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N-(Diethoxyphosphoryl)-*O*-benzylhydroxylamine—a convenient substrate for the synthesis of *N*-substituted *O*-benzylhydroxylamines

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Abstract—Easily available *N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine was shown to be convenient, orthogonally protected substrate for regioselective *N*-alkylation by means of diverse halides under basic conditions (sodium hydride/tetrabutylammonium bromide). An efficient procedure for dephosphorylation of *N*-substituted *N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine to provide *N*-substituted *O*-benzylhydroxylamines was also established.

Compounds with N–O linkage in their substructure are important class of chemical species due to their biological activity. Such derivatives are found, to name but a few, among iron sequestering siderophores,[1] inhibitors of 5-lipoxygenase,[2–4] inhibitors of DXP reductoisomerase,[5–7] and inhibitors of metalloproteinase.[8]

Among a plethora of different routes[9] leading to *N*-substituted hydroxylamines, a prominent position takes strategy in which *N*-alkylation of *N*,*O*-bis protected hydroxylamines provides a desired product as *N*-substituted *N*,*O*-bis protected hydroxylamines.[10] Generally, the presence of protecting groups on hydroxylamine template enhances the N–H acidity of the *N*,*O*-bis protected hydroxylamine, allows its chemoselective *N*-alkylation and, for orthogonal protection, gives also the chance for further chemoselective deprotection, after alkylation. *N*-Alkylation of such *N*,*O*-bis protected hydroxylamines can be accomplished by a range of alkylating agents under standard basic conditions[10] or alternatively Mitsunobu protocol can be applied.[10,11] There is a range of *N*,*O*-bis protected hydroxylamines commonly used for those purposes.[10,11]

On the other hand, an easy acidic cleavage of P–N bond in dialkyl phosphoramidates which depends on the steric and electronic factors around phosphorus atom is well known.[12,13] Therefore dialkyl phosphoryl groups may be regarded as convenient protecting groups for amines.[14] These features make *N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine **1** an attractive substrate for the preparation of *N*-substituted hydroxylamines.

To the best of our knowledge *N*-phosphorylated hydroxylamines have not yet been applied for this purpose.[15,16]

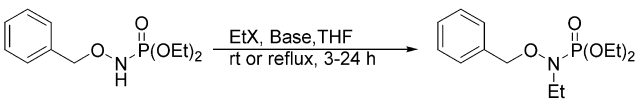
In this paper we disclose our results on the use of the easily available, orthogonally protected *N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine[17] **1** in the synthesis of *N*-substituted *O*-benzylhydroxylamines.

1. Results and discussion

The starting *N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine **1** was prepared according to the literature procedure[17] from *N*-benzylhydroxylamine hydrochloride and diethyl phosphonate using Atherton–Todd method.[18]

In order to optimize reaction conditions for *N*-alkylation we conducted our preliminary studies using different bases for metallation of **1** and bromoethane or ethanol as a model-alkylating agent, according to Scheme 1. The results are presented in Table 1

No progress of the reaction was observed when the solid–liquid two-phase system[19] was applied, in which a mixture



1 **2a**

Scheme 1.

Keywords: hydroxylamines; *N*-alkylation; *N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine.
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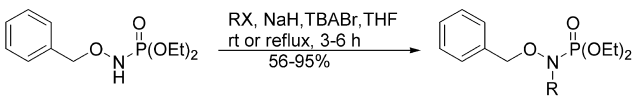
Table 1. *N*-Ethyl-*N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine **2a**

Entry	R	Alkylating agent RX	Reaction conditions	Isolated yield (%)
1	Et	EtBr (1.5 equiv.)	K_2CO_3 (2 equiv.)/$KHCO_3$ (2 equiv.)/TBABr (5 mol%), 5 h, rt	–
2		EtOH (1.2 equiv.)	Ph_3P (1.5 equiv.)/DEAD (1.5 equiv.)/THF, 24 h, rt	–
3		EtBr (1.5 equiv.)	NaH/THF/TBABr (5 mol%), 3 h, rt	92
4		EtBr (1.5 equiv.)	NaH/THF/TBABr (5 mol%), 3 h, reflux	73
5		EtBr (1.5 equiv.)	NaH/THF, 4 h, reflux	75

of potassium carbonate and potassium hydrogen carbonate acts as the base, and tetrabutylammonium bromide is used as phase-transfer catalyst (Table 1, entry 1). The same outcome was achieved when the reaction was carried out under standard Mitsunobu[20] conditions (triphenylphosphine/dietyl azodicarboxylate) using ethanol as alkylating agent (Table 1, entry 2). Those results suggest that compound **1** is too weak NH-acid for such reaction conditions.

Positive results were obtained only when stronger base such as sodium hydride in tetrahydrofuran was applied for metallation. The best chemical efficiency was obtained at room temperature when sodium hydride in the presence of catalytic amounts of tetrabutylammonium bromide (TBABr) was used (Table 1, entry 3). Conducting reaction at reflux with or without phase-transfer catalyst led to decreased yields (Table 1, entries 4 and 5, respectively).

All of the other alkylations were executed in compliance with this optimized protocol. Thus, according to Scheme 2, an excess of sodium hydride was added at 0°C to the solution of *N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine **1** in tetrahydrofuran, followed by the addition of tetrabutylammonium bromide (5 mol%) and organic halide at room temperature.



2	R	2	R
b	Me	g	$(CH_2)_4Br$
c	*i*-Pr	h	Bn
d	*i*-Bu	i	Bu
e	Allyl	j	$(CH_2)_3N(OBn)P(O)(OEt)_2$
f	$(CH_2)_3Br$	k	$(CH_2)_3P(O)(OEt)_2$

Scheme 2.

Progress of the alkylation was monitored by ^{31}P NMR spectroscopy (the signal of **1** at δ=7.72 ppm disappeared, while new peak of the *N*-alkylated product **2** was observed within the range 7.71–9.24 ppm). All of the reactions were completed in three up to 6 h at room temperature, or at reflux, depending on the halide used. Diverse halides were applied for alkylations (for details, see Table 2).

For primary, allyl and benzyl halides reactions occurred at room temperature (Table 2, entries 1, 3, 8, 4 and 7, respectively). All of the products were isolated with good to excellent yields (56–95%) and with good analytical purity, except for the benzyl bromide for which 'bulb-to-bulb' distillation was necessary to obtain analytically pure product (Table 2, entry 7). Also alkylation of **1** by means of diethyl 3-bromopropylphosphonate[21] gave product **2k** with high 79% yield, after chromatography (Table 2, entry 10).

For isopropyl bromide, it was necessary to carry out the alkylation under reflux to obtain completion (Table 2, entry 2). Otherwise compound **2c** was obtained with low yield (10%).

Next, ω,ω′-dihalides were used as electrophilic reagents. We found that alkylation of **1** with 1,4-dibromobutane occurred completely regioselectively to give only mono-alkylated product **2g** with 68% yield after flash chromatography (Table 2, entry 6). Contrary to the above-mentioned reaction, substitution of 1,3-dibromopropane by metallated **1** led to the mixture of mono- and bis-alkylated products **2f** and **2j** in ratio 100:2, respectively. Major product **2f** was isolated from crude reaction mixture with

Table 2. *N*-Substituted-*N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamines **2b-k** prepared

Entry	Compound	R	Alkylating agent RX	Reaction conditions (time (h), temp. (°C))	Yield (%)[a]
1	**2b**	Me	MeI (2 equiv.)	5, rt	91
2	**2c**	*i*-Pr	*i*-PrBr (2 equiv.)	6, reflux	64[b]
3	**2d**	*i*-Bu	*i*-BuBr (2 equiv.)	6, rt	56
4	**2e**	Allyl	AllylBr (1.3 equiv.)	4, rt	88
5	**2f**	$(CH_2)_3Br$	$Br(CH_2)_3Br$ (20 equiv.)	4, rt	63[c,d]
6	**2g**	$(CH_2)_4Br$	$Br(CH_2)_4Br$ (20 equiv.)	5, rt	68[c]
7	**2h**	Bn	BnBr (1.05 equiv.)	6, rt	79[e]
8	**2i**	Bu	BuBr (1.5 equiv.)	6, rt	95
9	**2j**	$(CH_2)_3N(OBn)\ P(O)(OEt)_2$	**2f** (1 equiv.)	5, rt	73[c]
10	**2k**	$(CH_2)_3P(O)(OEt)_2$	$Br(CH_2)_3P(O)(OEt)_2$ (1.3 equiv.)	3, rt	79[c]

[a] Yields of pure **2**, based on **1**.
[b] **2c** was formed in 10% yield after 24 h at room temperature.
[c] After flash chromatography.
[d] Crude product consists of the mixture of mono **2f** and bis-alkylated product **2j** in ratio 100:2, respectively. Isomer ratios measured by ^{31}P NMR.
[e] After bulb-to-bulb distillation.

Table 3. *N*-Substituted-*O*-benzylhydroxylamine hydrochlorides **3a-i**, **k** prepared

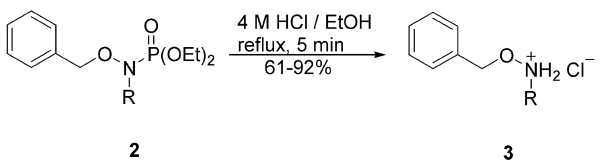
Entry	Compound	R	Reaction conditions (time (min), temp. (°C))	Yield (%)
1	**3a**	Et	5, reflux	77[a]
2	**3b**	Me	5, reflux	90
3	**3c**	*i*-Pr	5, reflux	71[b]
4	**3d**	*i*-Bu	5, reflux	61[c,d]
5	**3e**	Allyl	5, reflux	75
6	**3f**	$(CH_2)_3Br$	5, reflux	92
7	**3g**	$(CH_2)_4Br$	5, reflux	74
8	**3h**	Bn	5, reflux	66
9	**3i**	Bu	5, reflux	73[a]
10	**3k**	$(CH_2)_3P(O)(OEt)_2$	5, reflux	66[e]

[a] Isolated as hemioxalate.
[b] Compound **3c** was obtained in 40% yield when 30% HBr in AcOEt was used at room temperature for 24 h.
[c] Compound **3b** was obtained in 16% yield when 4 M HCl in AcOEt was applied at room temperature for 30 days.
[d] Compound **3d** was obtained in 61 and 56% yields when the mixture of 4 M HCl/EtOH and **2d** were heated at reflux for 15 and 90 min, respectively.
[e] Isolated as free amine.

63% yield, after flash chromatography (Table 2, entry 5). Attempts to improve the regioselectivity of alkylation by increasing the amount of 1,3-dibromopropane in relation to **1** have failed. The structure of the side, *bis*-substituted product **2j**, was confirmed on independent route, by alkylation of **1** by means of **2f** (Table 2, entry 9).

Having elaborated the efficient synthesis of *N*-substituted-*O*-benzylhydroxylamines **2**, we proceeded with their dephosphorylation, taking advantage of mentioned earlier acidic lability of the P–N bond in phosphoramidates.[12,13]

Our preliminary studies on chemoselective dephosphorylation were conducted by means of different acidic reagents. Application of 4 M HCl in ethyl acetate as well as 30% HBr in acetic acid led to divergent results, with long reaction times and poor yields (Table 3, footnotes b and c, respectively). Next, according to Scheme 3, 4 M HCl in ethanol was used for cleavage of the P–N bond in **2**. The



2 **3**

2,3	R	2,3	R
a	Me	**f**	$(CH_2)_3Br$
b	Et	**g**	$(CH_2)_4Br$
c	*i*-Pr	**h**	Bn
d	*i*-Bu	**i**	Bu
e	Allyl	**k**	$(CH_2)_3P(O)(OEt)_2$

Scheme 3.

dephosphorylation was conducted at reflux temperature. The progress of the reaction was controlled by ^{31}P NMR spectroscopy. The completion of dephosphorylation was observed as the decay of the signal of starting **2** (δ=7.71–9.24 ppm). It appeared that the shorter reaction time, the better the reaction yield (Table 3, footnote d). Eventually, treatment of *N*-alkylated *O*-benzylhydroxylamines **2** with 4 M hydrogen chloride in ethanol under reflux for 5 min gave the corresponding products of dephosphorylation **3** in good yields (61–92%). This optimized procedure allowed direct isolation of **3** as crystalline hydrochlorides or, in case when the latter were oils, as hemioxalates (**3b**, **3i**), or as a free amine (**3k**). The results were summarized in Table 3.

Finally, *N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine **1** was applied to the synthesis of 3-(*N*-hydroxyamino)propylphosphonic acid, the core precursor of fosmidomycin[5,22] [3-(*N*-formyl-*N*-hydroxyamino)propylphosphonic acid, FR-31564], which is an antibiotic, that specifically inhibits 1-deoxy-D-xylulose 5-phosphate reductoisomerase, which in turn, is indispensable for several bacteria, green algae and chloroplasts of higher plants in the non-mevalonate pathway for terpenoid biosynthesis.[5–7] Recently, derivatives of 3-(*N*-hydroxyamino)propylphosphonic acid were also found to act as potent antimalarial agents.[23]

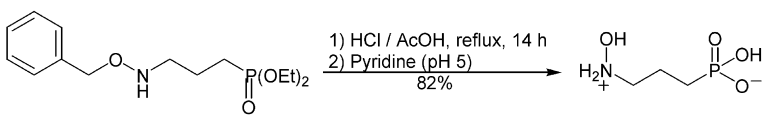
Thus, according to Scheme 4, heating compound **3k**, obtained in 52% overall yield from **1**, under reflux for 14 h with concentrated HCl and acetic acid (2:1, v/v) gave, after work up[5] 3-(*N*-hydroxyamino)propylphosphonic acid[5,24] **4** in 82% yield.

2. Conclusions

In summary, the protocol described here provides new and simple access to *N*-alkyl-*O*-benzylhydroxylamines. *N*-Alkylation of easily available, orthogonally protected *N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine **1** with primary and secondary halides as well as *bis*-halides occurred under mild conditions and led to *N*-alkylated derivatives of high purity with good to excellent yields. Next, *N*-substituted *N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamines were easily dephosphorylated under acidic conditions to afford appropriate *N*-substituted *O*-benzylhydroxylamines in good yields.

3. Experimental

NMR spectra were recorded on a Bruker Avance DPX 250 instrument at 250.13 MHz for ^{1}H and 101.3 MHz for ^{31}P NMR, respectively, in $CDCl_3$ or D_2O solution, using tetramethylsilane as internal and 85% H_3PO_4 as external standard. Positive chemical shifts are downfield from



3k **4**

Scheme 4.

external 85% H_3PO_4 for ^{31}P NMR spectra. Chemical shifts (δ) are indicated in ppm and coupling constants (J) in Hz. FAB/MS were recorded on a APO Electron (Ukraine) model MI 12001E mass spectrometer equipped with a FAB ion source (thioglycerol matrix). IR spectra were measured on a Specord M80 (Zeiss) instrument and are reported in wavenumbers (cm^{-1}). Flash chromatography was performed with glass column packed with Baker silica gel (30–60 μm). Eluents: AcOEt (A); AcOEt/hexane 30:1 (B). Melting points were determined in open capillaries and are uncorrected. All reagents were purchased from Fluka and used without further purification. Diethyl 3-bromopropylphosphonate was obtained according to the literature procedure via an Arbuzov reaction of 1,3-dibromopropane with triethyl phosphite.[21]

3.1. *N*-Substituted-*N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamines (2a-k)—general procedure

A solution of *N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine **1** (6 mmol, 1.55 g) in dry THF (2 mL) was added dropwise to a cooled to 0°C suspension of NaH (9 mmol, 0.22 g) in THF (15 mL). Then, the reaction mixture was allowed to warm to the room temperature and tetrabutylammonium bromide (TBABr) (5 mol%, 0.1 g) followed by alkylating agent (6.3–120 mmol) was added. The reaction was carried out at room temperature or at reflux for 3–6 h. Then the solvent was evaporated under reduced pressure, and the solid residue was partitioned between diethyl ether (150 mL) and water (5 mL). The organic layer was separated, washed with water (3×2 mL), and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the rest of the volatile material was removed at 30°C/0.1 Torr to give analytically pure *N*-substituted-*N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine **2** as a colorless or yellow oils. In some cases flash chromatography or bulb-to-bulb distillation was necessary to obtain pure product (for details, see Table 2).

3.1.1. *N*-Ethyl-*N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine (2a). Yield: 92%, colorless oil; ^1H NMR: δ=1.21 (dt, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.5 Hz, 3H, CH_3), 1.35 (dt, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.75 Hz, 6H, 2CH_3), 3.25 (dq, $^3J_{HH}$=7.0 Hz, $^3J_{HP}$=1.25 Hz, 2H, CH_2N,), 4.13–4.24 (m, 4H, 2CH_2), 4.84 (s, 2H, CH_2Ph,), 7.32–7.40 (m, 5H_{arom}); ^{31}P NMR: δ=7.71; IR (film): ν=2984, 1452, 1368, 1264, 1024; FAB/MS *m/z* (%): 288 (87). Anal. calcd for $C_{13}H_{22}NO_4P$ (287.28): C: 54.35; H: 7.72; N: 4.88. Found: C: 54.24; H: 7.61; N: 4.81.

3.1.2. *N*-Methyl-*N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine (2b). Yield: 91%, colorless oil; ^1H NMR: δ=1.35 (dt, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.75 Hz, 6H, 2CH_3), 2.85 (d, $^3J_{HP}$=12.75 Hz, 3H, CH_3), 4.04–4.29 (m, 4H, 2CH_2), 4.80 (s, 2H, CH_2Ph,), 7.30–7.42 (m, 5H_{arom}); ^{31}P NMR: δ=9.24; IR (film): ν=2984, 1456, 1368, 1268, 1024; FAB/MS *m/z* (%) 274 (42). Anal. calcd for $C_{12}H_{20}NO_4P$ (273.26): C: 52.74; H: 7.38; N: 5.13. Found: C: 52.57; H: 7.29; N: 5.07.

3.1.3. *N*-Isopropyl-*N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine (2c). Yield: 64%, colorless oil; ^1H NMR: δ=1.26 (d, $^3J_{HH}$=6.75 Hz, 6H, 2CH_3,), 1.35 (dt, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.5 Hz, 6H, 2CH_3), 3.72–3.85 (dheptet, $^3J_{HH}$=6.75 Hz, $^3J_{HP}$=4.5 Hz, 1H, C*H*), 4.11–4.28 (m, 4H, 2CH_2), 4.86 (s, 2H, CH_2Ph,), 7.30–7.40 (m, 5H_{arom}); ^{31}P NMR: δ=7.71; IR (film): ν=2976, 1456, 1368, 1264, 1024; FAB/MS *m/z* (%): 302 (78). Anal. calcd for $C_{14}H_{24}NO_4P$ (301.31): C: 55.80; H: 8.03; N: 4.65. Found: C: 55.69; H: 7.98; N: 4.60.

3.1.4. *N*-Isobutyl-(*N*-diethoxyphosphoryl)-*O*-benzylhydroxylamine (2d). Yield: 56%; colorless oil; ^1H NMR: δ=0.97 (d, $^3J_{HH}$=6.75 Hz, 6H, 2CH_3), 1.35 (dt, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.75 Hz, 6H, 2CH_3), 1.95–2.06 (m, 1H, C*H*), 2.97 (dd, $^3J_{HH}$=7.25 Hz, $^3J_{HP}$=5.0 Hz, 2H, CH_2N), 4.08–4.28 (m, 4H, 2CH_2), 4.89 (s, 2H, CH_2Ph,), 7.31–7.38 (m, 5H_{arom}); ^{31}P NMR: δ=9.13; IR (film): ν=2960, 1452, 1368, 1264, 1028; FAB/MS *m/z* (%): 316 (54). Anal. calcd for $C_{15}H_{26}NO_4P$ (315.34): C: 57.13; H: 8.31; N: 4.44. Found: C: 56.99; H: 8.20; N: 4.36.

3.1.5. *N*-Allyl-*N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine (2e). Yield: 88%; colorless oil; ^1H NMR: δ=1.36 (dt, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.75 Hz, 6H, 2CH_3), 3.80 (tt, $^3J_{HH}$=6.5 Hz, $^4J_{HP}$=$^4J_{HH}$=1.25 Hz, 2H, CH_2N), 4.82 (s, 2H, CH_2Ph), 5.17–5.31 (m, 2H, CH_2=), 5.88–6.04 (10 lines, $^3J_{HH}$=6.5 Hz, $^3J_{cis}$=10.25 Hz, $^3J_{trans}$=17.12 Hz, 1H, C*H*=), 7.32–7.37 (m, 5H_{arom}); ^{31}P NMR: δ=8.19; IR (film): ν=3416, 2984, 1648, 1368, 1264, 1028; FAB/MS *m/z* (%): 300 (47). Anal. calcd for $C_{14}H_{22}NO_4P$ (299.30): C: 56.18; H: 7.41; N: 4.68. Found: C: 56.01; H: 7.34; N: 4.61.

3.1.6. *N*-(3-Bromopropyl)-*N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine (2f). Yield: 63%; colorless oil; R_f=0.51 (B); ^1H NMR: δ=1.36 (dt, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.75 Hz, 6H, 2CH_3), 2.12 (qu, $^3J_{HH}$=6.5 Hz, 2H, CH_2), 3.31 (q, $^3J_{HH}$=$^3J_{HP}$=6.5 Hz, 2H, CH_2N), 3.41 (t, $^3J_{HH}$=6.5 Hz, 2H, CH_2Br), 4.12–4.26 (m, 4H, 2CH_2), 4.85 (s, 2H, CH_2Ph), 7.27–7.38 (m, 5H_{arom}); ^{31}P NMR: δ=8.26; IR (film): ν=2976, 1440, 1368, 1264, 1028; FAB/MS *m/z* (%): 380 (51), 382 (43.8). Anal. calcd for $C_{14}H_{23}BrNO_4P$ (380.21): C: 44.22; H: 6.10; N: 3.68. Found: C: 44.03; H: 5.99; N: 3.58.

3.1.7. *N*-(4-Bromobutyl)-*N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine (2g). Yield: 68%; colorless oil; R_f=0.5 (A); ^1H NMR: δ=1.36 (dt, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.75 Hz, 6H, 2CH_3), 1.70–1.96 (m, 4H, 2CH_2), 3.19 (q, $^3J_{HH}$=$^3J_{HP}$=7.0 Hz, 2H, CH_2N), 3.39 (t, $^3J_{HH}$=6.5 Hz, 2H, CH_2Br), 4.08–4.31 (m, 4H, 2CH_2), 4.86 (s, 2H, CH_2Ph), 7.33–7.39 (m, 5H_{arom}); ^{31}P NMR: δ=8.59; IR (film): ν=2928, 1444, 1368, 1164, 1264, 1028; FAB/MS *m/z* (%): 394 (55), 396 (49.9). Anal. calcd for $C_{15}H_{25}BrNO_4P$ (394.23): C: 45.70; H: 6.39; N: 3.55. Found: C: 45.55; H: 6.29; N: 3.47.

3.1.8. *N*-Benzyl-*N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine (2h). Yield: 79%; colorless oil; ^1H NMR: δ=1.35 (dt, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.75 Hz, 6H, 2CH_3), 4.01–4.29 (m, 4H, 2CH_2), 4.32 (d, $^3J_{HP}$=5.5 Hz, 2H, CH_2N), 4.49 (s, 2H, CH_2Ph), 7.12–7.43 (m, 10H_{arom}); ^{31}P NMR: δ=8.12; IR (film): ν=2984, 1496, 1488, 1368, 1260, 1164, 1028; FAB/MS *m/z* (%):350 (100). Anal. calcd for $C_{18}H_{24}NO_4P$ (349.35): C: 61.88; H: 6.92; N: 4.01. Found: C: 61.68; H: 6.79; N: 3.89.

3.1.9. *N*-Butyl-*N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine (2i). Yield: 95%; colorless oil; ^{1}H NMR: δ=0.92 (t, $^3J_{HH}$=7.5 Hz, 3H, CH_3), 1.35 (dt, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.75 Hz, 6H, 2CH_3), 1.31–1.40 (m, 2H, CH_2), 1.57–1.69 (m, 2H, CH_2), 3.17 (q, $^3J_{HH}$=$^3J_{HP}$=7.5 Hz, 2H, CH_2N,), 4.11–4.30 (m, 4H, 2CH_2), 4.85 (s, 2H, CH_2Ph), 7.32–7.38 (m, 5H_{arom}); ^{31}P NMR: δ=8.78; IR (film): ν=2960, 1456, 1368, 1260, 1164, 1028; FAB/MS *m*/*z* (%): 316 (55). Anal. calcd for $C_{15}H_{26}NO_4P$ (315.34): C: 57.13; H: 8.31; N: 4.44. Found: C: 57.01; H: 8.23; N: 4.38.

3.1.10. 1,3-Bis-(*O*-benzyloxy-*N*-diethoxyphosphorylamino)propane (2j). Yield: 73%; colorless oil; R_f=0.21 (B); ^{1}H NMR: δ=1.34 (dt, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.75 Hz, 12H, 4CH_3), 2.03 (bqu, $^3J_{HH}$=7.25 Hz, 2H, CH_2), 3.26 (bq, $^3J_{HH}$=$^3J_{HP}$=7.25 Hz, 4H, CH_2N), 4.09–4.27 (m, 8H, 4CH_2), 4.85 (s, 4H, 2CH_2Ph), 7.29–7.34 (m, 10H_{arom}); ^{31}P NMR: δ=8.51; IR (film): ν=2984, 2936, 1368, 1264, 1164, 1024; FAB/MS *m*/*z* (%): 559 (41). Anal. calcd for $C_{25}H_{40}N_2O_8P_2$ (558.53): C: 53.76; H: 7.22; N: 5.02. Found: 53.51; H: 7.09; N: 4.87.

3.1.11. Diethyl 3-[*N*-(diethoxyphosphoryl)-*N*-(benzyloxyamino)propylphosphonate (2k). Yield: 79%; colorless oil; R_f=0.4 (A); ^{1}H NMR: δ=1.32 (t, $^3J_{HH}$=7.0 Hz, 6H, 2CH_3), 1.36 (dt, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.75 Hz, 6H, 2CH_3) 1.72–2.04 (m, 4H, 2CH_2,), 3.24 (bq, $^3J_{HH}$=$^2J_{HP}$=7.0 Hz, 2H, CH_2P), 3.99–4.31 (m, 8H, 4CH_2), 4.85 (s, 2H, 2CH_2Ph), 7.28–7.38 (m, 5H_{arom}); ^{31}P NMR: δ=8.34, 32.30; IR (film): ν=2984, 2936, 1452, 1368, 1260, 1164, 1032; FAB/MS *m*/*z* (%): 438 (68). Anal. calcd for $C_{18}H_{33}NO_7P_2$ (437.40): C: 49.42; H: 7.61; N: 3.20. Found: C: 49.29; H: 7.50; N: 3.11.

3.2. *N*-Substituted-*O*-benzylhydroxylamines (3a-i, k)—general procedure

A solution of *N*-substituted *N*-(diethoxyphosphoryl)-*O*-benzylhydroxylamine **3** (1.5 mmol) in 4 M HCl in anhydrous EtOH (8 mL) was heated under reflux for 5 min. Then the solvent was evaporated under reduced pressure, and diethyl ether (35 mL) was added to the oil residue. The crystalline precipitates was washed with diethyl ether (2×10 mL) and dried in vacuum over P_2O_5 to afford analytically pure **3** as a colorless or cream crystals. In some cases products **3** were isolated as a hemioxalate, or free amine (for details, see Table 3).

3.2.1. *N*-Ethyl-*O*-benzylhydroxylamine hemioxalate (3a).[25] Yield: 77%; colorless flakes; mp 85–86°C, (lit.,[26] mp 92–94°C); ^{1}H NMR: δ=1.30 (t, $^3J_{HH}$=7.25 Hz, 2H, CH_3), 3.39 (q, $^3J_{HH}$=7.25 Hz, 2H, CH_2N), 5.13 (s, 2H, CH_2Ph,), 7.50 (s, 5H_{arom}); IR (KBr): ν=3408, 2664, 1720, 1636, 1456, 1280; FAB/MS *m*/*z* (%): 152 (17). Anal. calcd for $C_{11}H_{15}NO_5$ (241.23): C: 54.76; H: 6.27; N: 5.81. Found: C: 54.59; H: 6.16; N: 5.72.

3.2.2. *N*-Methyl-*O*-benzylhydroxylamine hydrochloride (3b).[26] Yield: 90%; cream needles; mp 90–93°C, (lit.,[25] mp 95°C) ^{1}H NMR: δ=3.02 (s, 3H, CH_3N,), 5.14 (s, 2H, CH_2Ph,), 7.51 (s, 5H_{arom}); IR (KBr): ν=3040, 2920, 2632, 2432, 1464; FAB/MS *m*/*z* (%): 138 (2). Anal. calcd for $C_8H_{12}ClNO$ (173.64): C: 55.33; H: 6.97; N: 8.07. Found: C: 55.18; H: 6.81; N: 7.96.

3.2.3. *N*-Isopropyl-*O*-benzylhydroxylamine hydrochloride (3c). Yield: 71%; colorless needles; mp 107–108°C; ^{1}H NMR: δ=1.34 (d, $^3J_{HH}$=6.75 Hz, 6H, 2CH_3), 3.74 (hp, $^3J_{HH}$=6.75 Hz, 1H, C*H*N), 5.14 (s, 2H, CH_2Ph), 7.51 (s, 5H_{arom}); IR (KBr): ν=2648, 2432, 1460, 1392; FAB/MS *m*/*z* (%): 166 (100). Anal. calcd for $C_{10}H_{16}ClNO$ (201.69): C: 59.55; H:8.00; N: 6.94. Found: C: 59.40; H: 7.87; N: 6.83.

3.2.4. *N*-Isobutyl-*O*-benzylhydroxylamine hydrochloride (3d). Yield: 61%; colorless prisms; mp 119–121°C; ^{1}H NMR: δ=1.00 (d, $^3J_{HH}$=6.75 Hz, 6H, 2CH_3), 2.22–2.08 (m, 1H, C*H*), 3.22 (d, $^3J_{HH}$=6.75 Hz, 2H, CH_2N), 5.14 (s, 2H, CH_2Ph), 7.50 (s, 5H_{arom}); IR (KBr): ν=2968, 2672, 2560, 1456, 1168; FAB/MS *m*/*z* (%): 180 (100). Anal. calcd for $C_{11}H_{18}ClNO$ (215.71): C: 61.24; H: 8.41; N: 6.49. Found: C: 61.00; H: 8.22; N: 6.32.

3.2.5. *N*-Allyl-*O*-benzylhydroxylamine hydrochloride (3e). Yield: 75%; colorless needles; mp 112.5–113.5°C; ^{1}H NMR: δ=3.98 (d, $^3J_{HH}$=6.75 Hz, 2H, CH_2), 5.15 (s, 2H, CH_2Ph), 5.53–5.62 (m, 2H, CH_2=), 5.88–5.99 (m, 1H, C*H*=), 7.51 (s, 5H_{arom}); IR (KBr): ν=2864, 2896, 2576, 2440, 1464, 1384; FAB/MS *m*/*z* (%): 164 (4). Anal. calcd for $C_{10}H_{14}ClNO$ (199.67): C: 60.15; H: 7.07; N: 7.02. Found: C: 59.93; H: 6.92; N: 7.03.

3.2.6. *N*-(3-Bromopropyl)-*O*-benzylhydroxylamine hydrochloride (3f). Yield: 92%; colorless solid; mp 104–105°C; ^{1}H NMR: δ=2.24–2.38 (m, 2H, CH_2), 3.52 (t, $^3J_{HH}$=7.25 Hz, 2H, CH_2N), 3.55 (t, $^3J_{HH}$=6.25 Hz, 2H, CH_2Br), 5.15 (s, 2H, CH_2Ph), 7.51 (s, 5H_{arom}); IR (KBr): ν=2960, 2872, 2664, 1448, 1240; FAB/MS *m*/*z* (%): 244 (100), 246 (95.6). Anal. calcd for $C_{10}H_{15}BrClNO$ (280.58): C: 42.80; H: 5.39; N: 4.99. Found: C: 42.60; H: 5.27; N: 4.96.

3.2.7. *N*-(4-Bromobutyl)-*O*-benzylhydroxylamine hydrochloride (3g). Yield: 74%; colorless needles; mp 82–84°C; ^{1}H NMR: δ=1.87–1.94 (m, 4H, 2CH_2), 3.37–3.43 (m, 2H, CH_2N), 3.49–3.54 (m, 2H, CH_2Br), 5.15 (s, 2H, CH_2Ph), 7.51 (s, 5H_{arom}); IR (KBr): ν=2952, 2600, 1484, 1296; FAB/MS *m*/*z* (%): 258 (100), 260 (99.4). Anal. calcd for $C_{11}H_{17}BrClNO$ (294.61): C: 44.84; H: 5.82; N: 4.75. Found: C: 44.62; H: 5.67; N: 4.76.

3.2.8. *N*-Benzyl-*O*-benzylhydroxylamine hydrochloride (3h).[27] Yield: 66%; colorless needles; mp 166–168°C, (lit.,[27] mp 174–176°C); ^{1}H NMR: δ=4.40 (s, 2H, CH_2Ph), 5.08 (s, 2H, CH_2N), 7.27–7.57 (m, 10H_{arom}); IR (KBr): ν=3008, 2944, 1488, 1448; FAB/MS *m*/*z* (%): 214 (8.06). Anal. calcd for $C_{14}H_{16}ClNO$ (249.73): C: 67.33; H: 6.46; N: 5.61. Found: C: 67.21; H: 6.40; N: 5.59.

3.2.9. *N*-Butyl-*O*-benzylhydroxylamine hemioxalate (3i). Yield: 73%; colorless solid; mp 122–124°C; ^{1}H NMR: δ=0.91 (t, $^3J_{HH}$=7.25 Hz, 3H, CH_3), 1.38 (bsextet, $^3J_{HH}$=7.25 Hz, 2H, CH_2), 1.63–1.76 (m, 2H, CH_2), 3.34 (t, $^3J_{HH}$=7.75 Hz, 2H, CH_2N), 5.13 (s, 2H, CH_2Ph), 7.50 (s, 5H_{arom}); IR (KBr): ν=2960, 2696, 1696, 1640, 1456, 1128; FAB/MS *m*/*z* (%): 180 (100). Anal. calcd for $C_{13}H_{19}NO_5$ (269.29): C: 57.98; H: 7.11; N: 5.20. Found: C: 57.72; H: 7.02; N: 5.21.

3.2.10. Diethyl 3-(*N*-benzyloxyamino)propylphosphonate (3k). Yield: 66%; colorless oil; ^{1}H NMR: δ=1.24 (t, $^3J_{HH}$=7.0 Hz, 6H, 2CH_3); 1.64–1.83 (m, 4H, 2CH_2), 2.88–2.93 (m, 2H, CH_2N), 3.94–4.08 (m, 4H, 2CH_2), 4.62 (s, 2H, CH_2Ph), 7.21–7.28 (m, 5H_{arom}); IR (KBr): ν=3448, 2984, 1456, 1368, 1240, 1028; FAB/MS *m/z* (%): 302 (100). Anal. calcd for $C_{14}H_{24}NO_4P$ (301.31): C: 55.80; H: 8.03; N: 4.65. Found: C: 55.59; H: 7.91; N: 4.60.

3.2.11. 3-(*N*-hydroxyamino)propylphosphonic acid (4).[5,22d,24] The mixture of amine **3k** (2.8 mmol, 0.85 g), 36% HCl aq. (15 mL) and acetic acid (7.5 mL) was heated under reflux for 14 h. Then the solution was evaporated under reduced pressure, and the residue was dissolved in ethanol (17 mL). Pyridine was added to the solution until pH 5 was reached. The precipitate was washed with ethanol, and crystallized from water-ethanol to give 0.43 g (82% yield) of 3-(*N*-hydroxyamino)propylphosphonic acid **4** as a colorless solid, mp 157–159°C (lit.[24] mp 158–160°C). ^{1}H NMR (D_2O): δ=1.63–1.76 (m., 2H, CH_2P), 1.89–2.06 (m., 2H, CH_2), 3.36 (t, $^3J_{HH}$=7.25 Hz, 2H, CH_2N); ^{31}P NMR: δ=24.34; IR (KBr): ν=2792, 2288, 1628, 1280, 1240, 1216, 1124.

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