J. Org. Chem. **1993**, *58*, 5005–5007 **5005**

The Species Prepared from Sodium Borohydride and *N,N*-Dimethylformamide Reduces or Dimethylaminates Organic Halides

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Received May 17, 1993

The danger of mixing sodium borohydride and DMF at elevated temperature is well known.[1-3] Following an induction period, rapid evolution of a flammable gas can result, identified as trimethylamine.[3] It has been suggested[3] that adventitious acid present in DMF could initiate reaction between that solvent and sodium borohydride. When we mixed sodium borohydride with DMF, we noted trimethylamine,[3] but concomitant evolution of bis(dimethylamino)methane also occurred. Formation of these amines suggested that a new species had been generated *in situ* which was capable of reducing or reductively aminating DMF.[4] We were interested to learn if metal complexes added in measured amounts could replace any adventitious catalysts so that the reactivity of this new species could be exploited.

When NaBH$_4$ (1.135 g, 30 mmol) was dissolved in DMF (30 mL) and the reaction mixture was warmed to 95 °C, product formation was slow, even after 2 h. (We followed the reaction by measuring evolution of trimethylamine.) When lithium salt was added (254 mg, 6 mmol, LiCl) to a fresh mixture of NaBH$_4$ (1.152 g, 30 mmol) in DMF (30 mL), a 1-h induction period was noted, followed by rapid effervescence. Adding Cp$_2$TiCl$_2$[16] also reduced the induction period. For example, heating a mixture of NaBH$_4$ (30 mmol) and Cp$_2$TiCl$_2$ (0.6 mmol) in 30 mL of DMF at 95 °C gave Me$_3$N with an induction period of 30 min (Figure 1a). When the Cp$_2$TiCl$_2$ was reduced to 0.3 mmol, the induction period increased to 50 min (Figure 1b). No Me$_3$N was observed after heating NaBH$_4$ (30 mmol) in DMF (30 mL) for 1.5 h at 95 °C whereupon 0.16 mmol of Cp$_2$TiCl$_2$ was added to the mixture. An induction period of 60 min was noted (Figure 1c). Adding LiCl (30 mmol) to a mixture of NaBH$_4$ (30 mmol) and Cp$_2$TiCl$_2$ (0.3 mmol) in DMF (30 mL) gave Me$_3$N evolution which was too fast to monitor, but the reaction of Cp$_2$TiCl$_2$ (0.6 mmol) and Pr$_4$N$^+$BH$_4^-$ (30 mmol) in DMF at 95 °C gave no burst of Me$_3$N, even after 2 h. Thus, formation of the active reducing agent and/or subsequent attack on DMF seems to be enhanced rate-wise by the presence of an oxyphilic metal species (or, perhaps, proton[3] acting as the oxyphile): The combination of Ti^{IV} and Na$^+$ is about 20 times more reactive than that of Li$^+$ and Na$^+$; the combination of Li$^+$ and Ti^{IV} gives uncontrollable reaction. In all cases the amount of amines evolved was about 15 mmol of each, and the rate of Me$_3$N formation was qualitatively independent of catalyst concentration after the induction period. Thus, the addition of the Ti species seems only to shorten the induction period for formation of the active reducing agent; a Ti reagent, *per se*, is not the active reagent for DMF reduction.

Scheme I

Reaction between NaBH$_4$ and DMF appears to generate an adduct, tentatively formulated as Na$^+$BH$_3$(OCH$_2$NMe$_2$)$^-$,[17] (1). Indeed, when NaBH$_4$ (1.1 mmol) and Cp$_2$TiCl$_2$ (0.04 mmol) in DMF-d_7 (1 mL) were heated to 96 °C for *ca.* 1 h and then rapidly cooled to 25 °C, ^{11}B NMR analysis of the reaction mixture showed, in addition to the quintet for BH$_4^-$ at δ −39.11 (versus Et$_2$OBF$_3$; $^{1}J_{B-H} = 80.9$ Hz), a new quartet at δ −7.95 ($^{1}J_{B-H} = 97$ Hz), comparable in chemical shift to CH$_3$OBH$_3^-$ (δ −7.0; $^{1}J_{B-H} = 88$ Hz).[18]

A mixture of NaBH$_4$ (30 mmol) and Cp$_2$TiCl$_2$ (0.3 mmol) in DMF (30 mL) was heated to 96 °C for *ca.* 1 h until the onset of Me$_3$N evolution signaled the *in situ* formation of 1. The mixture was then rapidly cooled to 40 °C and 1-chlorooctane was added (the solution of 1 could be filtered at room temperature with no adverse effect). Disappearance of chlorooctane occurred with $k_{obs} = 3.9 \times 10^{-5}$ s^{-1}. After 7 h, the chlorooctane had been converted to octane, but (*N,N*-dimethylamino)octane was also observed (60% total conversion; 5:1). Further conversion of the chlorooctane (37%) was achieved in 20 min at 95 °C (octane:(*N,N*-dimethylamino)octane = 4.4:1). No trimethylamine or bis(dimethylamino)methane were produced by reaction between NaBH$_4$ and DMF at 40 °C even after 7 h. Although reaction between 1-chlorooctane and NaBH$_4$ (30.0 mmol) in 30 mL of DMF occurred at 40 °C at a rate comparable to that noted in the activated mixture ($k_{obs} = 3.0 \times 10^{-5}$s^{-1}), only octane and no (*N,N*-dimethylamino)octane was formed.

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(4) Amides are normally inert to sodium borohydride alone but can be reduced to amines using combination reagents of NaBH$_4$ and pyridine,[5] or LiBH$_4$ and amines,[6] CoCl$_2$,[7], TiCl$_4$,[8] SnCl$_4$,[9] I$_2$,[10] Me$_3$SiCl,[11] PCl$_5$,[12] (O)PCl$_3$,[13] R$_2$SeX$_2$,[14] or ZnCl$_2$–NR$_3$.[15]

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(16) Among the titanium complexes surveyed, Cp$_2$TiCl$_2$ was the best catalyst for promotion of formation of 1. Other complexes tried include CpTiCl$_3$, (acac)$_2$TiCl$_2$, (TPP)Ti=O, (salen)TiCl$_2$, (salen)$_2$Ti, [tris(3,5-dimethylpyrazoyl)borate]TiCl$_3$, TiCl$_3$, and titanium boride.

(17) Similar structures have been suggested in reduction of amides by LiAlH$_4$ or LiBEt$_3$H. (a) Weygand, F.; Linde, H.; Schafer, F.; Eigen, I. *Angew. Chem.* **1953**, *65*, 525. (b) Brown, H. C.; Kim, S. C.; Krishnamurthy, S. *J. Org. Chem.* **1980**, *45*, 1. (c) Brown, H. C.; Kim, S. C. *Synthesis* **1977**, 635. (d) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567.

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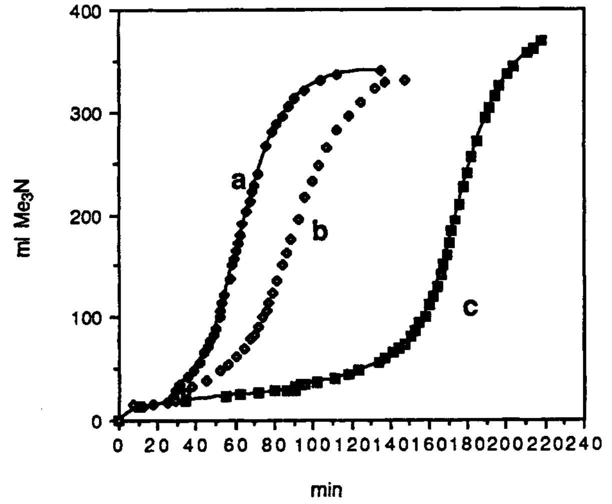


Figure 1. Induction periods for *in situ* formation of 1, at 95 °C. (a) DMF (30.0 mL); NaBH$_4$ (30 mmol); Cp$_2$TiCl$_2$ (0.60 mmol). (b) DMF (30.0 mL); NaBH$_4$ (30 mmol); Cp$_2$TiCl$_2$ (0.30 mmol). (c) DMF (30.0 mL); NaBH$_4$ (30 mmol); 1.5 h at 95 °C and then Cp$_2$TiCl$_2$ (0.16 mmol) added.

6-Bromo-1-hexene[19,20] and cyclopropylcarbinyl chloride[20,21] are used as classical probes for free alkyl radical intermediates by noting formation of cyclic and acyclic products, respectively. When a fresh solution of 1 was treated with 6-bromo-1-hexene, only hexene-1 was observed; no methylcyclopentane was detected. Similarly, cyclopropylcarbinyl chloride gave only methylcyclopropane and [(*N*,*N*-dimethylamino)methyl]cyclopropane;[22] no butene, butane, or acyclic *N*,*N*-dimethylamino analogs could be detected. Thus reduction or dialkylamination occurs by nonradical, likely nucleophilic, routes. It is interesting to contrast our observations with reductions[23,24] of alkyl polyhalides by an organoboronate hydride initiated by AIBN, suggesting a radical process for this other system.

Little reaction occurred between NaBH$_4$ and 1,2,4,5-tetrachlorobenzene in the absence of Cp$_2$TiCl$_2$ (Figure 2a). A mixture of 1,2,4,5-tetrachlorobenzene (3 mmol), NaBH$_4$ (30 mmol), and Cp$_2$TiCl$_2$ (0.3 mmol) in DMF (30 mL) was heated at 95 °C. After an induction period (Figure 2b) and further reaction (total time 130 min) analysis showed 1,2,4-trichlorobenzene and 2,4,5-trichloro-*N*,*N*-dimethylaniline (1:1.2). When 1,2,4,5-tetrachlorobenzene (3 mmol) was added to a 25 °C solution of 1 which was then rewarmed to 95 °C, product formation occurred rapidly with no induction period. In a simple competition, 1-chlorooctane reacted faster than 1,2,4,5-tetrachlorobenzene: After 1.5 h at 52 °C, 74% of chlorooctane was converted to octane and (dimethylamino)octane (1:1.6) but only traces (<2%) of 1,2,4-trichlorobenzene and 2,4,5-trichloro-*N*,*N*-dimethylaniline were obtained. After 17 h further at 52 °C, tetrachlorobenzene was converted (69%) to 1,2,4-trichlorobenzene and 2,4,5-trichloro-*N*,*N*-dimethylaniline (1:1.3).

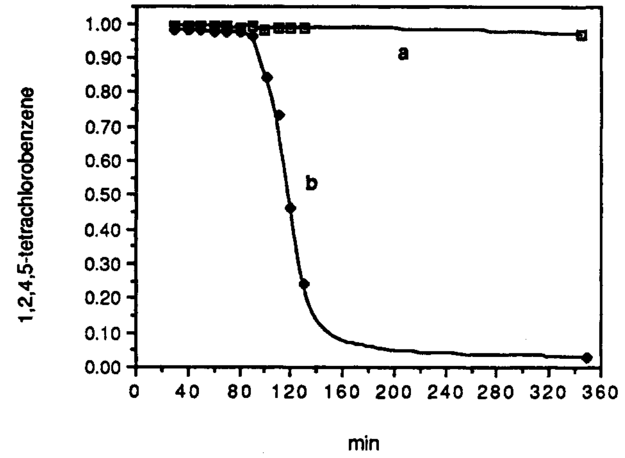
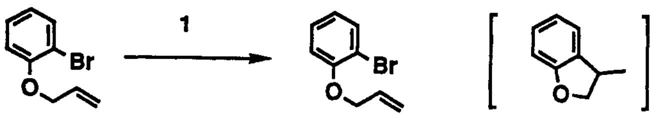


Figure 2. Reaction of 1,2,4,5-tetrachlorobenzene with *in situ* generated 1 at 95 °C. (a) DMF (30.0 mL); NaBH$_4$ (30 mmol). (b) DMF (30.0 mL); NaBH$_4$ (30 mmol); Cp$_2$TiCl$_2$ (0.30 mmol).

As a mechanistic probe for aryl halide reduction,[25] *o*-bromophenyl allyl ether was treated with a freshly prepared solution of 1 at 95 °C (9% conversion after 1.5 h). Only allyl phenyl ether was obtained; no 3-methylbenzodihydrofuran was detected. Thus reduction of the aryl halide also appears to proceed by a nonradical mechanism (Scheme II).

Scheme II



We suggest that added cation assists the initial attack of BH$_4^-$ on DMF to give 1. The apparent autocatalysis shown in Figures 1 and 2 is proposed to be due to subsequent reaction between 1 and DMF to give 2, and rapid ligand metathesis between 2 and BH$_4^-$ generates 2 equiv of 1[26] (Scheme III). The observation of both reduced and dimethylaminated products from alkyl halide reactions[27] is also consistent with (CH$_3$)$_2$NBH$_3^-$ (3) being a primary reaction product of 1 and BH$_4^-$. (Although dimethylamination of aryl halides by 3 had not been noted,[27] we find that 3 reacts with 1,2,4,5-tetrachlorobenzene to give both reduced and dimethylaminated products.) That 1 can be cleaved by BH$_4^-$ is supported by the observation of methanol on hydrolysis of reaction mixtures, and reaction among BH$_4^-$, DMF, and 1,2,4,5-tetrachlorobenzene yielded some trichloroanisole. However, when a freshly prepared solution of 1 was heated to 95 °C for 1 h, no (CH$_3$)$_2$NBH$_3^-$ (δ −12.22; J = 66 Hz in DMF-d_7; *cf.* δ −14.7 in diglyme[28]) or CH$_3$OBH$_3^-$ could be detected. Unfortunately, dimethylaminoborohydride is unstable in DMF at elevated temperature, yielding both trimethylamine[27] and bis(dimethylamino)methane, and methoxyborohydride rapidly disproportionates[17d,18] at 0 °C to BH$_4^-$ and B(OCH$_3$)$_4^-$ (δ 3.2 in CH$_3$OH[29]). We did observe a strong signal at δ 2.4 (*cf.* δ 1.4 for the hydrolysis product

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[22] [(Dimethylamino)methyl]cyclopropane was characterized spectroscopically: MS *m/e* = 99 (M$^+$), 58 (M$^+$ − cyclopropyl); ^{1}H NMR (CDCl$_3$, 25 °C) δ 2.18 (s, N(CH_3)$_2$), 2.08 (d, NMe$_2$CH_2CH, J_{HH} = 6.8 Hz); 0.80 (m, CH_2), 0.43 (m, CH_2), 0.04 (m, CH).

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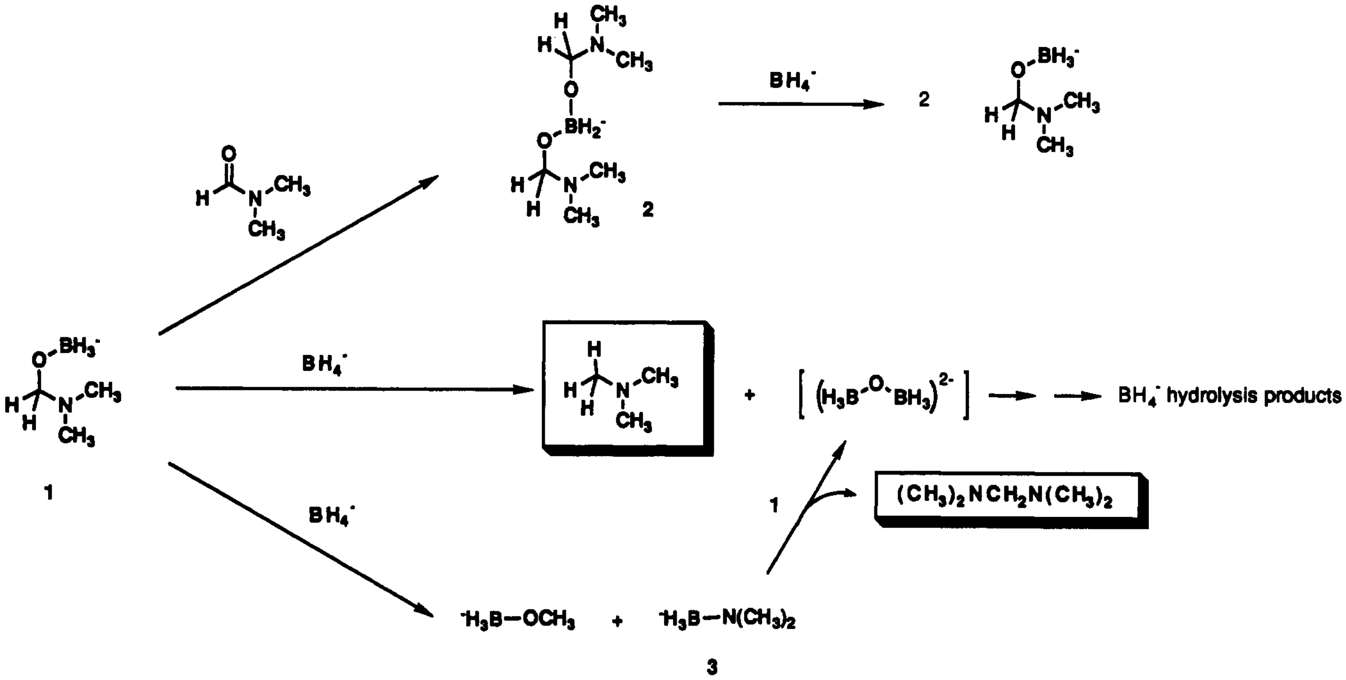
Scheme III



of BH$_4^-$ in D$_2$O) which increased in intensity even as the solution of 1 remained at room temperature and which may be due to mixed oxymethoxyborohydride decomposition products. Thus, it is not possible to ascertain whether observed (dimethylamino)alkyl and -aryl reaction products can be attributed either uniquely to 1 or to a mixture of 1 and (CH$_3$)$_2$NBH$_3^-$.

Experimental Section

Dimethylformamide, NaBH$_4$ (Aldrich), and Cp$_2$TiCl$_2$ (Aldrich) were used as received. All reactions were performed in vessels open to the atmosphere or vented through a bubbler. ^{11}B NMR spectra were recorded in DMF using a Brucker WM250 spectrometer operating at 80.254 MHz, and chemical shifts were calibrated against Et$_2$OBF$_3$ (capillary).

Reaction between NaBH$_4$ and DMF in the Presence of Cp$_2$TiCl$_2$. A mixture of Cp$_2$TiCl$_2$ (75 mg; 0.3 mmol) and NaBH$_4$ (1.135 gm; 30 mmol) was heated in 30 mL of DMF for 1 h at 92 °C under air in a flask equipped with a reflux condenser and a calibrated manometer. Little gas evolution was noted for 60 min after which time rapid evolution of trimethylamine occurred (300 mL; *ca.* 15 mmol). Similarly, a mixture of NaBH$_4$ (40 mg; 1.06 mmol) and Cp$_2$TiCl$_2$ (10 mg; 0.04 mmol) in DMF-d_7 (1 mL) was heated at 96 °C for 1 h, it was then rapidly cooled to 25 °C, filtered through a glass wool plug, and analyzed by ^{11}B NMR.

Reaction between NaBH$_4$ and DMF-d_7 in the Presence of Cp$_2$TiCl$_2$. When a similar reaction was performed in DMF-d_7, (CD$_3$)$_2$NCH$_2$D (m/z = 66) and (CD$_3$)$_2$NCHDN(CD$_3$)$_2$ (m/z = 115) were obtained. Hydrolysis of the reaction mixture gave CH$_2$DOH (m/z = 33); no (CD$_3$)$_2$NH was observed.

Reaction between 1 and *o*-Bromophenyl Allyl Ether. A flask was charged with NaBH$_4$ (1.135 gm; 30 mmol), Cp$_2$TiCl$_2$ (75 mg; 0.3 mmol), and DMF (30 mL) was heated at 95 °C until gas evolution started. Then 2-bromophenyl allyl ether (0.153 gm, 0.72 mmol) was added. The mixture was heated at 95 °C for 1.5 h. The reaction mixture was then hydrolyzed, and organic products were extracted with ether. Analysis of the ether layer by GC showed 9% allyl phenyl ether and 91% recovered starting material.

Reaction between (CH$_3$)$_2$NBH$_3^-$ and 1,2,4,5-Tetrachlorobenzene. A flask was charged with NaBH$_3$N(CH$_3$)$_2$[27] (1.2 gm; 14.8 mmol), and 1,2,4,5-tetrachlorobenzene (324 mg; 1.5 mmol), and diglyme (20 mL). The mixture was heated at 95 °C for 10 h. After hydrolysis and standard workup, GC analysis showed C$_6$H$_3$Cl$_2$(NMe$_2$), C$_6$H$_2$Cl$_2$(NMe$_2$)$_2$, and C$_6$H$_4$Cl(NMe$_2$) in relative amounts 83:12:5.

Acknowledgment. The authors acknowledge Texas Eastern Gas Pipeline Co. and the National Science Foundation, in part, for research support. They also thank Dr. G. Medding for useful information.