Reductive Alkylations of Dimethylylamine Using Titanium(IV) Isopropoxide and Sodium Borohydride: An Efficient, Safe, and Convenient Method for the Synthesis of N,N-Dimethylated Tertiary Amines

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The development of safe and efficient methods for the synthesis of amines remains an important theme in chemical research because of their versatile utility as intermediates for drugs and agrochemicals. The N,N-dimethylalkylamines are particularly useful as ligands in homogeneous catalytic asymmetric transformations, as a modifier for reversed phase chromatography, and as a buffer in sequential analysis of proteins and peptides, among other applications. Methods described for the synthesis of N,N-dimethylated tertiary amines via alkylation of dimethylylamine often involve a large excess of the gaseous dimethylamine and elevated temperatures and pressures. Nevertheless, many of these procedures suffer from limitations. In particular, yields are often low, quaternary salt formation is common, and secondary alkylation agents cannot be used due to the preponderant elimination reactions. Moreover, many of these methods are described in the patent literature.

The most direct approach for the preparation of amines is the reductive amination of an appropriate aldehyde or ketone. Among the hydride reagents, sodium cyanoborohydride (Borch reduction) has been widely used to effect this transformation in recent years. However, the use of expensive and highly toxic sodium cyanoborohydride risks the presence of residual cyanide in the product and workup system makes this procedure less attractive to industry. In the context of our interest in the development of a mild and environmentally benign reagent system for reductive amination reactions, we have recently reported on an efficient method for the reductive aminations of formaldehyde using the combination of titanium(IV) isopropoxide and sodium borohydride. In a complementary study, this paper presents results for the application of this reagent system in the reductive alkylations of dimethylylamine with a variety of aldehydes and ketones at room temperature, an effective and very simple method for the preparation of N,N-dimethylylalkylamines of high purity in good to excellent yields. A mixture of dimethylylamine hydrochloride and triethylamine has been employed as the convenient source of nucleophilic dimethylamine; this requires no special handling techniques and obviates the use of excess gaseous amine. The reaction is possible proceeding through the formation of (dimethylamino)carbinolotitannium(IV) complex 1 (Scheme 1) as an intermediate which is reduced either directly or via transient iminium species. Titanium(IV) isopropoxide has been utilized as a mild reagent compatible with a variety of potentially acid-sensitive functional groups such as acetals, lactams, acetonide, and tert-butylmethylylsiyl ethers. The method is general for a variety of aldehydes and ketones containing potentially acid-sensitive functional groups. The molar ratio of the reactants and the results

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Notes were distilled or recrystallized from appropriate solvent mixtures; ketones and pure products were isolated by simple extraction with hydrochloric acid (2 N). It is noteworthy that, in contrast to the existing methods, the high yields of pure products, and the compatibility of this one-pot procedure with a number of normally reducible and acid-sensitive functional groups, this method should find wide application. Further studies addressing the possibility of asymmetric induction in the reductive aminations of unsymmetrical ketones using chirally modified titanium(IV) isopropoxide as well as application of this methodology in the synthesis of primary and secondary amines are currently underway.

**Experimental Section**

**General Procedure for the Reductive Alkylations of Dimethylamine**. To a solution of triethylamine (2.0 g, 20 mmol) in absolute ethanol (15 mL) were added dimethylamine hydrochloride (1.65 g, 20 mmol), titanium(IV) isopropoxide (5.7 g, 20 mmol), and the starting aldehyde (10 mmol). The reaction mixture was stirred at 25 °C for 9–10 h, after which sodium borohydride (0.57 g, 20 mmol) was added and the resulting reaction mixture was further stirred for a period of 10 h at 25 °C. The reaction was then quenched by pouring the mixture into aqueous sodium hydroxide (pH = 10) by slow addition of (10%), w/v aqueous sodium hydroxide and extracted with dichloromethane (50 mL × 2). The combined dichloromethane extracts were dried (K₂CO₃) and concentrated in vacuo to give pure N,N-dimethylated tertiary amines.

For the reductive aminations of ketones, the same general procedure was used except that the combined dichloromethane extracts were next extracted with hydrochloric acid (10 mL × 2, 2 N) to separate the neutral materials. The acidic aqueous solution was made alkaline (pH = 10) by slow addition of (10%), w/v aqueous NaOH and extracted with dichloromethane (50 mL × 2). The combined organic extracts were dried (K₂CO₃) and concentrated in vacuo to give pure N,N-dimethylated amines.

**Supporting Information Available**: H NMR spectra of entries 1–6, 8, 10, 11, 14, and 15 (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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