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Phase-transfer catalysis for the synthesis of hydroxylamines from oximes using benzyltriethylammonium borohydride in methanol and under solid-phase conditions

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Effective phase-transfer catalysis methodologies for the reduction of oximes to hydroxylamines by a selective and versatile reducing agent, benzyltriethylammonium borohydride (BTEABH), in methanol and under solid-phase conditions are presented.

The modification of sodium borohydride[1–5] has attracted a great deal of attention in synthetic organic chemistry since it has led to selective reduction of functional groups, which are otherwise inert to sodium borohydride alone. For instance, the reductions of acid chlorides to aldehydes[6] or alkenes to saturated hydrocarbons[7] can be achieved using a combination of sodium borohydride with Cu^{I} or Co^{II}, respectively.

The Borsch method utilising sodium cyanoborohydride[8] and zinc borohydride[9] is currently the most popular way of converting oximes into hydroxylamines. Other methods include the use of sodium borohydride and trifluoroacetic acid[10] or aqueous sulfuric acid,[11] zinc borohydride,[12] zinc modified cyanoborohydride[13] and 1-benzyl-1-azonia-4-azabicyclo[2.2.2]octane tetraborate.[14] Butyltriphenylphosphonium tetraborate[15] was used as a selective reducing agent for the reduction of oximes, enamines and imines under solid-phase conditions. However, phosphonium salts are expensive, and by-products are harmful to the environment.

Hydroxylamines are known as anti-bacterial, antifungal and antileukemic agents; *N*-hydroxyurea is an effective antineoplasmic agent,[16] and cyclopiroxolamine has a broad-spectrum antifungal activity.[17]

We found benzyltriethylammonium borohydride† (BTEABH) as an efficient phase-transfer catalyst for the synthesis of these biologically significant compounds. In continuation of the development of environmentally benign methods using solid supports,[18–20] we have developed an environmentally safe and clean synthesis of hydroxylamines using methanol as a solvent or grinding in a mortar (Scheme 1).

† *Synthesis of* BTEABH. Sodium borohydride (3.78 g, 100 mmol) was added to a solution of benzyltriethylammonium chloride (39.94 g, 100 mmol) in methanol (100 ml). The reaction mixture was stirred at room temperature for 90 min; the resulting white solid product was collected, washed with water (200 ml) and dried in a vacuum desiccator over calcium chloride to yield a white solid product (41.2 g, 98%), mp 140–143 °C. ^{1}H NMR ($CDCl_3$) δ: 7.58–7.57 (m, H_{Ar}), 4.45 (s, 2H), 3.28 (q, 2H), 1.43 (t, 3H), H_{BH_4} did not appeared in the spectrum. ^{13}C NMR ($CDCl_3$) δ: 9.74 (Me), 54.95 (CH_2), 62.63 (benzylic C), 135.0–131.9 (C_{Ar}), 149 (ipso-C). IR: (KBr, ν/cm^{-1}): 3471, 3403, 2979, 2832, 1598, 1258.

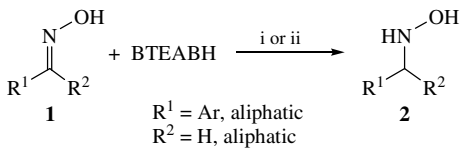
Table 1 Selective reduction of 4-methoxybenzaldoxime with BTEABH (1 mmol scale) at room temperature.

Entry	Solvent	*t*/min	Yield[a] (%)
1	None	16	86
2	Methanol	38	75
3[b]	None	16	84
4[b]	Methanol	38	73

[a]Isolated yield of the reduced product. [b]The reaction was carried out in 100 mmol scale using BTEABH (33 g).

A model reaction was performed by reducing 4-methoxybenzaldoxime with BTEABH. The use of 330 mg (1 mmol) of BTEABH was found sufficient for the highly effective and selective reduction of 4-methoxybenzaldoxime to a corresponding hydroxylamine in 86% yield in a 1 mmol scale experiment at room temperature for 16 min under solid-phase conditions (Table 1, entry 1), by simple grinding with a pestle and a mortar (P/M). The reduction of the oxime with the reducing agent in methanol proceeded smoothly in 75% yield at room temperature for 38 min in solution (entry 2) with stirring with a magnetic stirrer. Moreover, a quantitative conversion (84% yield) was accomplished in a 100 mmol scale experiment using 33 g of BTEABH and 15.1 g of an oxime after P/M grinding at room temperature for 10 min (entry 3). The reduction in methanol proceeded with quantitative conversion (73% yield) in a 100 mmol scale experiment during 38 min at room temperature (entry 4).

As can be seen in Table 2, oximes are cleanly reduced to the corresponding hydroxylamines‡ in good to excellent yields in



Scheme 1 Selective reduction of oximes to hydroxylamines using BTEABH. *Reagents and conditions*: i, pestle and mortar, solid-phase; ii, magnetic stirrer, methanol.

Table 2 Selective reduction of oximes to hydroxylamines with BTEABH in methanol and under solid-phase conditions.

Entry	Product **2**[a]		In methanol		Under solid-phase conditions	
	R^1	R^2	*t*/min	Yield (%)[b]	*t*/min	Yield (%)[b]
1	Ph	H	30	82	8	95
2	3-$NO_2C_6H_4$	H	29	79	10	88
3	4-$NO_2C_6H_4$	H	27	80	11	89
4	3-FC_6H_4	H	31	78	13	85
5	4-FC_6H_4	H	30	79	12	86
6	2-ClC_6H_4	H	33	80	14	85
7	3-ClC_6H_4	H	30	78	13	88
8	4-ClC_6H_4	H	29	71	11	90
9	2-BrC_6H_4	H	35	78	13	86
10	4-BrC_6H_4	H	32	73	12	88
11	4-MeC_6H_4	H	35	72	16	84
12	4-HOC_6H_4	H	33	70	15	80
13	4-$MeOC_6H_4$	H	38	75	16	86
14	2-MeO-4-HOC_6H_3	H	40	70	18	79
15	3,4-$(MeO)_2C_6H_3$	H	42	69	20	76
16	3,4,5-$(MeO)_3C_6H_2$	H	45	65	22	76
17	furan-2-yl	H	32	80	9	93
18	thiophen-2-yl	H	35	79	12	90
19	$R^1 + R^2 = (CH_2)_4$		25	72	11	82
20	$R^1 + R^2 = (CH_2)_5$		23	74	11	84
21	Ph	Me	35	80	13	89
22	4-FC_6H_4	Me	32	81	12	87
23	4-ClC_6H_4	Me	33	82	11	90
24	4-BrC_6H_4	Me	30	80	14	89
25	3-$NO_2C_6H_4$	Me	35	78	12	87
26	4-$NO_2C_6H_4$	Me	33	80	10	89
27	4-MeC_6H_4	Me	40	78	15	85
28	4-HOC_6H_4	Me	38	76	17	86
29	4-$MeOC_6H_4$	Me	42	73	18	84
30	2-MeO-4-HOC_6H_3	Me	45	70	20	81

[a]All the products are characterised on the basis of IR, ^{1}H NMR and MS spectral data as well as by comparing with authentic samples prepared according to literature. [b]Isolated yields of products.

the presence of BTEABH both under solid-phase conditions and in the presence of methanol. The former method makes use of local heat produced by the P/M grinding of oximes in the presence of BTEABH for driving the chemical reactions. The latter method employs simple stirring of BTEABH and oximes in methanol. Note that various structurally diverse benzaldoximes and ketoximes are selectively reduced to the corresponding hydroxylamines probably due to the efficiency of the reducing agent.

‡ *Typical experimental procedure for the synthesis of* N-*benzylhydroxylamine* (**2**, R^1 = Ph, R^2 = H).

(A) *With a pestle and a mortar (P/M) under solid-phase conditions.* A mixture of benzaldoxime (1 mmol) and BTEABH (1 mmol) was P/M ground for 8 min. On completion of the reaction, as monitored by TLC, the reaction mixture was taken up in ethyl acetate (2×15 ml) and dried over anhydrous Na_2SO_4 followed by evaporation of the solvent *in vacuo* to furnish the corresponding reduction product. It was purified by column chromatography on silica gel using a mixture of ethyl acetate and light petroleum (20:80) as an eluent, yield 95%.

(B) *Stirring with a magnetic stirrer in solution.* Benzaldoxime (1 mmol) was added to a stirred solution of BTEABH (1 mmol) in methanol (15 ml). The mixture was stirred at room temperature with a magnetic stirrer for 30 min and then the mixture was worked up and purified as described above. IR spectra were recorded with a Nicolet Avatar-360 FT-IR spectrophotometer in KBr pellets. ^{1}H NMR spectra were recorded on a Bruker AMX-400 spectrometer (400 MHz) in $CDCl_3$ using TMS as an internal standard. ^{13}C NMR spectra were recorded on a Bruker AMX-400 spectrometer (100 MHz) in $CDCl_3$. Mass spectra were recorded on a Finnigan MAT 8230 mass spectrometer.

In conclusion, we have demonstrated the utility of BTEABH as a selective and versatile phase-transfer catalyst for the reduction of oximes to the corresponding hydroxylamines both under solid-phase conditions and in methanol without the environmental disadvantages of toxic butyltriphenylphosphonium tetraborate.[15] In the reduction of oximes with this reducing agent, no trace of over reduction to the amine was observed.

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