A New Synthesis of Oxime Derivatives from Carbonyl Compounds and *N,O*-Bis(trimethylsilyl)hydroxylamine

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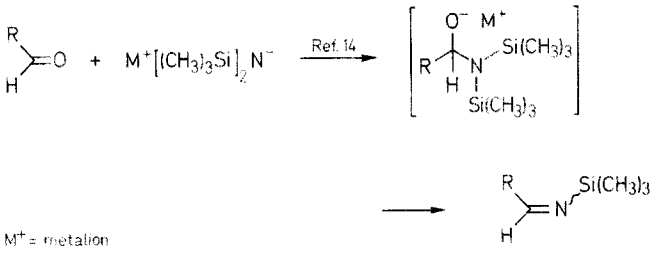
Reaction of a series of aldehydes and ketones with the potassium salt of *N,O*-bis(trimethylsilyl)hydroxylamine **(2)** gave high yields of the corresponding oximate anion **5**. This anion, formed in a Peterson-type reaction, could be protonated to the oxime **7** or trapped *in situ* with a variety of electrophiles to give *O*-substituted oxime derivatives.[8]

Oximes and their *O*-substituted derivatives are synthetically useful in a wide variety of transformations. They undergo a number of rearrangements including the Beckmann rearrangement,[1] to give amides, and the Neber rearrangement,[2] to yield α-aminoketones. They are reported to react with Grignard reagents[3] and alkyl lithiums[4] to give amines and hydroxylamines, respectively. A recent report indicates that *O*-silylated oximes provide a very important new route to nitrones.[5]

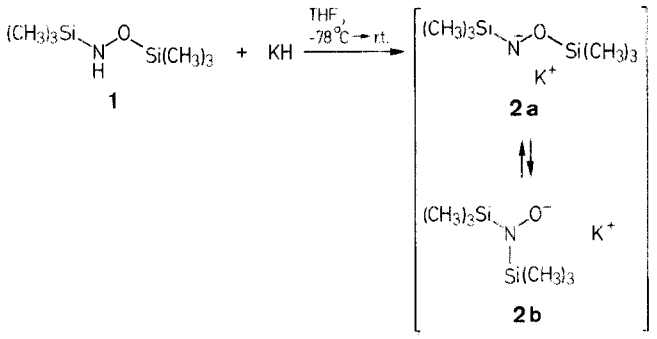
Typically oximes are prepared by the reaction of a carbonyl compound with hydroxylamine hydrochloride and a base such as pyridine.[6] Other routes to oximes include the reduction of nitro compounds,[7,8] oxidation of amines,[9] and reaction of Grignard reagents with the conjugate bases of nitro compounds.[10] Substitution on the oxime oxygen to give an *O*-substituted derivative is usually carried out in a separate step.

In connection with current research interests, an efficient route to *O*-silylated oximes was needed. Although silylation of oximes is well-known,[11,12] as well as the reaction of an *O*-silylated hydroxylamine with aldehydes and ketones,[13] recent work by Hart[14] detailing the preparation of *N*-silylimines suggested a new route. In that study, a Peterson-type reaction between lithium bis(trimethylsilyl)amide and aldehydes yielded *N*-silyl imines directly.



If a metallated *N,O*-bis(trimethylsilyl)hydroxylamide **(2)** were to react with carbonyl compounds analogously, a direct preparation of *O*-silylated oximes could result. We wish to report that **2** reacts readily with both aldehydes and ketones and provides a one-pot synthesis of a variety of *O*-substituted oxime derivatives.

N,O-Bis(trimethylsilyl)hydroxylamine **(1)** was prepared by the procedure of West[15] and converted to its potassium salt **2** with potassium hydride (see Scheme below). Based on precedent of the lithium derivative, a rapid equilibrium between **2a** and its *N,N*-bissilylated isomer, **2b** is likely present. This was not expected to pose problems, since consumption of the more reactive **2a** should shift the equilibrium in that direction.



Addition of cyclohexanone (1 equiv) to **2** followed by quenching with 10% ammonium chloride gave a quantitative yield of cyclohexanone oxime **(7a)**. It was independently determined that cyclohexanone *O*-trimethylsilyl oxime was unaffected by the work-up, thus desilylation occurred during the reaction. Closer examination of the reaction mixture revealed that a volatile by-product was also produced which gave only a high-field singlet in its ^{1}H-NMR spectrum and was postulated to be

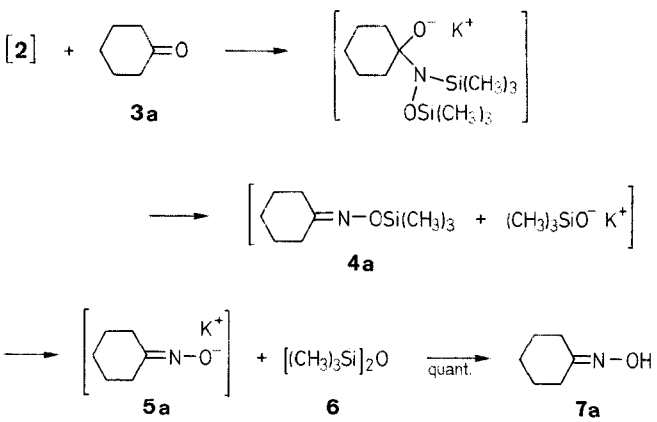


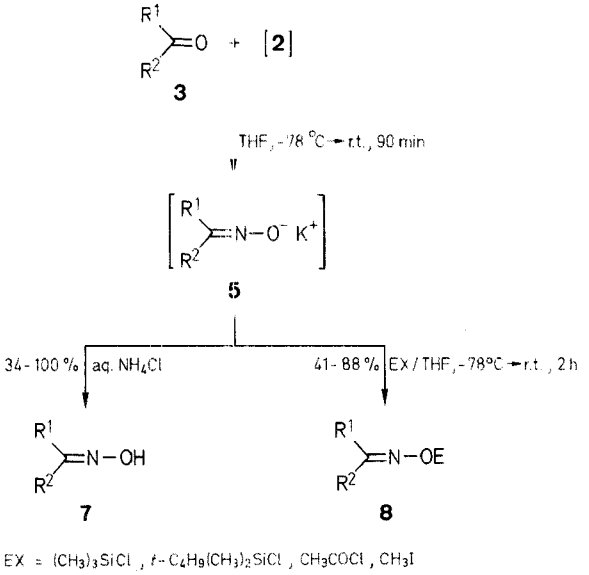
Table. Yields[a] of Oximes **7** and *O*-Substituted Oximes **8**

3, 5, 7, 8	R^1	R^2	Yield (%) of 7[23]	Yield (%) of 8, E			
				TMS[b]	TBS[c]	OAc	Me
a	$-(CH_2)_5-$		100	88[24]	59	43[25]	70[d,26]
b	$-(CH_2)_4-$		100	...	68	50[27]	...
c	C_2H_5	C_2H_5	87	41	61	60	...
d	C_6H_5	CH_3	34[e]	46[e,24]	57	55[28]	...
e	C_6H_5	H	70	...	75[f]	50[29]	...
f	t-C_4H_9	t-C_4H_9	92[16]				
g	C_6H_5	mesityl	100[18]				

[a] Isolated yields of pure product.
[b] TMS = trimethylsilyl.
[c] *tert*-butyldimethylsilyl.
[d] Yield determined by NMR due to contamination of the product with ketone.
[e] Yield determined by NMR. Acetophenone reactions returned 27–34% starting ketone, which was not separated.
[f] Yield based on NMR. A by-product believed to be the *N*-(*tert*-butyldimethylsilyl)nitrone contaminated product.

hexamethylsiloxane (**6**). It is thus clear that the oxime anion **5a**, formed by desilylation of **4a**, is the primary product of the reaction as illustrated below. A series of aldehydes and ketones was converted to their corresponding oximes in generally high yields (Table).

The oxime anion **5** could be trapped *in situ* by addition of electrophiles to the reaction mixture. Amide **2** thus serves as a common starting point for the preparation of a number of *O*-substituted oxime derivatives **8** in a one pot procedure. Both trimethylsilyl chloride and *tert*-butyldimethylsilyl chloride, added to the reaction mixture, gave *O*-silylated oximes in good yields, while *O*-acetylation with acetyl chloride gave slightly lower yields. The results are collected in the Table.



There are several points worth noting about the reaction of **2** with carbonyl compounds. First, yields were good to excellent although no attempt at optimization was made. The efficacy of the method is particularly apparent for di-(*tert*-butyl) ketone and phenyl mesityl ketone. These two sterically hindered ketones are converted to oximes only very slowly under normal conditions. For instance conversion of di-(*tert*-butyl) ketone to its oxime requires heating with hydroxylamine for 20 hours at 75 °C at 140.000 psi (70%),[16] or refluxing with hydroxylamine for 5 days (yield unreported).[17] Phenyl mesityl ketoxime was prepared from the ketone (16%) by reaction with hydroxylamine/potassium *tert*-amylate for 450 days at room temperature.[18] In contrast the present method gives di-(*tert*-butyl) ketoxime and phenyl mesityl ketoxime in 92% and 100% yields, respectively, by refluxing overnight in tetrahydrofuran. Dimesityl ketone was unreactive, however. The procedure is particularly easy to carry out since it is a one-pot sequence and the work-up consists of removing the solvent under reduced pressure and distilling the residue by Kugelrohr.

Secondly, although anion **5** was not actually observed, its presence is strongly inferred from the *O*-substituted products obtainable and the formation of hexamethyldisiloxane. Furthermore **5** is produced in high yields, as noted from the high yields of oximes. The lowered yields of *O*-substituted products reflects the chemistry of anion **5** with electrophiles. Oximates are known to give both-*N*- and *O*-substitutions in ratios that often depend on steric factors in the oximate and the electrophile.[19,20]

Finally, it is interesting that the silylated hydroxylamide **2** appears to react primarily as a nucleophile towards carbonyl compounds rather than as a base. Hart reported that lithium bis(trimethylsilyl)amide added to non-enolizable aldehydes to give *N*-trimethylsilylimines; aldehydes with α-protons, however, gave predominately enolates by α-proton removal[14] in accord with the more common use of bis(trimethylsilyl)amides as strong, hindered bases.[21]

Enolization does not appear to be a complication in the reaction of **2** with most carbonyls; an exception was acetophenone, where all reactions returned about 30% of the ketone. It may be that this fraction is enolized by **2**. It could be that **2** is a much better nucleophile than bis(trimethylsilyl)amide, since the oxygen atom renders it more nucleophilic by the *alpha*-effect. Similar considerations hold for the recently described reaction of *N*-methyl-*N*,*O*-bis(trimethylsilyl)hydroxylamine with carbonyl compounds to give nitrones.[22] The net result is that **2** behaves preferentially as a nucleophile towards aldehydes and ketones.

^{1}H-NMR spectra were recorded on a Varian XL-200 spectrometer in $CDCl_3$ solution using TMS as an internal standard, IR spectra were recorded on a Perkin-Elmer 283B spectrometer, and mass spectra were recorded on a Hitachi RMU-6E instrument. Gas chromatography columns were (a) 3 m × 6 mm 10% QF-1 on Anachrome ABS (preparative), and (b) 10 m × 0.53 mm Superox fused silica column (Altech; analytical). THF was dried by stirring over KOH followed by reflux over and distillation from LAH, and storage over Na. All glassware and syringes were oven dried before use. All reactions were carried out under dry nitrogen, and reagent transfers were accomplished using syringe techniques. Oximes[6] and *O*-substituted oximes[11,12] were prepared by known methods for comparison purposes if not documented in the literature.

Preparation of Oximes 7; 3-Pentanone Oxime (7c; $R^1 = R^2 = C_2H_5$); Typical Procedure:

To a cold (−78°) stirred suspension of potassium hydride (150 mg, 35% oil dispersion, 1.34 mmol) in THF (5 mL) is added a solution of *N,O*-bis(trimethylsilyl)hydroxylamine (**1**; 250 mg, 1.41 mmol) in THF (2 mL). The heterogeneous mixture is warmed to room temperature for 30 min, then recooled to −78°. A solution of 3-pentanone (**3c**; 120 mg, 1.34 mmol) in THF (2 mL) is added slowly in one portion. The mixture is warmed to room temperature for 90 min and then poured into ice-cold 10% NH_4Cl solution (40 mL). Extraction with CH_2Cl_2 (3 × 25 mL), drying of the organic layer ($MgSO_4$), and solvent removal under reduced pressure gives the crude oxime in >95% purity (Column b). Purification of the residue by Kugelrohr distillation (25 Torr) at 50°C gives **7c**; yield: 131 mg (87%).

All the oximes prepared were compared by IR and ^{1}H-NMR with authentic[23] samples. Yields are reported in the Table.

Di-(tert-butyl) Ketoxime (**7f**): This ketoxime is prepared by the procedure described above except that 1.5 equivalents of **1** are employed, and the reaction mixture is refluxed 15 h. Standard quenching and work-up gave **7f**; yield: 92%; m.p. 157–160°C (Lit.[16] m.p. 156–158°C).

Phenyl Mesityl Ketoxime (**7g**): This ketoxime is prepared by the procedure described above except that 2.5 equivalents of **1** are employed, and the reaction mixture is refluxed 20 h. Standard quenching and work-up gave **7g**; yield: 100%; m.p. 148–149°C (Lit.[18] m.p. 150°C).

Preparation of *O*-Substituted Oximes 8; 3-Pentanone *O*-(*tert*-Butyldimethylsilyl)oxime (8c; E = TBS); Typical Procedure:

The formation and reaction of **2** with **3c** is carried out as described above. After stirring at room temperature for 90 min, the reaction mixture is cooled to −78° and a solution of *tert*-butyldimethylsilyl chloride (200 mg, 1.34 mmol) in THF (2 mL) is added. After stirring at room temperature for 2 h, the solvent is removed under reduced pressure, and the sticky white residue is subjected to Kugelrohr distillation (25 Torr), first at 30°C to remove hexamethyldisiloxane and then at 70°C to give **8c** as a clear, colorless liquid; yield: 180 mg (61%).

Other *O*-substituted oximes were prepared analogously by adding the appropriate electrophilic trapping agents [trimethylsilyl chloride (TMSCl), *tert*-butyldimethylsilyl chloride (TBSCl), AcCl, MeI]. As noted in the Table, known compounds were identified by comparison with literature data. New compounds are reported below:

Cyclohexanone O-(tert-Butyldimethylsilyl)oxime (**8a**; E = TBS):

$C_{12}H_{25}NOSi$	calc.	C 63.37	H 11.08	N 6.16
(227.4)	found	63.18	11.16	6.63

IR (neat) ν = 2948, 2855, 1645 (weak C=N), 1462, 1415, 1209, 921 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 0.16 (s, 6 H); 0.93 (s, 9 H); 1.76 (m, 6 H); 2.42 (m, 4 H).

Hydrolysis (DMSO/H_2O, 25:1, reflux, 18 h) returned cyclohexanone oxime.[19]

Cyclopentanone O-(tert-Butyldimethylsilyl)oxime (**8b**, E = TBS):

$C_{11}H_{23}NOSi$	calc.	C 61.91	H 10.86	N 6.56
(213.4)	found	61.99	11.09	6.63

IR (neat): ν = 2951, 2887, 2855, 1647 (weak C=N), 1465, 1417, 1209, 924 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 0.16 (s, 6 H); 0.93 (s, 9 H); 1.42 (m, 4 H); 1.73 (m, 4 H).

3-Pentanone O-(Trimethylsilyl)oxime (**8c**, E = TMS):

$C_8H_{19}NOSi$	C 55.43	H 11.05	N 8.08	
(173.3)	55.34	11.41	8.28	

IR (neat): ν = 2963, 2932, 1624 (weak C=N), 1455, 1372, 1247, 914 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 0.18 (s, 9 H); 1.06 (overlapping t, 6 H); 2.22 (q, 2 H, J = 7.6 Hz); 2.35 (q, 2 H, J = 7.2 Hz).

3-Pentanone O-(tert-Butyldimethyl-silyl)oxime (**8c**; E = TBS):

$C_{11}H_{25}NOSi$	calc.	C 61.33	H 11.70	N 6.50
(215.4)	found	61.44	11.96	6.75

IR (neat): ν = 2950, 2925, 2880, 2848, 1628 (weak), 1485, 1247, 917 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 0.167 (s, 6 H); 0.959 (s, 9 H); 1.08 (overlapping t, 6 H); 2.23 (q, 2 H, J = 7.2 Hz); 2.36 (q, 2 H, J = 7.0 Hz).

3-Pentanone O-(Acetyl)oxime (**8c**, E = Ac):

$C_7H_{13}NO_2$	calc.	C 58.72	H 9.78	N 9.15
(143.2)	found	58.34	9.78	8.97

IR (neat): ν = 2970, 2931, 2874, 1762 (C=O), 1634 (weak C=N), 1458, 1362, 1224, 1196, 994, 917 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.15 (overlapping t, 6 H); 2.17 (s, 3 H); 2.38 (q, 4 H, J = 7.1 Hz).

Structure proof supported by hydrolysis (2.5 molar HCl, 30 min, 25°C) to 3-pentanone oxime.

Acetophenone O-(tert-Butyldimethylsilyl)oxime (**8d**, E = TBS):

$C_{14}H_{23}NOSi$	calc.	C 67.41	H 9.29	N 5.62
(249.4)	found	67.41	9.54	5.62

IR (neat): ν = 3052, 2952, 2925, 1464, 1361, 1248, 987, 924 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 0.22 (s, 6 H); 0.99 (s, 9 H); 2.25 (s, 3 H); 7.35 (m, 3 H); 7.69 (m, 2 H).

O-(tert)-Butyldimethylsilyl)benzaldoxime (**8e**, E = TBS):

$C_{13}H_{21}NOSi$	calc.	C 66.32	H 8.99	N 5.95
(235.4)	found	66.06	8.72	6.27

IR (neat): ν = 3058, 3018, 2925, 2852, 1461, 1331, 1248, 947 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 0.24 (s, 6 H); 0.99 (s, 9 H); 7.36 (m, 3 H); 7.58 (m, 2 H); 8.20 (s, 1 H).

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