

## Use of Zinc Borohydride in Reductive Amination: An Efficient and Mild Method for *N*-Methylation of Amines

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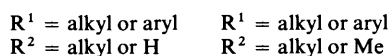
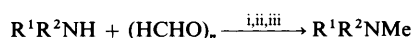
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An efficient method for the reductive methylation of amines using paraformaldehyde, zinc chloride and zinc borohydride is described.

Reductive alkylation of primary and secondary amines with aldehydes and ketones is widely used in amine synthesis,<sup>1,2</sup> the Borch method utilizing sodium cyanoborohydride<sup>3</sup> being, currently, the most popular way to effect the transformation. Other methods include the use of sodium borohydride and trifluoroacetic acid<sup>4</sup> or aqueous sulfuric acid;<sup>5</sup> use of sodium cyanoborohydride risks the presence of residual cyanide in the product or work-up 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. Such factors led us to explore the use of zinc borohydride as a safe, easily available and less expensive hydride alternative to sodium cyanoborohydride. Zinc borohydride, prepared from anhydrous zinc chloride and sodium borohydride,<sup>6d</sup> is a uniquely mild reducing agent already employed<sup>6</sup> for the selective reduction of carbonyl groups and reductive cleavages of ethers and epoxides. Recently, in connection with a study on the reduction of azomethines to amines using zinc borohydride, Kotsuki *et al.*<sup>6k</sup> reported their failure to effect reductive amination of carbonyl compounds with this reagent. Here we present preliminary results for the novel use of zinc borohydride in the reductive aminations of formaldehyde<sup>7</sup> mediated by zinc chloride, an efficient method for the synthesis of tertiary methylated amines of high purity in good to excellent yields (Scheme 1). Zinc chloride has been used as a very mild catalyst compatible with a variety of acid-sensitive functional groups including acetals.<sup>8</sup>



**Scheme 1** Reagents and conditions: i, ZnCl<sub>2</sub>, THF; ii, Zn(BH<sub>4</sub>)<sub>2</sub>, THF, 25 °C, 8–12 h; iii, aqueous NH<sub>3</sub>

Methylation of dibenzylamine entailed the use of 2 mol equiv. of paraformaldehyde, 1 mol equiv. of zinc chloride and 1.5 mol equiv. of zinc borohydride in anhydrous THF which was prepared from zinc chloride (1 mol equiv.) and sodium borohydride (2 mol equiv.) according to the reported procedures.<sup>‡</sup> The reaction mixture was stirred at room temperature for 8 h, poured into aqueous ammonia and extracted with diethyl ether. Drying of the organic extract (Na<sub>2</sub>CO<sub>3</sub>) and

concentration provided pure *N*-methyl dibenzylamine directly in 90% yield. In contrast, the reaction was very sluggish without zinc chloride, only 15% *N*-methylation being realized after the reaction mixture had been stirred for 48 h. Paraformaldehyde was used as the convenient source of formaldehyde and, like other reductive methylation procedures,<sup>7</sup> the reaction medium was never exposed to protic acids or protic solvents; THF proved to be the solvent of choice. The method is general for a wide variety of aliphatic and aromatic primary and secondary amines. The results are summarized in Table 1.

As shown in Table 1, the secondary amines reacted faster than the primary amines and pure products were isolated by simple diethyl ether extraction. Steric hindrance seems to pose no problem; the hindered amines dicyclohexylamine and diisopropylamine underwent clean and complete methylation in 8 h. The hydroxylamines needed no protection of the hydroxy groups. The reaction conditions were found to be tolerant to a number of groups such as chloro, methoxy, carboxylic esters, nitro and amide. The primary amines afforded the *N,N*-dimethylamines in good yields; the crude products were purified by column chromatography or crystallization. The very weak base *m*-nitroaniline (p*K*<sub>a</sub> 2.47) was also *N,N*-dimethylated under these conditions. It is of note that, in general, the aromatic primary amines reacted slowly compared to the aliphatic primary amines. Since the reductive amination of formaldehyde with secondary amines is invariably faster<sup>9</sup> than with the primary amines, it has not been possible to *N*-monomethylate primary amines under our conditions.

Because of the neutral reaction conditions, easy work-up, the high yields of pure products and compatibility of zinc borohydride and zinc chloride with a variety of normally reducible functional groups and ketals<sup>6,8</sup> this method promises to be the method of choice for reductive methylation of amines. Moreover, this procedure is both safe and cheap.

In summary, an efficient method for reductive methylation of amines has been developed which features the use of zinc borohydride, a very mild and selective reducing agent, zinc chloride and paraformaldehyde. Particularly noteworthy is the neutral and nonaqueous reaction medium that can tolerate a number of sensitive functional groups. These advantages make zinc borohydride an excellent alternative to the toxic sodium cyanoborohydride in reductive aminations. The generality of using this system in reductive aminations is currently being explored and will be reported elsewhere.

### Experimental

**Typical Reductive Methylation of Dibenzylamine.**—A mixture of dibenzylamine (980 mg, 5 mmol), paraformaldehyde (300 mg, 10 mmol) and zinc chloride (680 mg, 5 mmol) in anhydrous THF (20 cm<sup>3</sup>) was stirred for 1 h at room temperature. To this

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<sup>‡</sup> A stock solution of zinc borohydride in dry THF prepared according to the reported procedure (ref. 6d) can be stored in a sealed container at 0–5 °C for 2–3 weeks. This solution showed absence of chloride with AgNO<sub>3</sub>–HNO<sub>3</sub>.

**Table 1** Reductive methylation of amines with paraformaldehyde-ZnCl<sub>2</sub>-Zn(BH<sub>4</sub>)<sub>2</sub> at 25 °C

Entry	Starting amine <sup>a</sup> R <sup>1</sup> R <sup>2</sup> NH	Time (h)	Product <sup>b</sup> R <sup>1</sup> R <sup>2</sup> R <sup>3</sup> N	Yield <sup>c</sup> (%)
1	R <sup>1</sup> = Pr, R <sup>2</sup> = H	10	R <sup>1</sup> = Pr, R <sup>2</sup> = R <sup>3</sup> = Me	70
2	R <sup>1</sup> = PhCH <sub>2</sub> , R <sup>2</sup> = H	10	R <sup>1</sup> = PhCH <sub>2</sub> , R <sup>2</sup> = R <sup>3</sup> = Me	65
3	R <sup>1</sup> = EtO <sub>2</sub> CCH <sub>2</sub> , R <sup>2</sup> = H	10	R <sup>1</sup> = EtO <sub>2</sub> CCH <sub>2</sub> , R <sup>2</sup> = R <sup>3</sup> = Me	70
4	R <sup>1</sup> = HO(CH <sub>2</sub> ) <sub>4</sub> CH <sub>2</sub> , R <sup>2</sup> = H	10	R <sup>1</sup> = HO(CH <sub>2</sub> ) <sub>4</sub> CH <sub>2</sub> , R <sup>2</sup> = R <sup>3</sup> = Me	72
5	R <sup>1</sup> = R <sup>2</sup> = PhCH <sub>2</sub>	8	R <sup>1</sup> = R <sup>2</sup> = PhCH <sub>2</sub> , R <sup>3</sup> = Me	90
6	R <sup>1</sup> = R <sup>2</sup> = Pr	8	R <sup>1</sup> = R <sup>2</sup> = Pr, R <sup>3</sup> = Me	92
7	R <sup>1</sup> , R <sup>2</sup> = $\overline{\text{CH}_2\text{CH}_2(\text{Ph})\text{C}(\text{OH})\text{CH}_2\text{CH}_2}$	8	R <sup>1</sup> = R <sup>2</sup> = $\overline{\text{CH}_2\text{CH}_2(\text{Ph})\text{C}(\text{OH})\text{CH}_2\text{CH}_2}$ , R <sup>3</sup> = Me	92
8	R <sup>1</sup> = R <sup>2</sup> = Pr <sup>i</sup>	8	R <sup>1</sup> = R <sup>2</sup> = Pr <sup>i</sup> , R <sup>3</sup> = Me	90
9	R <sup>1</sup> = R <sup>2</sup> = cyclohexyl	8	R <sup>1</sup> = R <sup>2</sup> = cyclohexyl, R <sup>3</sup> = Me	94
10	R <sup>1</sup> = <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> = H	12	R <sup>1</sup> = <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> = R <sup>3</sup> = Me	62
11	R <sup>1</sup> = <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> = H	12	R <sup>1</sup> = <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> = R <sup>3</sup> = Me	65
12	R <sup>1</sup> = <i>m</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> = H	12	R <sup>1</sup> = <i>m</i> -O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> = R <sup>3</sup> = Me	60
13	R <sup>1</sup> = <i>p</i> -AcNHC <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> = H	12	R <sup>1</sup> = <i>p</i> -AcNHC <sub>6</sub> H <sub>4</sub> , R <sup>2</sup> = R <sup>3</sup> = Me	68

<sup>a</sup> All amines were either distilled over KOH or recrystallized from appropriate solvent mixtures prior to use. Reactions were carried out in dry THF at room temperature, ratio of amine:paraformaldehyde:zinc chloride:zinc borohydride: entries 1–4, 1:4:2:2; entries 5–9, 1:2:1:1.5; entries 10–13, 1:6:2:3. <sup>b</sup> All products were identified by IR, <sup>1</sup>H NMR and physical constants data and comparison with the data reported in the literature or authentic compounds. <sup>c</sup> Yields are of isolated and purified (flash chromatography or distillation) products.

mixture a solution of zinc borohydride (7.5 mmol) in THF was added dropwise over 10 min. The contents were further stirred for 8 h. Ammonium hydroxide (2 mol dm<sup>-3</sup>, 20 cm<sup>3</sup>) was then added to the mixture dropwise and the whole mixture was stirred for 10 min. The organic part was extracted with diethyl ether (25 cm<sup>3</sup> × 3) and the combined extracts were concentrated and dried (Na<sub>2</sub>CO<sub>3</sub>) to afford a colourless oil which was distilled to give pure *N*-methyl dibenzylamine (950 mg, 90%); b.p. 123 °C at 0.7 mmHg; δ(CDCl<sub>3</sub>) 2.18 (s, 3 H), 3.52 (s, 4 H) and 7.23–7.43 (m, 10 H).

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