One-Pot Synthesis of α-Substituted Hydroxylamine Derivatives from Aldehydes Using Lithium Perchlorate/Diethyl Ether as a Catalyst

Akbar Heydari,*[a] Morteza Mehrdad,[b] Hossein Tavakol[a]

[a] Chemistry Department, Tarbiat Modarres University, P. O. Box 14155-4838, Tehran, Iran
Fax +98(21)8006544; E-mail: akbar.heydari@gmx.de

[b] Department of Phytochemistry, Shahid Beheshti University, Evin 1983963113, Tehran, Iran

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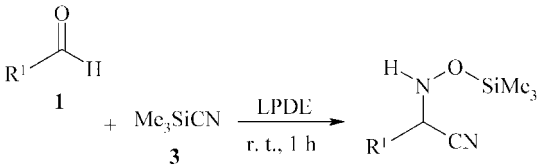
Abstract: *O*-(Trimethylsilyl)oxime ethers, generated in situ by reaction of aldehydes and *O*-(trimethylsilyl)hydroxylamine in lithium perchlorate/diethyl ether solution, are highly reactive species and undergo facile reaction with silylated nucleophiles, such as trimethylsilyl cyanide and the binary reagent $(MeO)_3P/Me_3SiCl$, to give α-substituted hydroxylamine derivatives.

Key words: lithium perchlorate, oximes, α-substituted hydroxylamines

The addition of nucleophiles to a carbon–nitrogen double bond has become an extremely useful process for the synthesis of a variety of amines, α-amino acids, α-aminophosphonates, and other compounds of interest.[1] Typically organometallic reagents can be utilized to achieve this carbon–carbon bond formation reaction.[2] Three factors which often diminish the versatility of these reactions are poor electrophilicity of imines, enolization of substrates that contain α-hydrogens, and the formation of reductive coupling products.[3] In many cases, these problems can be overcome by using more activated imine derivatives (iminium salts, acylimines, sulfonimines, nitrones, hydrazones and oximes) or less basic reagents. With oximes the same problems are encountered since oximes are often less electrophilic and less easily activated than the corresponding imine derivatives. The facile α-deprotonation of oximes, the existence of mixtures of *E*- and *Z* isomers of oximes, the lability of the nitrogen–oxygen bond, and the poor oxime reactivity are the factors that contribute to the complexity of the reaction.[4] In addition, oximes having a quaternary carbon adjacent to the carbonyl group are prone to undergo fragmentation as a major reaction pathway, furnishing nitriles.[5]

Recently, we have demonstrated the synthetic utility of lithium perchlorate/diethyl ether (LPDE) solution (1.0–5.0 M) in the preparation of several nitrogen-containing compounds.[6] We have now focused our attention on the use of LPDE medium for oxime activation. In this paper we wish to report a mild, simple and efficient conversion of aldehydes **1** to α-cyano(silyloxy)amines **4** in LPDE medium. In this reaction an oxime trimethylsilyl ether, formed in situ from a mixture of aldehyde and *O*-(trimethylsilyl)hydroxylamine, is submitted to a nucleophilic attack with trimethylsilyl cyanide (Scheme 1). In all cases, the desired products were obtained in high yields.



	R¹	Yield
a	*i*-Pr	96
b	*n*-Pr	100
c	*t*-Bu	98
d	Ph	95
e	2-Furyl	96
f	3-Pyridyl	98
g	*p*-$NO_2C_6H_4$	ca. 100
h	*p*-BrC_6H_4	ca. 100

Scheme 1

In order to evaluate the scope and limitations of this new one-pot three-component reaction, the modification of the structure of the nucleophiles was studied. As an analog of α-(hydroxyamino)alkyl(aryl)carboxylic acids, α-(hydroxyamino)alkyl(aryl)phosphonic acids and their derivatives are reported to show strong antibacterial activity.[7] To the best of our knowledge, only a few examples of the synthesis of α-(hydroxylamino)alkyl(aryl)phosphonic acids have been reported. These include the controlled reduction of α-nitroalkyl phosphonates with zinc and ammonium chloride,[8] addition of dialkyl phosphite to 1-oxoaldoxime at elevated temperature,[9] the nucleophilic addition of lithium and potassium dialkyl phosphite anions to *N*-glycosyl nitrone followed by glycoside cleavage and hydrolysis,[10] the condensation of α-(benzyloxyamino)alkylphosphonic acid with *O*-alkylisourea followed by subsequent treatment with boron tris(trifluoroacetate)[11] and the controlled reduction of α-(hydroxylimino)alkyl(aryl)phosphosphonates with borane-pyridine complex.[12] Unfortunately, these methods are limited by a narrow scope, by competition with other reactions, and difficulties in the preparation of the starting materials. In this paper, we wish to report a facile synthesis of α-(hy-

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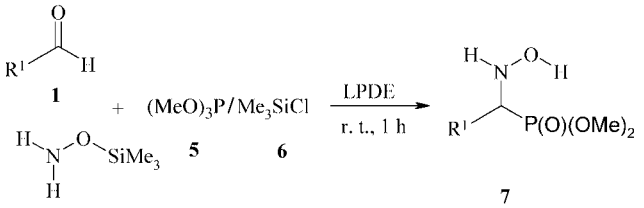
droxyamino)alkyl(aryl)phosphonates **7** in good yields by a new three-component synthesis in which an *O*-trimethylsilyl oxime ether [generated in situ from aldehyde **1** and *O*-(trimethylsilyl)hydroxylamine (**2**)] is reacted with the binary reagent $(MeO)_3P/Me_3SiCl$ in LPDE solution (5.0 M) at room temperature within 1 hour. Examples are shown in Scheme 2.[13]



	R^1	Yield (%)
a	*i*-Pr	91
b	*n*-Pr	94
c	*t*-Bu	98
d	Ph	96
f	3-Pyridyl	90
g	*p*-$NO_2C_6H_4$	74
h	*p*-BrC_6H_4	71

Scheme 2

In summary, three-component reactions between aldehydes, *O*-(trimethylsilyl)hydroxylamine, and silylated nucleophiles (the formation of dimethyltrimethylsilyl phosphite has been postulated[14]) have been successfully carried out by using LPDE solution to afford α-substituted hydroxylamine derivatives **4** and **7** in high yields. The reactions are very clean and the procedure is very easy; simple mixing almost equimolar amounts of an aldehyde, *O*-(trimethylsilyl)hydroxylamine, and the nucleophile.

α-Cyano(silyloxy)amines 4; General Procedure

To a mixture of aldehyde **1** (2 mmol) in 5.0 M LPDE (4 ml) was added *O*-(trimethylsilyl)hydroxylamine (232 mg, 2.2 mmol) at r.t. The mixture was stirred for 15 min and trimethylsilyl cyanide (218 mg, 2.2 mmol) was added. After stirring the mixture for 1 h, H_2O (10 mL) was added. The H_2O layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The product was purified by flash chromatography (hexane–EtOAc). ^1H NMR, ^{13}C NMR, IR, and mass spectra were entirely consistent with the assigned structures. Some typical examples are given below.

4c (R^1 = *t*-Bu)

^1H NMR (90 MHz, $CDCl_3$): δ = 4.0 (s, 1 H, H-1), 1.06 (s, 9 H, *t*-C_4H_9), 0.15 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (22.5 MHz, $CDCl_3$): δ = 119.23 (CN), 70.77 (CH), 35.71 [$C(CH_3)_3$], 24.84 [$C(CH_3)_3$], 0.62 [$Si(CH_3)_3$].

4h (R^1 = *p*-Br-C_6H_4)

^1H NMR (90 MHz, $CDCl_3$): δ = 7.6–7.25 (m, 4 H, ArH), 5.4 (s, 1 H, CH), 0.15 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.62 (C, Ar), 132.5 (CH, Ar), 128.23 (CH, Ar), 123.77 (C, Ar), 119.01 (CN), 63.31 (CH), 0.15 ($SiCH_3$).

α-(Hydroxylamino)alkyl(aryl)phosphonates 7; General Procedure

To a mixture of aldehyde (2 mmol) in 5 M LPDE (4 mL) was added *O*-(trimethylsilyl)hydroxylamine (232 mg, 2.2 mmol) at r.t. The mixture was stirred for 15 min and a mixture of trimethyl phosphite/trimethylsilyl chloride (2.2 mmol) was added. After the mixture was stirred for 1 h, H_2O (10 mL) was added. The H_2O layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organics were washed with sat. aq $NaHCO_3$ solution (20 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated. The product was purified by flash chromatography (hexane–EtOAc). ^1H NMR, ^{13}C NMR, IR and MS spectra of all the products were entirely consistent with the assigned structures. Selected data are given below.

7c (R^1 = *t*-Bu)

^1H NMR (500 MHz, $CDCl_3$): δ = 3.76 (d, $^3J_{P-H}$ = 10 Hz, 3 H, OCH_3), 3.74 (d, $^3J_{P-H}$ = 10 Hz, 3 H, OCH_3), 3.57 (d, $^2J_{P-H}$ = 10 Hz, 1 H, H-1), 3.4–3.2(br s, 2 H, NH, OH), 1.05 (s, 9 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 75.6 (d, $^2J_{P-C}$ = 158 Hz, C-1), 53.14 (d, $^3J_{P-C}$ = 6.3 Hz, OCH_3), 52.7 (d, $^3J_{P-C}$ = 7 Hz, OCH_3), 34.55 (s, CH), 26.4 (s, CH_3).

7d (R^1 = Ph)

^1H NMR (90 MHz, $CDCl_3$): δ = 7.6–7.2 (m, 5 H, ArH), 5.09 (d, $^2J_{P-H}$ = 16 Hz, 1 H, H-1), 3.78 (d, $^3J_{P-H}$ = 10 Hz, 3 H, OCH_3), 3.74 (d, $^3J_{P-H}$ = 10 Hz, 3 H, OCH_3), 3.5–3.3 (br s, 2 H, NH, OH).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.21 (C), 128.47 (CH, Ar), 128.35 (CH, Ar), 127.01 (CH, Ar), 70.6 (d, $^2J_{P-C}$ = 159 Hz, C-1), 54.04 (d, $^3J_{P-C}$ = 7.5 Hz, OCH_3), 52.7 (d, $^3J_{P-C}$ = 7.5 Hz, OCH_3).

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