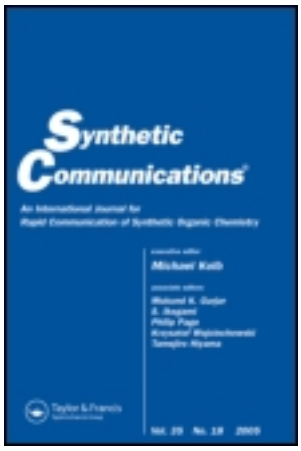

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A General Uncatalyzed Method for the Synthesis of O-Silylated Oximes

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A General Uncatalyzed Method for the Synthesis of *O*-Silylated Oximes

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ABSTRACT

Aldoximes and ketoximes were smoothly and efficiently *O*-silylated at room temperature with diverse chlorosilanes such as TMSCl, TBSCl, or TIPSCl in dichloromethane or THF, using imidazole as a base to trap the generated hydrochloric acid.

Oximes and oxime ethers are used as convenient intermediates for the preparation of a variety of organic molecules[1–7] and pharmaceutical products[8–10] due to their convenient preparation from carbonyl compounds and their facile transformations to other functional groups. *O*-Silylated aldoximes and ketoximes are widely known stable derivatives

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used as intermediates for the synthesis of nitrogen containing compounds such as: hydroxylamines,[5] amines,[11–13] nitrones,[14] isoxazoles,[15] nitriles,[16] and other compounds.[17–20]

A large number of procedures are reported for the direct hydroxyl group silylation of alcohols,[21] phenols,[22] and carboxylic acids[23] using the commercially available silyl chlorides as silylating reagents. However, there is a need of well established methods for the synthesis of *O*-silylhydroxylamines[24] and oximes.[25] Most of the known procedures for the silylation of oximes were directed toward the characterization of derivatives by gas chromatographic analysis,[26a,b] or for the in situ preparations of aldoxime intermediates in multi-step synthesis without their complete characterization.[27]

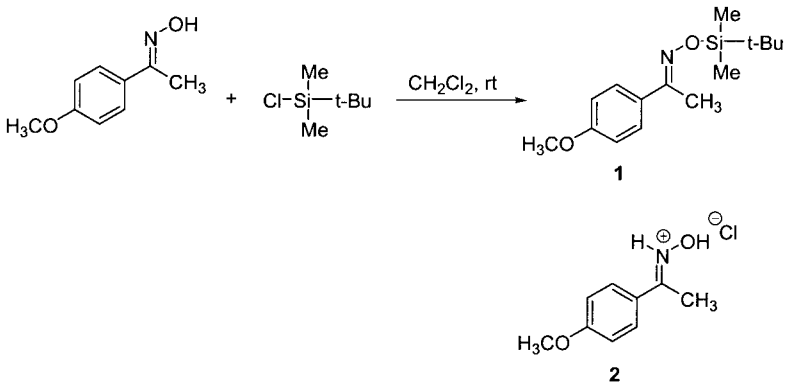
In general, the synthesis of *O*-trimethylsilyl oximes has been accomplished by refluxing the oximes with hexamethyldisilazane in the presence of a catalytic amount of trimethylchlorosilane;[14,28a] or by the oxime reaction with trimethylchlorosilane using different liquid bases, such as pyridine (used also as solvent),[28b] or triethylamine in CCl_4,[27c,28c,d,29] CH_2Cl_2,[27b] or ether.[28e]

Although the bulkier aldoximes and ketoximes silylethers are more stable and potentially useful as synthetic intermediates, methods for their preparation have been less studied.[25b] In 1983, Barret and coworker[30a] applied to oximes the conditions used by Corey et al.[21a] for the *tert*-butyldimethylsilyl (TBS) group protection of alcohols, e.g., TBSCl/imidazole/*N*,*N*-dimethylformamide. However, this silylating method has been reported to be sluggish[26] and requires forcing reaction conditions such as: excess of chlorosilane and imidazole, longer reaction times,[30a,30b] molecular sieves as catalyst[31] or heating.[32]

We report here an efficient silylating procedure that presents several advantages over the existing methods. It requires shorter reaction times for the large-scale preparation of a variety of silylethers (TMS-, TBS-, TIPS-, or MDPS-groups) at room temperature without the need for a catalyst and it has a simple workup that produces highly pure aliphatic and aromatic aldoximes and ketoximes derivatives in very good yield.

In a preliminary experiment, the formation of the silyl ether **1** and the corresponding oxime hydrochloride **2** was observed by GC when 4-methoxyacetophenone oxime was mixed in an equal molar ratio with TBSCl in CH_2Cl_2, (Sch. 1). Product **2** was isolated and characterized by its IR, ^1H and ^{13}C NMR spectra.[33,34]

To optimize this method, the silylation of 4-methoxyacetophenone oxime using one equivalent of TBSCl with the subsequent addition of 1.5 equivalents of imidazole as a base was carry out in CH_2Cl_2, THF, and

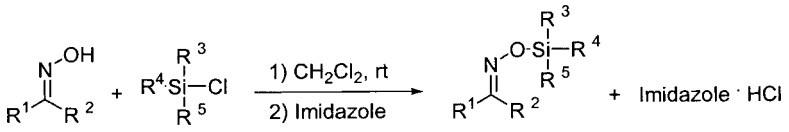


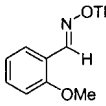
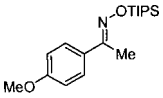
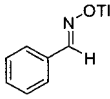
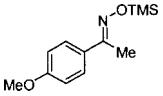
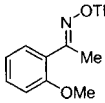
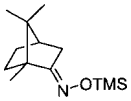
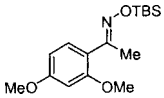
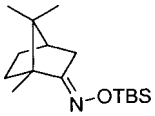
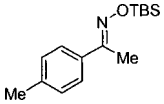
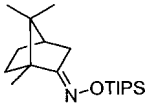
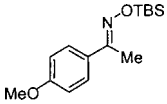
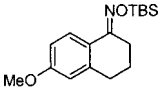
Scheme 1.

diethyl ether, accomplishing a 98%, 90%, and 88% yield, respectively, in 15 min as analyzed by GC/MS. We extended our approach to the synthesis of other silylated oximes using one equivalent of the oxime, one equivalent of the chlorosilane in CH_2Cl_2 (or THF depending on the solubility of the oxime), followed by the addition of 1–2 equivalent of imidazole in CH_2Cl_2. Immediately after the reagents were mixed, the imidazolinium hydrochloride salt precipitated. Analysis of the solutions by GC indicated that the reactions were completed in less than 1 h with excellent product purity. The precipitate was removed from the mixture by filtration, the crystals were washed with a small amount of CH_2Cl_2 and the filtrate was concentrated under vacuum. The oily residue was redissolved in dry hexane and passed through a short pad of silica gel in hexane. In an alternative pre-purification wet process, the filtrated was washed with cold bicarbonate and/or a brine solution, dried and concentrated to afford the silylated oxime. Further purification by vacuum distillation, recrystallization, or column chromatography on silica gel with hexane as eluting phase, yielded a highly pure product (GC/MS).

By this procedure, a variety of oximes were conveniently and efficiently silylated with different silyl groups, as indicated in Table 1. As expected, benzaldoximes provided the silylated oximes without a trace of the corresponding nitrile due to the mild reaction conditions. One important feature of our reported silylating method is that the substitution reaction at the silicon atom proceeds swiftly even for the bulky *tert*-butyldimethyl- and triisopropylsilyl groups. We have observed that when the addition of imidazole to the oxime and chlorosilane reaction mixture is too abrupt, the reaction rate decreases significantly. Therefore,

Table 1. Synthesis of oxime silyl ethers.



Entry	Silyl ether	*E*/*Z* ratio[a]	Yield (%)[b]	Entry	Silyl ether	*E*/*Z* ratio[a]	Yield (%)[b]
1a		90/10	77	**1g**		92/8	77
1b		93/7	87	**1h**		99/1	68
1c		84/16	88	**1i**		96/4	69
1d		92/8	66	**1j**		99/1	80
1e		98/2	81	**1k**		100	87
1f		97/3	79	**1l**		99/1	66

[a]*E*/*Z* ratios.
[b]Isolated yields of pure products characterized by their FT-IR, ^{1}H, and ^{13}C NMR and GC/MS spectroscopic data.

a hypothesis for the high efficiency of our method with these bulky silyl groups is the prevention of the in situ formation of the less reactive $R^1R^2R^3$Si-imidazole intermediates.[25a]

In conclusion, we have described a general uncatalyzed, inexpensive, facile, and efficient method for the synthesis of new ketoximes and aldoximes silylethers.

EXPERIMENTAL SECTION

All experiments were carried out under an atmosphere of dry nitrogen, and using standard procedures for handling air sensitive compounds. ^{1}H and ^{13}C NMR spectra were recorded on a GE 500 MHz in $CDCl_3$ solution using TMS as internal reference. Mass spectra were measured at 70 eV on a HP 5996 instrument. Analytical gas chromatography (GC) was performed using a flame ionization detector and a capillary column (25 mm × 0.33 mm bonded 5% phenyl methylsilicone). Commercial grade reagents and solvents were used after standard purification procedures. The silica gel, used for column chromatography was Merck, 230–400 mesh from Aldrich. Dry THF was distilled from sodium benzophenone ketyl. Dichoromethane was distilled over CaH_2, prior to use.

Representative procedure for silylation of oximes used for the synthesis of *O*-triisopropylsilyl camphor oxime (1k): To a stirred solution of camphor oxime (3.0 g, 18 mmol) and triisopropylsilyl (TPS) chloride (3.84 mL, 3.45 g, 18 mmol) in CH_2Cl_2 (5 mL) was added dropwise (30 min) a solution of imidazole (2.44 g, 36 mmol) in CH_2Cl_2 (15 mL) at room temperature. GC analysis indicated the complete formation of the product after one hour. The white precipitate was removed by filtration under nitrogen, the solution was concentrated in a rotorevaporator (20 mmHg) and then under high vacuum (0.01 mmHg). The crude product (5.8 g, 99%) was passed through a silica gel pad (28 g) with hexane and fractional distilled under vacuum. Yield 87% (5.1 g); B.p. 94–97°C (0.05 mmHg); IR (neat): 1665 (C=N); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.5 (dt, 1H, CH), 2.0 (d, 1H, CH), 1.86 (t, 1H), 1.8 (m, 1H), 1.6 (m, 1H), 1.4 (m, 1H), 1.2 (m, 1H), 1.2 (m, 3H, Si–CH), 1.0 (d, 18H), 0.97 (s, 3H), 0.87 (s, 3H), 0.77 (s, 3H); and ^{13}C NMR δ: 172.1 (C=N), 51.8 (C_1), 48.0 (C_7), 43.7 (C_4), 33.4 (C_3), 32.8 (C_6), 27.3 (C_5), 19.4 (C_8), 18.6 (C_9), 18.0 (CH_3–CH–Si), 11.9 (C_{10}), 11.1 (Si–CH); MS m/z: 324.2 (M^+), 298 (100). Anal. calcd. for $C_{19}H_{37}NOSi$: C, 70.52; H, 11.53; N, 4.33. Found: C, 70.12; H, 11.62; N, 4.37.

***O*-(*tert*-Butyldimethylsilyl)-2-methoxybenzaldoxime (1a):** Compound **1a** was prepared from 2-methoxybenzaldoxime (5.4 g, 39.6 mmol) using the previous procedure for silylation. The clear oily crude product (8.4 g, 80%, E/Z ratio: 92/8 by GC, Rt 10.3 min and 9.5 min) was purified by column chromatography on silica gel (2 cm diameter,15 cm length, 30 g) in hexane (8.0 g, 77% yield, 97% purity by GC): FT-IR (neat, cm^{-1}) 1605 (C=N), 1250 (SiMe, vs); ^{1}H NMR δ: 8.65 (s, 1H), 6.89–7.89 (m, 4H), 3.8 (s, 3H), 1.05 (s, 9H), 0.30 (s, 6H); ^{13}C NMR δ: 149.1, 157.4, 126.3, 131.0, 120.6, 121.2, 110.9, 55.4, 26.1, 18.2, 5.2; MS m/z: 266.5 (M^+, 100), 208

($M^{\cdot+}$-*t*-Bu), 134 ($M^{\cdot+}$ − OTBS). Anal. calcd. for $C_{14}H_{23}NO_2Si$: C, 63.35; H, 8.73; N, 5.28. Found: C, 63.45; H, 9.07; N, 5.23.

***O*-(Triisopropylsilyl)benzaldoxime (1b):** Compound **1b** was prepared from benzaldoxime (2.2 g, 18 mmol) using the described procedure for silylation. The clear oily crude product (4.7 g, 94%, *E*/*Z* ratio: 93/7 by GC, Rt 12.2 min and 11.9 min) was purified by column chromatography on silica (16 cm × 2.0 cm diameter) /hexane (4.3 g, 87%): ^{1}H NMR δ: 8.3 (s, 1H), 7.7–7.4 (m, 5H), 1.41 (m, 3H), 1.27 (d, 18H); ^{13}C NMR δ: 152.9, 149.6, 130.8, 129.6, 128.6, 126.9, 17.9, 11.9; MS *m*/*z*: 278 ($M^{\cdot+}$), 252 (100). Anal. Calcd. for $C_{16}H_{27}NOSi$: C, 69.26; H, 9.81; N, 5.05. Found: C, 69.02; H, 10.18; N, 4.84.

***O*-(*tert*-Butyldimethylsilyl)-2-methoxyacetophenone oxime (1c):** This compound was obtained from 2-methoxyacetophenone oxime (5.0 g, 30 mmol) using the described procedure for silylation, followed by dilution with hexane, filtration of the imidazole hydrochloride salt, extraction with a cold brine solution (50 mL) and subsequent drying the organic phase with $MgSO_4$, as a clear liquid (7.8 g, 93%, *E*/*Z* ratio: 87/13 by GC, Rt 10.6 min and 8.6 min). After purification by fractional distillation, **1c** was obtained (7.4 g, 88%): B.p. 88°C/0.45 mmHg. IR (film, cm^{-1}) 1248 (SiMe, vs); ^{1} H NMR ($CDCl_3$, TMS) δ: 7.4 (m, 2H), 6.9 (m, 2H), 3.8 (s, 3H), 2.2 (s, 3H), 1.1 (s, 9H), 0.26 (s, 6H); ^{13}C NMR δ: 160.9, 157.4, 129.9, 129.6, 127.4, 120.4, 111.0, 55.3, 26.1, 18.1, 15.8, −5.1; MS *m*/*z*: 280.4 ($M^{\cdot+}$ + 1) 149.2 ($M^{\cdot+}$ − HOTBS, 100). Anal. calcd. for $C_{15}H_{25}NO_2Si$: C, 64.47; H, 9.02; N, 5.01. Found: C, 64.30; H, 8.79; N, 5.03.

***O*-(*tert*-Butyldimethylsilyl)-2,4-dimethoxyacetophenone oxime (1d):** This compound was prepared as described above from 2,4-dimethoxyacetophenone oxime (4.0 g, 20 mmol), followed by filtration of the imidazole hydrochloride salt, concentration of the filtrate under vacuum, extraction with a cold brine solution (40 mL) and subsequent drying the organic phase with Na_2SO_4. The crude product was a clear colorless liquid (5.36 g, 85%, *E*/*Z* ratio: 92/8 by GC, Rt 12.6 min and 10.8 min). After purification by fractional distillation, **1d** was obtained as a clear liquid (4.2 g, 66%, 98% purity): B.p. 123°C/0.85 mmHg; IR (film, cm^{-1}) 1248 (SiMe, vs); ^{1} H NMR ($CDCl_3$, TMS) δ: 7.3 (d, 1H), 6.4 (m, 2H), 3.8 (s, 3H), 3.8 (s, 3H), 2.2 (s, 3H), 1.0 (s, 9H), 0.23 (s, 6H); ^{13}C NMR δ: 161.4, 160.6, 158.6, 130.1, 120.4, 104.2, 98.8, 55.3, 26.1, 18.1, 15.9, −5.1; MS *m*/*z*: 310.1 ($M^{+\cdot}$), 177.8 ($M^{\cdot+}$ − HOTBS, 100). Anal. calcd. for $C_{16}H_{27}NO_3Si$: C, 62.10; H, 8.79; N, 4.53. Found: C, 61.82; H, 9.02; N, 4.50.

***O*-(*tert*-Butyldimethylsilyl)-4-methylacetophenone oxime (1e):** Prepared by the typical silylation method described previously from the 4-methyl-

acetophenone oxime (3.00 g, 20.2 mmol) as an oily clear product (5.1 g, 95%, *E*/*Z* ratio: 98/2 by GC, Rt 11.6 min and 10.1 min): After purification by fractional distillation, **1e** was obtained as a clear liquid (4.3 g, 81%): B.p. 40°C/0.2 mmHg. The spectral data corresponded exactly to the previous reported values.[32]

***O*-(*tert*-Butyldimethylsilyl)-4-methoxyacetophenone oxime (1f):** Prepared by the typical silylation method described previously from 4-methoxyacetophenone oxime (6.00 g, 36.4 mmol) as a clear oily product. After purification by fractional distillation, **1f** was obtained as a viscous liquid (8.0 g, 79%): B.p. 116°C/0.1 mmHg, (*E*/*Z* ratio: 97/3 by GC, Rt 11.5 min and 10.6 min). The spectral data corresponded exactly to the previous reported values.[12b]

***O*-(Triisopropylsilyl)-4-methoxyacetophenone oxime (1g):** Prepared from 4-methoxyacetophenone oxime (1.5 g, 26 mmol) as an oily clear product (2.6 g, 90%, *E*/*Z* ratio: 92/8 by GC, Rt 18.1 min and 16.2 min). After purification by fractional distillation, **1g** was obtained as a clear viscous liquid (2.2 g, 77%, 99% purity, *E*/*Z* ratio: 95/5): B.p. 180°C/0.3 mmHg; ^{1}H NMR δ: 7.7 (d, $J = 8.8$ Hz,1H), 6.9 (d, $J = 8.8$ Hz, 2H), 3.8 (s, 3H), 2.3 (s, 3H), 1.3 (m, 3H), 1.2 (d, 18H); ^{13}C NMR δ: 160.2, 157.7, 129.6, 127.2, 6, 113.6, 55.2, 12.1, 11.9; MS *m*/*z*: 148 (100). Anal. calcd. for $C_{18}H_{31}NO_2Si$: C, 67.31; H, 9.73; N, 4.36. Found: C, 67.21; H, 10.05; N, 4.27.

***O*-(Trimethylsilyl)-4-methoxyacetophenone oxime (1h):** Prepared from the 4-methoxyacetophenone oxime (3.5 g, 21.1 mmol) as an oily viscous product (4.4 g, 88%, 93% purity, *E*/*Z* ratio: 99/1 by GC, Rt 10.8 min and 9.3 min). After purification by fractional distillation, **1h** was obtained as a clear viscous liquid, (3.0 g, 68%, 99.7% purity by GC), b.p. 78°C/0.05 mmHg; IR (film, cm^{-1}) 1249 (SiMe, vs); ^{1}H NMR δ: 7.7 (d, $J = 9$ Hz, 2H), 6.9 (d, $J = 9$ Hz, 2H), 3.8 (s, 3H), 2.3 (s, 3H), 0.3 (s, 3H); ^{13}C NMR δ: 160.4, 158.2, 129.5, 127.4, 113.6, 55.2, 12.2, −0.60; MS *m*/*z*: 237 ($M^{\cdot+}$), 148 ($M^{\cdot+} - OSiMe_3$, 100). Anal. calcd. for $C_{12}H_{19}NO_2Si$: C, 60.72; H, 8.07; N, 5.90. Found: C, 61.04; H, 8.17; N, 6.08.

***O*-(Trimethylsilyl)camphor oxime (1i):** Compound **1i** was prepared from camphor oxime (4.2 g, 25.2 mmol) using the previous procedure for silylation. The clear oily crude product (5.1 g, 85%, 90% purity by GC, Rt 7.96 min) was purified by fractional distillation (4.1 g, 69%, only *E* isomer by GC/MS): B.p. 94–98°C/4 mmHg; FT IR (film, cm^{-1}) 1664 (C=N), 1250 (SiMe, vs); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.47 (dt, 1H, CH), 2.0 (d, 1H, CH), 1.85 (t, 1H), 1.8 (m, 1H), 1.7 (m, 1H), 1.4 (m, 1H), 1.2 (m, 1H), 0.99 (s, 3H), 0.89 (s, 3H), 0.76 (s, 3H), 0.16; ^{13}C NMR δ: 173.83 (C=N), 51.7, 48.0, 43.7 , 33.8, 32.7, 27.3, 19.4, 18.5, 11.1, 0.72; MS *m*/*z*:

239 ($M^{\cdot+}$), 75 (100). Anal. calcd. for $C_{13}H_{25}NOSi$: C, 65.21; H, 10.52; N, 5.85. Found: C, 65.30; H, 11.00; N, 5.63.

***O*-(*tert*-Butyldimethylsilyl)camphor oxime (1j):** Compound **1j** was prepared from camphor oxime (2.8 g, 16.8 mmol) using the previous procedure for silylation. The clear oily crude product (4.7 g, 99%, only one peak, 95% purity, Rt 9.2 min) was purified by fractional distillation (3.6 g, 80%, >98%, *E*/*Z* ratio: 95/5 by GC/MS, Rt 18.1 and 17.9 min): B.p. 70–73°C/0.3 mmHg; FT IR (film, cm^{-1}) 1666 (C=N), 1249 (SiMe, vs); ^{1}H NMR ($CDCl_3$) δ (ppm): 2.5 (tt, 1H, CH), 2.0 (s, 1H, CH), 1.85 (t, 1H), 1.81 (m, 1H), 1.68 (m, 1H), 1.44 (m, 1H), 1.23 (m, 1H), 1.0 (m, 3H), 0.92 (s, 9H), 0.89 (s, 3H), 0.90 (s, 3H), 0.77 (s, 3H), 0.13 (s, 6H); ^{13}C NMR δ: 173.28 (C=N), 51.8, 48.1, 43.7, 33.7, 32.7, 27.3, 26.2, 19.4, 18.6, 11.1, −5.2; MS *m*/*z*: 280 ($M^{\cdot+}$), 75 (100). Anal. calcd. for $C_{16}H_{31}NOSi$: C, 68.26; H, 11.10; N, 4.98. Found: C, 67.97; H, 11.35; N, 4.79.

***O*-(*tert*-Butyldimethylsilyl)-6-methoxytetralone oxime (1l):** This compound was prepared as described above from 6-methoxytetralone oxime (3.6 g, 18.8 mmol) in CH_2Cl_2 (35 mL), *tert*-butyldimethylsilyl chloride (3.12 g, 20.7 mmol) and a solution of imidazole (2.56 g, 37.6 mmol) in CH_2Cl_2 (25 mL). After Schlenk filtration of the imidazole hydrochloride salt, the filtrate was concentrated under vacuum. The clear oily residue was dissolved in hexane (20 mL), extracted the organic phase with a cold $NaHCO_3$ aqueous solution (20 mL), and dried with Na_2SO_4. The crude product was an oily compound (4.76 g, 83%, *E*/*Z* ratio: 99/1 by GC/MS, Rt 15.9 min and 15.3 min) that was purified by column chromatography on silica gel (2 cm diameter, 13 cm length, 24 g) in hexane (3.76 g, 66% yield, 99% purity by GC): IR (film, cm^{-1}) 1613 (C=N); ^{1}H NMR ($CDCl_3$, TMS) δ: 8.0 (d, $J = 8.7$ Hz, 1H), 6.8 (d, $J = 8.7$ Hz,1H), 6.6 (s, 1H), 3.8 (s, 3H), 2.83 (t, $J = 6.5$ Hz, 2H), 2.76 (t, $J = 5.9$ Hz, 2H), 1.87 (m, $J = 6.3$ Hz, 2H), 1.0 (s, 9H), 0. 27 (s, 6H); ^{13}C NMR δ: 160.1, 157.7, 141.1, 125.8, 124.0, 112.8, 112.6, 55.1, 30.1, 26.2, 24.0, 21.2, 18.2, −5.1; MS *m*/*z*: 306.3 ($M^{+\cdot}$, 100). Anal. calcd. for $C_{17}H_{27}NO_2Si$: C, 66.84; H, 8.91; N, 4.59. Found: C, 66.87; H, 9.16; N, 4.66.

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33. 4-Methoxyacetophenone oxime (7.27 mmol) was mixed in an equal molar ratio with TBSCl in CH_2Cl_2, producing compound **2** (1.14 g,

5.6 mmol, 77% yield) as a crystalline salt: M.p. 115–118°C, IR (KBr): 2695.7 (broad, NH^+, OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm): 2.47 (s, 3H, CH_3), 3.85 (s, 3H, CH_3 O), 7.8 (d, 2H, Ar), 7.0 (d, 2H, Ar), 12.4 (s, 2H, NH, OH); and ^{13}C NMR: 164.23 (C_4-OCH_3), 133.56 (C=N), 130.72 (C_2), 120.52 (C_1), 114.84 (C_3), 15.68 (CH_3).

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