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Titanium(IV) Isopropoxide and Sodium Borohydride : A Reagent of Choice for Reductive Amination

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Abstract: The preliminary results on the novel use of titanium(IV) isopropoxide and sodium borohydride in reductive amination reactions are reported. A highly efficient and mild procedure for reductive aminations of formaldehyde with a variety of primary and secondary amines is described.

The reductive amination of aldehydes and ketones with primary and secondary amines is one of the most useful reactions in the synthesis of amines.[1,2] Among the hydride reagents, sodium cyanoborohydride[3] has been widely utilised to effect this transformation in recent years.The other current methods include the combinations of sodium borohydride and acetic acid[4] or aqueous sulphuric acid.[5] However, the use of toxic sodium cyanoborohydride raises the risk of residual cyanide in the product or in the work-up waste system and the presence of acid or protic solvents in the reaction medium restricts its use for molecules containing acid-sensitive and easily solvolysed groups. These factors demonstrate the need for further exploration beyond the existing reductive amination based synthetic repertoire. In our research, we have been working to overcome these shortcomings and, recently, we have reported[6] the use of zinc borohydride, a uniquely mild reducing agent, in the reductive alkylations of amines.

This paper presents the combination of titanium (IV) isopropoxide and sodium borohydride as a mild, safe and efficient one-pot reagent system in the reductive aminations of formaldehyde.[7] A wide variety of primary and secondary amines is reductively methylated in the presence of acid-sensitive functional groups in excellent yields. Presumably, titanium (IV) isopropoxide is functioning as a Lewis acid catalyst as well as an excellent water scavanger to generate imines which are reduced by sodium borohydride. In another possible mechanism, formation of stable alkyl- or dialkylaminomethanolato titanium complexes has been proposed[8,9] as intermediates which are reduced either directly or via transient iminium species. Titanium (IV) isopropoxide has been found[9,10] to be compatible with a number of functional groups such as acetonide, lactam, tert-butyldimethylsilyl ether and acetals.

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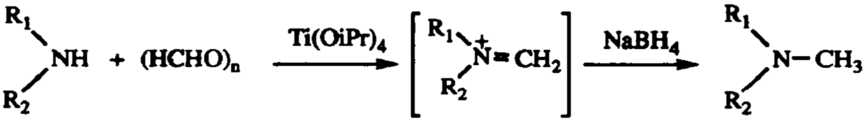
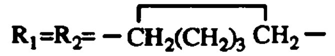
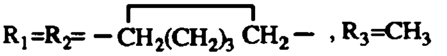
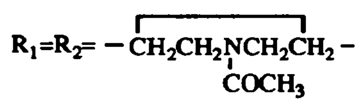
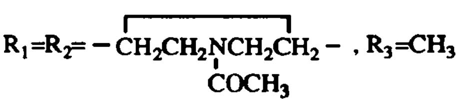
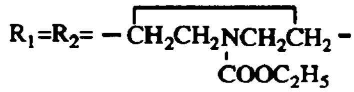
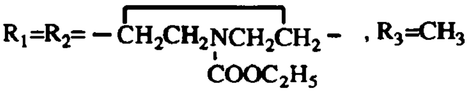
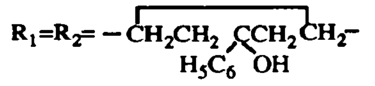
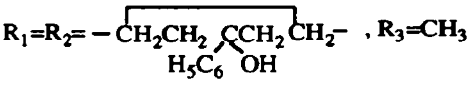
Table 1: Representative Reductive Aminations of Formaldehyde with Titanium (IV) Isopropoxide and Sodium Borohydride



Entry	Starting amine[a] R_1R_2NH	Time (h)	Product[b] $R_1R_2R_3N$	Yield[c] (%)
1	$R_1=CH_3(CH_2)_2CH_2, R_2=H$	5	$R_1=CH_3(CH_2)_2CH_2, R_2=R_3=CH_3$	80
2	$R_1=C_6H_5CH_2, R_2=H$	5	$R_1=C_6H_5CH_2, R_2=R_3=CH_3$	85
3	$R_1=C_6H_5(CH_2)_2CH_2, R_2=H$	5	$R_1=C_6H_5(CH_2)_2CH_2, R_2=R_3=CH_3$	88
4	R_1=1-Adamantyl, $R_2=H$	6	R_1=1-Adamantyl, $R_2=R_3=CH_3$	90
5	$R_1=HO(CH_2)_4CH_2, R_2=H$	6	$R_1=HO(CH_2)_4CH_2, R_2=R_3=CH_3$	85
6	$R_1=H_5C_2OOCCH_2, R_2=H$	5	$R_1=H_5C_2OOCCH_2, R_2=R_3=CH_3$	75
7	$R_1=(H_5C_2O)_2CH(CH_2)_2CH_2, R_2=H$	5	$R_1=(H_5C_2O)_2CH(CH_2)_2CH_2, R_2=R_3=CH_3$	92
8	$R_1=(CH_3)_2C(CH_2OH), R_2=H$	6	$R_1=(CH_3)_2C(CH_2OH), R_2=R_3=CH_3$	85
9	$R_1=R_2=C_6H_5CH_2$	4	$R_1=R_2=C_6H_5CH_2, R_3=CH_3$	94
10	$R_1=R_2=(CH_3)_2CH$	4	$R_1=R_2=(CH_3)_2CH, R_3=CH_3$	95
11	$R_1=R_2$=Cyclohexyl	4	$R_1=R_2$=Cyclohexyl, $R_3=CH_3$	95
12	 $R_1=R_2=-CH_2(CH_2)_3CH_2-$	4	 $R_1=R_2=-CH_2(CH_2)_3CH_2-, R_3=CH_3$	82
13	 $R_1=R_2=-CH_2CH_2\underset{COCH_3}{N}CH_2CH_2-$	4	 $R_1=R_2=-CH_2CH_2\underset{COCH_3}{N}CH_2CH_2-, R_3=CH_3$	92
14	 $R_1=R_2=-CH_2CH_2\underset{COOC_2H_5}{N}CH_2CH_2-$	4	 $R_1=R_2=-CH_2CH_2\underset{COOC_2H_5}{N}CH_2CH_2-, R_3=CH_3$	95
15	 $R_1=R_2=-CH_2CH_2\underset{H_5C_6\ OH}{C}CH_2CH_2-$	4	 $R_1=R_2=-CH_2CH_2\underset{H_5C_6\ OH}{C}CH_2CH_2-, R_3=CH_3$	90

(a) The amines were either distilled over KOH or recrystallised from appropiate solvent mixtures prior to use. Reactions were performed in distilled diglyme for primary amines and in abs. EtOH or diglyme for secondary amines, ratio of amine:paraformaldehyde :titanium (IV) isopropoxide :sodium borohydride :: entries 1-8, 1: 4: 2: 1.5; entries 9-14, 1: 2: 1: 1.

(b) All products were characterised by their IR, ^1H NMR and physical constant data and comparison with the data reported in the literature or authentic compounds.

(c) Yields are of isolated and purified products.

The utility of this method is evaluated by reacting a mixture of paraformaldehyde and various amines containing potentially acid-sensitive or reducible functional groups with titanium (IV) isopropoxide and sodium borohydride. The molar ratio of the reactants and the results obtained for a representative group of amines are shown in Table 1.[11] The reducing agent was added only after the mixture of amine, paraformaldehyde and titanium (IV) isopropoxide had been stirred for 30 min. at 60^0 and again for 30 min. at room temperature. Diglyme was the solvent of choice for the primary amines; the competitive carbonyl group reduction is very slow[12] in this solvent. The secondary amines reacted equally well both in diglyme and in absolute ethanol. The reaction mixture was stirred at room temperature for 2-3 h and then at 60^0 for 2-3 h, poured into aqueous ammonia and extracted with diethyl ether. Drying of the organic extracts and concentration provided N-methylated amines which were purified by distillation or flash chromatography. Paraformaldehyde was used as the convenient source of formaldehyde and like other reductive methylation procedures[7] the reaction medium was not exposed to protic acids.

As shown in Table-1, both the primary and secondary amines provided the corresponding tertiary methylated amines in high yields. The secondary amines reacted faster than the primary amines and the products were isolated in a pure form by simple diethyl ether extraction. Steric hindrance posed no problem; the hindered amines diisopropylamine and dicyclohexylamine (entries 10 and 11) underwent clean and complete methylation in 4 h. The reaction conditions were found to be tolerant to a number of groups such as acetal (entry 7), carboxylic ester (entry 6), amide (entry 13) and carbamate (entry 14).The hydroxyamines (entries 5, 8 and 15) could be alkylated without protection of the hydroxy groups. This reaction, however, failed with weakly basic amines such as 2,4-dichloroaniline and nitroanilines. Since the reductive amination of formaldehyde with secondary amines is invariably faster[13] than with the primary amines, it has not been possible to N-monomethylate primary amines under these conditions.

The mild reaction conditions, easy work-up, the high yields of pure products and compatibility of this one-pot procedure with a variety of normally reducible and acid-sensitive functional groups offer significant advantages over the existing reductive amination methods. This reagent system is, therefore, a good alternative to sodium cyanoborohydride; its use obviates the problem of the presence of residual cyanide in the product and in the waste stream.

In conclusion, an efficient alternative to the Borch reductive alkylations of amines has been developed which features the use of titanium (IV) isopropoxide, a very mild Lewis acid, and sodium borohydride. Work is now underway to extend its utility and will be reported shortly.

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11. **Typical Experimental** : A mixture of 1-adamantyl amine (0.76g, 5 mmol), paraformaldehyde (0.6g, 20 mmol) and titanium (IV) isopropoxide (2.85g, 10 mmol) in freshly distilled diglyme (5 mL) was stirred at 60^0 (bath Temp., 30 min.) and at room temp. (30 min.). Sodium borohydride (0.29g, 7.5 mmol) was then added and the resulting mixture was stirred at room temp. for 3 h and then at 60^0 for 3 h. The cooled (ice-bath) reaction mixture was quenched by addition of aqueous ammonia (25 mL, 2N). The resulting inorganic precipitate was filtered and washed with diethyl ether (25 mL). The aqueous part was extracted with diethyl ether (25 mLx3) and the combined organic extracts were dried (Na_2SO_4) and concentrated in *vacuo* to give a colourless oil which was purified by flash chromatography on neutral alumina. Elution with 1:4 diethyl ether and hexane mixture afforded 0.8g (90%) of pure 1-(N,N-dimethylamino)adamantane.
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