

Convenient Methods for the Reduction of Amides, Nitriles, Carboxylic Esters, Acids and Hydroboration of Alkenes Using NaBH_4/I_2 System

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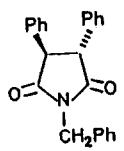
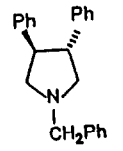
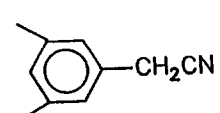
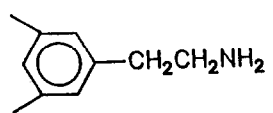
Abstract: Reaction of amides with $\text{NaBH}_4\text{-I}_2$ system in THF gives the corresponding amines in 70-76% yields. Reduction of nitriles yields the corresponding amines in 70-75% yields. The I_2/NaBH_4 system is useful in the hydroboration of olefins and the corresponding alcohols are obtained in 78-92% yields after $\text{H}_2\text{O}_2/\text{OH}^-$ oxidation. The reagent system is also useful for the reduction of carboxylic esters and acids to the corresponding alcohols in 60-90% yields.

The NaBH_4 does not reduce amides, nitriles, carboxylic esters and acids under ambient conditions. The efforts to increase the reactivity of NaBH_4 towards esters using Lewis acids lead to the discovery of hydroboration of olefins¹ and methods for generation of diborane which is now commercially available in various forms (e.g. $\text{BH}_3\text{:THF}$, $\text{BH}_3\text{:SMe}_2$ and $\text{BH}_3\text{:NR}_3$). However, efforts are still continuing for developing convenient methods for the reduction of functional groups using NaBH_4 along with other additives. For example, it has been recently reported that carboxylic acid esters and amides are reduced to the corresponding alcohols and amines using $\text{NaBH}_4/\text{ZnCl}_2$ in THF in the presence of a tertiary amine under reflux conditions.² It has been also reported that a mixture of R_2SeBr_2 ($\text{R} = \text{CH}_2\text{CH}_2\text{Br}$ or C_2H_5) and NaBH_4 reduces amides and nitriles to the corresponding amines.³ It has been shown that the $\text{R}_2\text{SeBr}_2/\text{NaBH}_4$ system in THF gives borane. We describe here convenient procedures for the reduction of amides and nitriles to amines, carboxylic esters and acids into alcohols and also hydroboration of alkenes using the NaBH_4/I_2 system.

Although, it has been known for a long time that pure diborane can be obtained by the reaction of I_2 with NaBH_4 in diglyme,⁴ this readily accessible reagent system did not receive much attention in synthetic applications. We have reported that the I_2/NaBH_4 system is useful for the generation of diborane for utilization in the preparation of amine boranes.⁵ Addition of I_2 to $\text{RCOOH}/\text{NaBH}_4$ mixture leads to selective reduction of carboxylic acid group to alcohol.⁶ We wish to report here that the addition of I_2 (10 mmol) into a mixture of an amide (or) imide (10 mmol) and NaBH_4 (23 mmol) in THF for 2.5h at 0°C followed by refluxing for 3h gives the corresponding amine in 70-76% yield (entries 1-4 in Table I). The yields are comparable to those reported using $\text{BH}_3\text{:SMe}_2$,⁷ $\text{NaBH}_4/\text{ZnCl}_2/\text{N,N}$ -diethylaniline² in THF and $\text{NaBH}_4/\text{R}_2\text{SeBr}_2$.³ It has been reported that hydroboration of olefins with I_2/NaBH_4 in THF followed by oxidation with NaBO_3 give alcohols.⁸

We have observed that addition of I_2 (2.8 mmol) to NaBH_4 (7 mmol) in THF (25 ml) at 0°C followed by olefin (15 mmol); stirring for 2h at room temperature and oxidation with $\text{H}_2\text{O}_2/\text{NaOH}$ or $\text{H}_2\text{O}_2/\text{NaOAc}$ gives the corresponding alcohols in 78-92% yields (entries 1-5 in Table 2). The regio and stereoselectivities observed here are similar to those reported previously using $\text{BH}_3\text{:THF}$,⁹ $\text{BH}_3\text{:SMe}_2$ ⁹ and $\text{BH}_3\text{:N,N}$ -diethylaniline⁵ complexes for the hydroboration of alkenes.

Table 1: Reduction of amides and nitriles using $I_2/NaBH_4$.^a

S.No.	Substrate	Conditions Temp. (Time)	Product ^d	Yield (%)
1.		70°C (6h) ^b		76
2.	PhNCH ₃ COCH ₃	70°C(3h) ^c	PhNCH ₃ C ₂ H ₅	74
3.	PhNHCOCH ₃	70°C (3h) ^c	PhNHC ₂ H ₅	75
4.	PhCONH ₂	70°C (3h) ^c	PhCH ₂ NH ₂	70
5.		70°C (3h) ^c		74
6.	PhCH ₂ CN	70°C (3h) ^c	PhCH ₂ CH ₂ NH ₂	72
7.	PhCN	70°C (3h) ^c	PhCH ₂ NH ₂	70
8.	CH ₃ (CH ₂) ₇ CN	70°C (3h) ^c	CH ₃ (CH ₂) ₇ CH ₂ NH ₂	75

a) The experiments were carried out by taking the substrates and $NaBH_4$ in THF (25 ml) and adding I_2 in THF (20 ml) in portions for 2.5h at 0°C. (b) $NaBH_4$ (27 mmol), I_2 (12 mmol) and imide (5 mmol) were used. (c) $NaBH_4$ (23 mmol), I_2 (10 mmol) and amide/nitrile (10 mmol) were used. (d) The products were identified by spectral data (IR, 1H NMR and ^{13}C NMR).

Selective hydroboration of olefinic group can be achieved when it is present along with an ester group as illustrated by the hydroboration-oxidation of methyl-10-undecenoate (entry 5, Table 2).

However, carboxylic esters can be reduced to the corresponding alcohols in 86-89% by the addition of I_2 (5 mmol) and $NaBH_4$ (12 mmol) in THF (30 ml) at 0°C for 2.5h and refluxing the mixture for 0.5h after the addition of carboxylic esters (entries 1 and 3, Table 3).

We have also observed that addition of I_2 (5 mmol) to $NaBH_4$ (12 mmol) in THF (30 ml) at 0°C for 2.5h followed by the addition of Ph_3P (10 mmol) in THF (20 ml) gives $Ph_3P:BH_3$ in 94% yield, indicating the formation of $BH_3:THF$ in the reaction of $NaBH_4$ with I_2 .

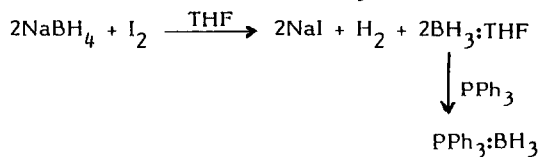

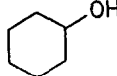

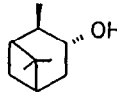
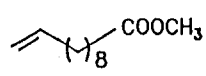
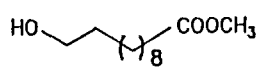


Table 2: Hydroboration of alkenes using I_2/NaBH_4 in THF.^a

S.No.	Substrate	Conditions Temp. (Time)	Product ^e	Yield (%)
1.	$\text{PhCH}=\text{CH}_2$	25°C (2h) ^b	$\text{PhCH}_2\text{CH}_2\text{OH}^f$	90
2.	$\text{C}_8\text{H}_{17}\text{CH}=\text{CH}_2$	25°C (2h) ^b	$\text{C}_8\text{H}_{17}\text{CH}_2\text{CH}_2\text{OH}$	92
3.		25°C (4h) ^c		85
4.		25°C (4h) ^c		81
5.		25°C (2h) ^d		78

(a) The experiments were carried out by taking NaBH_4 (7 mmol), I_2 (2.8 mmol), followed by the addition of alkenes. Products were purified by column chromatography. (b) Alkenes (15 mmols) were utilized and the organoboranes were oxidised using $\text{H}_2\text{O}_2/\text{OH}^-$. (c) Alkenes (10 mmol) were used and the organoboranes were oxidised using $\text{H}_2\text{O}_2/\text{OH}^-$. (d) Olefinic ester (15 mmol) was utilized and the organoborane species was oxidized using $\text{H}_2\text{O}_2/\text{NaOAc}$. (e) The products were identified by spectral data (IR, ^1H NMR and ^{13}C NMR) and also by comparison with data reported in the literature. (f) Contains the isomeric 1-phenylethanol upto 20% (^1H NMR analysis).

In all cases, we have used NaBH_4 more than required by the stoichiometry, since it is known that the ' BH_3 ' complexes also react with iodine to give >B-I species which are known to cleave ethers.¹⁰ Also, the I_2 in THF was added slowly in portions to NaBH_4 in THF at 0°C in order to avoid possible cleavage of THF. However, the addition time can be reduced to 0.5h at 0°C without significant change in results.

We have recently reported that successive addition of RCOOH and I_2 into NaBH_4 in THF leads to reduction of carboxylic acids.⁶ This method gives good results in 10 mmol scale. When the reduction of carboxylic acid was attempted in >50 mmol scale substantial amounts of products (I and/or II) derived from THF cleavage were also obtained.

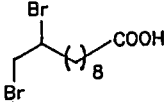
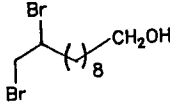
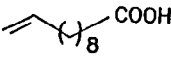
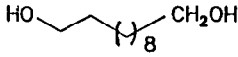
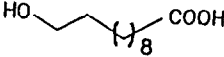


However, this problem can be circumvented by the addition of I_2 into NaBH_4 at 0°C followed by the addition of carboxylic acid. The corresponding alcohols are obtained in good

yields after work up (entries 3 and 4, Table 3). However, the chemoselectivity observed in the reduction of olefinic acids is lost by performing the reaction in this way. For example, the reduction of 10-undecenoic acid gives 10-undecanol in 89% yield by the addition of the acid into NaBH_4 in THF at room temperature followed by addition of I_2 at 0°C .⁶ However, addition of I_2 into NaBH_4 at 0°C followed by addition of carboxylic acid leads to the hydroboration of the double bond and a mixture of 1,11-undecanediol (59%) and 11-hydroxyundecanoic acid (20%) (entry 5 in Table 3) are obtained after oxidation with $\text{H}_2\text{O}_2/\text{OH}^-$ and protonolysis.

In conclusion, the readily accessible I_2/NaBH_4 reagent system is useful in the reduction of amides, nitriles, carboxylic esters and acids and also for hydroboration of alkenes.

Table 3: Reduction of carboxylic esters and acids using I_2/NaBH_4 in THF.^a

S.No.	Substrate	Conditions Temp. (Time)	Product(s) ^d	Yield (%)
1.	$\text{PhCH}_2\text{COOEt}$	70°C (0.5h) ^b	$\text{PhCH}_2\text{CH}_2\text{OH}$	85
2.	$\text{CH}_3(\text{CH}_2)_8\text{COOCH}_3$	70°C (0.5h) ^b	$\text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{OH}$	89
3.	$\text{CH}_3(\text{CH}_2)_8\text{COOH}$	25°C (1h) ^c	$\text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{OH}$	90
4.		25°C (1h) ^c		86
5.		25°C (1h) ^c	 	59 20

(a) Experiments were carried out by adding I_2 (5 mmol) in THF (30 ml) in portions to NaBH_4 (12 mmol) at 0°C for 2.5h. (b) After the addition of the ester, the reaction mixture was refluxed for 0.5h. (c) The acids were added at 25°C to the I_2/NaBH_4 reagent. (d) The products were isolated by chromatography on silica gel column (hexane/ethylacetate eluent) and identified by spectral data (IR, ^1H NMR, ^{13}C NMR).

EXPERIMENTAL SECTION

General: Tetrahydrofuran distilled freshly over benzophenone-sodium was used for all the experiments. Infrared spectra were recorded on a Perkin-Elmer IR spectrometer 1310 with polystyrene as reference. NMR spectra were recorded on a JEOL-FX-100 spectrometer in deuterated chloroform using tetramethyl silane as internal standard. The chemical shifts (δ) are expressed in ppm downfield from the signal for internal Me_4Si . For TLC plates coated

with silica gel were run in hexane/ethyl acetate mixture and spots were developed in iodine chamber. For column chromatographic purification under gravity, column grade silica gel (100-200 mesh size) was employed.

Reduction of imide: Imide (1.7 g, 5 mmol) in dry THF (15 ml) was added to a slurry of NaBH_4 (1 g, 27 mmol) in dry THF (15 ml) in a two-neck septem capped round-bottom flask. I_2 (3 g, 12 mmol) in dry THF (20 ml) was added under nitrogen atmosphere at 0°C for 2.5h. The mixture was refluxed for 6h; cooled to 0°C and the excess hydride was carefully destroyed with 3N HCl (5 ml). After the gas evolution ceased, it was neutralized using 3N NaOH (8 ml). The organic layer was separated and aqueous layer was extracted with ether (3 x 10 ml). The combined organic extracts were washed with water, brine and dried over anhydrous MgSO_4 . The solvent was evaporated and the amine borane residue was treated with $\text{F}_3\text{B}\cdot\text{OEt}_2$ followed by aq.NaOH to liberate the free amine. The product (entry 1, Table 1) was purified by chromatography on silica gel column (hexane:ethyl acetate/85:15). Yield: 1.2g (76%). IR(cm^{-1}): 3050, 3025, 2900, 2850, 1600, 1450, 730, 690. ^1H NMR(CDCl_3) δ : 3.08-3.6 (m, 6H), 3.96(s, 2H), 7.16-7.68(m, 15H). ^{13}C NMR(25 MHz) : 144.9, 139.8, 129.8, 129.0, 128.0, 127.6, 126.1, 63.1, 60.8, 53.8.

Reduction of N-methylacetanilide: The amide (1.49 g, 10 mmol) and NaBH_4 (0.88 g, 23 mmol) were taken in dry THF (25 ml) in a two-neck septem capped round-bottom flask. Iodine (2.54 g, 10 mmol) in dry THF (20 ml) was added in portions under nitrogen atmosphere at 0°C for 2.5h. The reaction mixture was refluxed (70°C) for 3h; cooled to 0°C , the excess hydride destroyed by careful addition of 3N HCl (6 ml). After the gas evolution ceased, it was neutralized using 3N NaOH (8 ml). The organic layer was separated and the aqueous layer was extracted with ether (2 x 15 ml). The combined organic extract was washed with water, brine and dried over anhydrous MgSO_4 . The solvent was removed and the product was purified by column chromatography on silica gel (hexane:ethylacetate/95:5). Yield: 1g (74%). IR(cm^{-1}): 3020, 2950, 2800, 1600, 1450, 740, 690. ^1H NMR(CDCl_3) δ : 1.12 (t, 3H), 2.84(s, 3H), 3.38(q, 2H), 6.54-6.7(m, 2H), 7.08-7.24(m, 2H). ^{13}C NMR(25 MHz) : 149.1, 129.1, 116.0, 112.4, 46.6, 37.2, 11.0.

Reduction of 3,5-dimethylbenzylcyanide: In a two-neck septem capped round-bottom flask, NaBH_4 (0.88 g, 23 mmol) and 3,5-dimethylbenzylcyanide (1.45g, 10 mmol) were taken in dry THF (30 ml). I_2 (2.54 g, 10 mmol) in dry THF (20 ml) was added under nitrogen atmosphere at 0°C for 2.5h. The reaction mixture was refluxed (70°C) for 3h. It was cooled to 0°C , 6N HCl (8 ml) was added slowly and the contents were refluxed for 0.5h. The mixture was cooled to 0°C and 3 g of NaOH was added. The organic layer was separated and the aqueous layer was extracted with ether (3 x 10 ml). The combined organic extract was washed with water, brine and dried over anhydrous MgSO_4 . It was concentrated and chromatographed on silica gel column (hexane:ethylacetate/60:40). Yield: 1.1 g (74%). IR(cm^{-1}): 3400, 2950, 2800, 1600, 750, 660. ^1H NMR(CDCl_3) δ : 1.9 (s, 6H), 2.6(m, 4H), 5.3(bs, 2NH), 6.5(s, 3H). ^{13}C NMR(25 MHz) : 138.4, 136.7, 128.5, 126.5, 41.5, 34.2, 20.9.

Hydroboration of styrene: In a two-neck spetem capped round-bottom flask NaBH_4 (0.27 g, 7 mmol) was taken in dry THF (25 ml). Iodine (0.71 g, 2.8 mmol) in dry THF (15 ml) was added under nitrogen atmosphere over 2.5h at 0°C . Styrene (1.5 g, 15 mmol) was added and the reaction mixture was stirred for 2h at 25°C . It was quenched with water (2 ml), THF (20 ml) was added and oxidized using H_2O_2 (30%, 30 ml)/NaOH (3N, 30 ml). The organic layer was separated and the aqueous layer was extracted with ether (3 x 10 ml). The combined organic extract was washed with water, brine and dried over anhydrous MgSO_4 . On evaporation of solvent and purification by chromatography on silica gel column (hexane:ethylacetate/90:10), 1.68 g (90%) of alcohols were isolated. IR(cm^{-1}): 3300, 1600, 1050. ^1H NMR(CDCl_3) δ : 1.44(d, 3H), 2.44(bs, 1H), 2.78(t, 2H), 3.7(t, 2H), 4.72(q, 1H), 7.0-7.32(m, 5H). The signals at 1.44 and 4.72 ppm corresponding to the presence 1-phenylethanol to the extent of 20% are also observed.

Reduction of 10,11-dibromoundecanoic acid (50 mmol scale) using NaBH_4/I_2 : NaBH_4 (2.1 g, 60 mmol) in dry THF (120 ml) was taken in two-necked round-bottom flask. To the slurry I_2 (6.4 g, 25 mmol) in THF (60 ml) was added slowly during 2.5h through a pressure equalizer at 0°C . To this 10,11-dibromoundecanoic acid (17.2 g, 50 mmol) in THF (30 ml) was added through a cannula. The contents were further stirred for 1h at 25°C . Dil.HCl (20 ml, 3N) was carefully added. The aqueous layer was extracted with ether (3 x 20 ml). The combined organic layer was washed with 3N NaOH solution, brine and dried over MgSO_4 . Evaporation of solvent afforded 10,11-dibromoundecanol. Yield: 15 g (90%). IR(cm^{-1}): 3325, 2900, 2850, 1450, 1050. ^{13}C NMR(25 MHz) : 62.1, 52.8, 36.1, 35.7, 32.2, 29.1, 28.5, 26.4, 25.4.

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