

SYNTHESIS OF SECONDARY METHYLALKYLAMINES

David B. Repke*
P.O. Box 899, Los Altos, California 94022
Wilfred J. Ferguson
Research Organics Inc., 4353 E. 49th St.
Cleveland, Ohio 44125
Dallas K. Bates
Department of Chemistry and Chemical Engineering
Michigan Technological University
Houghton, Michigan 49931

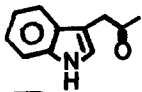
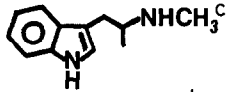
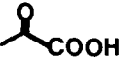
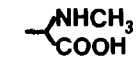

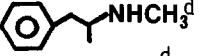

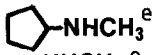
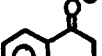
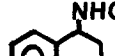





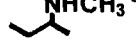
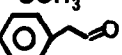
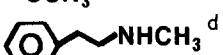

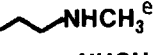
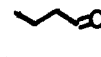

A number of secondary methylalkylamines have been prepared by reductive alkylation of N-methylbenzylamine with carbonyl compounds followed by hydrogenolysis.

Our efforts to prepare analogs of psilocin (3-[2-dimethylaminoethyl]-indol-4-ol)¹ required a number of secondary methylalkylamines. A review of the literature showed that these compounds could be prepared by a number of routes. The classical method involves reductive alkylation of amines with carbonyl compounds²⁻⁴. Variations include the substitution of nitro compounds for amines⁵ or the alkylation of amines with alcohols⁶ or other amines^{7,8}. The Leuckart-Wallach reaction^{9,10} and its variations require acidic conditions. The major difficulties encountered with these reactions are the production of by-products, overalkylation², or the need for high hydrogen pressures¹¹. Methods which have been developed to overcome these problems involve alkylation of such derivatives as N-benzylideneamines¹², trifluoroacetamides¹³, or phenacysulfonamides¹⁴, followed by hydrolysis. A novel approach to reductive alkylation utilizes metal cyanoborohydrides as selective reducing agents^{15,16}, but reaction conditions can be complex since the pH can be a controlling factor. Other methods involve the hydrolysis of aminophosphonium salts¹⁷⁻²⁰ or quaternary cyclic methylenimines²¹, hydride reduction of bridged imidates²², N-formates²³, and urethanes²⁴, and photo-reductive cleavage of p-toluenesulfonamides²⁵.

A number of asymmetric syntheses of primary amino compounds from ketones²⁶ and keto-acids^{27,28} have been effected by using optically active α -alkylbenzylamines. These reactions are usually carried out in two steps involving formation of a Schiff base and subsequent hydrogenation and hydrogenolysis. Primary amines have been produced from aldehydo- and keto-sugars in one step using reductive amination with benzylamine²⁹. Primary and secondary aminoalditols have been prepared by two-stage reductive alkylation of benzylamines³⁰.

We have extended the scope of this reaction with the synthesis of secondary N-methylalkylamines in one step using carbonyl compounds and N-methylbenzylamine. This method avoids overalkylation, especially with lower aliphatic aldehydes.

General Procedure.- An equimolar mixture of carbonyl compound and N-methylbenzylamine and 20% by weight of 10% Pd/C in absolute ethanol was shaken under 50 p.s.i. hydrogen for 16 hours. The mixture was acidified with conc. hydrochloric acid, filtered (Celite), and the filtrate concentrated under reduced pressure. The residue was dissolved in water, basified with 10*N* sodium hydroxide, and the amine extracted into ether. The organic solution was dried (MgSO₄), filtered, and the filtrate acidified to produce the appropriate derivative. The precipitate was collected and recrystallized from ethanol/ether. All products exhibited satisfactory analytical and NMR spectral data. Melting points agreed with literature values.

Carbonyl compound	Product ^a	Yield ^b	Carbonyl compound	Product	Yield
		65%			89%
		95%			95%
		32%			85%
		86%			70%
					87%
					80%

^aProducts with an asymmetric center are racemic ^bisolated ^cmaleate ^dhydrochloride ^eoxalate

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