aromatic triazenes, on reductive work-up[9], furnish aromatic amines. It occurred to us that if the reaction of an organolithium compound with tosyl azide is subjected to reductive work-up, aromatic amines could result. This was indeed found to be the case. Thus reduction of the reaction mixture with Ni-Al/KOH in aqueous medium furnished the aromatic amine in a one-pot reaction.

A typical procedure is as follows : Anisole (2.16 g, 0.01 mol) in ether, was treated with n-butyllithium (0.025 mol in ether; prepared from 0.350 g lithium and 2.7 ml of n-butyl bromide). After stirring for 24 hr the reaction mixture was cooled to 0° and tosyl azide (3.95 g, 0.02 mol) in ether, was added in one lot. The reaction mixture was stirred for additional 1 hr and decomposed with crushed ice. KOH (5 ml, 50%) and nickel aluminium alloy (1 g, 1 g and 2 g) were added at 1 hr intervals. The reaction mixture was allowed to warm to 25° (over 2 hr). The residual alloy was filtered. Extraction with ether and purification by dilute acid extraction followed by basification gave o-anisidine in 80% yield.

The above procedure was used to synthesise several amines shown below including N-methyl amide of m-methoxyanthranilic acid. The ready availability of the reagent and simple experimental procedure make the method a valuable one for obtaining aromatic amines not readily synthesised by other methods.



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