Mendeleev Commun., 2000, 10(4), 142–143

N,C-Cross-coupling of trimethylsilyl derivatives of azoles with *N*,*N*-bis(silyloxy)enamines

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10.1070/MC2000v010n04ABEH001293

N-Trimethylsilyl derivatives of di- and triazoles smoothly undergo N,C-cross-coupling reactions with terminal and internal *N*,*N*-bis(silyloxy)enamines to give α-azolyl-substituted oximes.

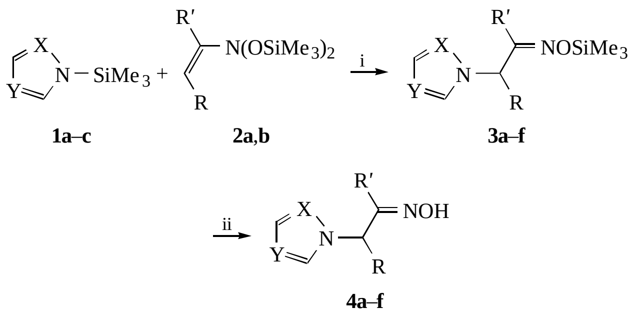
Bis(trialkylsilyloxy)enamines[1] (BSENA) are convenient reagents for organic synthesis.[2]

BSENA, as formal β-carbon electrophiles, smoothly undergo C,C-cross-coupling reactions with α-nitro carbanions[3] or trimethylsilyl derivatives of aliphatic nitro compounds.[4] They also enter into N,C-cross-coupling with trimethylsilyl derivatives of *N*-nitramines[5] and primary[6] or secondary[1] amines. The main products of these processes are α-substituted oximes, and the main side reaction is the rearrangement of BSENA into trimethylsilyl derivatives of 2-trimethylsilyloxy-substituted oximes, which is catalysed by Lewis or Brönsted acids[1,7] and amines.[6]

It was found[3] that at least some of the above reactions can proceed *via* α-nitroso alkenes as key intermediates. It is interesting that N,C-cross-coupling reactions of BSENA with alkyl-*N*-nitroamines, which are N–H acids, can be performed using trimethylsilyl derivatives of *N*-nitramines; however, *N*-trimethylsilyl derivatives of amines do not react with BSENA. Therefore, it is very interesting to examine the N,C-cross-coupling reaction of azoles with BSENA since the N–H acidity of azoles and *N*-nitroamines is almost the same,[8] whereas the basicity of azoles is close to that of amines.[9]

We found that trimethylsilyl derivatives of azoles **1** containing at least two nitrogen atoms react smoothly with model terminal and internal BSENA **2**[†] without a solvent at room temperature to give derivatives of oximes **3**,[‡] which could be transformed into free α-azolyl-substituted oximes **4**[§] after alcoholysis (Scheme 1).

The target products can be purified by fractionation *in vacuo* (for **3**) and by crystallization (for **4**). The reactions between **1** and **2** afforded derivatives **3** in good yields only when BSENA



1: **a** X = N, Y = CH
b X = CH, Y = N
c X = Y = N

2: **a** R = H, R′ = Me
b R = Me, R′ = H

3,**4**: **a** X = N, Y = CH, R = H, R′ = Me
b X = N, Y = CH, R = Me, R′ = H
c X = CH, Y = N, R = H, R′ = Me
d X = CH, Y = N, R = Me, R′ = H
e[¶] X = Y = N, R = H, R′ = Me
f[¶] X = Y = N, R = Me, R′ = H

Scheme 1 *Reagents and conditions*: i, molar ratio **1**:**2** = 1:1, without a solvent, room temperature, 24 h; ii, an excess of EtOH, room temperature, 20 h.

were dried by azeotropic evaporation of water with benzene followed by distillation before the N,C-cross-coupling reaction.

The structure of compounds **3** and **4** was confirmed by ^{1}H and ^{13}C NMR data and additionally by elemental analysis for oximes **4** (the error was no higher than 0.19% for carbon or 0.35% for hydrogen). The (*E*)-configuration of an oximino fragment for oximes **4a**,**c**,**e** and their derivatives **3a**,**c**,**e** was found using the published rules.[3,5,6] Oximes **4b**,**d**,**f** and their derivatives **3b**,**d**,**f** represent mixtures of (*Z*)- and (*E*)-isomers. ¶

The reactions of 1,2,4-triazole **1c** with BSENA **2** are not regioselective (Scheme 2).

However, only pure 1-substituted triazoles **3e**,**f** and **4e**,**f** were isolated from the reaction mixture by distillation *in vacuo* or by crystallization.

† A solution of BSENA **2** (1 mmol) in dry hexane (3 ml) was added dropwise to the TMS derivative of azole **1** (1 mmol) at 20 °C in an inert atmosphere. The mixture was stirred at 20 °C for 30 min, evaporated at 20 °C (10 Torr), then stirred for 24 h. Finally, the residue was dried *in vacuo* at 20 °C (0.1 Torr) to constant weight. Target derivative **3** was isolated by distillation of the residue *in vacuo*.

‡ NMR spectra were recorded on a Bruker AM 300 spectrometer at 300.31 MHz and 75.47 MHz for ^{1}H and ^{13}C, respectively; TMS as an internal standard.

3a: yield 95%, bp 53 °C (0.06 Torr). ^{1}H NMR ($CDCl_3$) δ: 0.19 (s, 9H, $SiMe_3$), 1.57 (s, 3H, Me), 4.80 (s, 2H, CH_2), 6.25 (t, 1H, 4-H, $^{3}J_{H,H}$ 2 Hz), 7.33 and 7.47 (d, 2H, 3-H and 5-H, $^{3}J_{H,H}$ 2 Hz). ^{13}C NMR ($CDCl_3$) δ: –0.75 ($SiMe_3$), 11.91 (Me), 55.89 (CH_2), 106.38 (4-C), 128.99 and 139.44 (3-C and 5-C), 157.44 (C=N).

3b: yield 78%, bp 44 °C (0.08 Torr).

3c: yield 88%, bp 65 °C (0.08 Torr).

3d: yield 97%, bp 73 °C (0.09 Torr). $E/Z \approx 6:1$. ^{1}H NMR ($CDCl_3$) δ: (*E*)-isomer: 0.20 (s, 9H, $SiMe_3$), 1.65 (d, 3H, Me, $^{3}J_{H,H}$ 7 Hz), 4.90 (m, 1H, CH, $^{3}J_{H,H}$ 7 Hz), 6.90 and 7.05 (br. s, 2H, 4-H and 5-H), 7.51 (d, 1H, CH=N, $^{3}J_{H,H}$ 7 Hz), 7.67 (s, 1H, 2-H); (*Z*)-isomer: 0.19 (s, 9H, $SiMe_3$), 1.63 (d, 3H, Me, $^{3}J_{H,H}$ 7 Hz), 5.50 (m, 1H, CH, $^{3}J_{H,H}$ 7 Hz), 6.90 and 7.05 (br. s, 2H, 4-H and 5-H), 7.43 (d, 1H, CH=N, $^{3}J_{H,H}$ 7 Hz), 7.67 (s, 1H, 2-H). ^{13}C NMR ($CDCl_3$) δ: (*E*)-isomer: –0.90 ($SiMe_3$), 19.00 (Me), 52.31 (CH), 117.14 and 129.76 (4-C and 5-C), 135.55 (2-C), 153.18 (C=N); (*Z*)-isomer: –0.90 ($SiMe_3$), 18.00 (Me), 47.63 (CH), 117.30 and 129.76 (4-C and 5-C), 135.55 (2-C), 153.91 (C=N).

3e: yield ~100%, bp 60 °C (0.08 Torr).

3d: yield 95%, bp 64 °C (0.08 Torr).

§ **4a**: yield 91%, mp 94–95 °C (from H_2O).

4b: yield ~100%, oil. $E/Z \approx 5:2$. ^{1}H NMR ($CDCl_3$) δ: (*E*)-isomer: 1.65 (d, 3H, Me, $^{3}J_{H,H}$ 6.6 Hz), 5.10 (m, 1H, CH, $^{3}J_{H,H}$ 6.6 Hz), 6.24 (d, 1H, 4-H, $^{3}J_{H,H}$ 2 Hz), 7.42 and 7.53 (d, 2H, 3-H and 5-H, $^{3}J_{H,H}$ 2 Hz), 7.58 (d, 1H, CH=N, $^{3}J_{H,H}$ 6.6 Hz), 9.36 (br. s, 1H, OH); (*Z*)-isomer: 1.66 (d, 3H, Me, $^{3}J_{H,H}$ 6.6 Hz), 5.72 (m, 1H, CH, $^{3}J_{H,H}$ 6.6 Hz), 6.24 (d, 1H, 4-H, $^{3}J_{H,H}$ 2 Hz), 6.95 (d, 1H, CH=N, $^{3}J_{H,H}$ 6.6 Hz), 7.45 and 7.55 (d, 2H, 3-H, 5-H, $^{3}J_{H,H}$ 2 Hz), 9.36 (br. s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: (*E*)-isomer: 18.54 (Me), 56.71 (CH), 105.95 (4-C), 128.00 and 139.59 (3-C and 5-C), 149.58 (C=N); (*Z*)-isomer: 17.69 (Me); 52.15 (CH); 105.59 (4-C), 128.57 and 139.83 (3-C and 5-C), 150.30 (C=N).

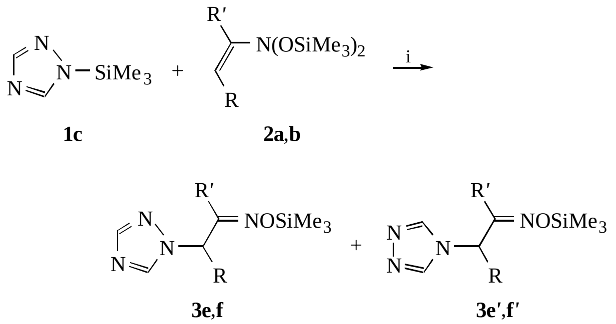
4c: yield ~100%, mp 162–167 °C (from H_2O). ^{1}H NMR ([$^{2}H_6$]DMSO) δ: 1.63 (s, 3H, Me), 4.66 (s, 2H, CH_2), 6.88 and 7.08 (br. s, 2H, 4-H and 5-H), 7.61 (s, 1H, 2-H), 10.92 (s, 1H, OH). ^{13}C NMR ([$^{2}H_6$]DMSO) δ: 11.37 (Me), 49.87 (CH_2), 119.56 and 128.55 (4-C and 5-C), 137.64 (2-C), 151.58 (C=N).

4d: yield 95%, mp 109–112 °C (from H_2O).

4e: yield ~100%, mp 149–151 °C (from EtOH).

4f: yield ~100%, mp 109–113 °C (from H_2O).

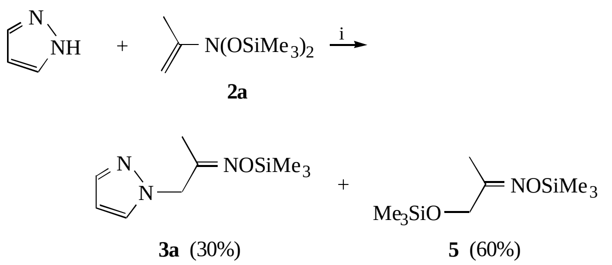
¶ A mixture of two regio isomers (see Scheme 2).



Molar ratio **3e**:**3e′** ~ 6:1; **3f**:**3f′** ~ 2:1

Scheme 2 *Reagents and conditions*: i, molar ratio **1**:**2** = 1:1, without a solvent, room temperature, 20 h.

The interaction of BSENA with free azoles was studied using a model reaction of enamine **2a** with pyrazole. This process is not chemoselective and includes a rearrangement of **2a** into **5**[††] catalysed by pyrazole (Scheme 3).



Scheme 3 *Reagents and conditions*: i, molar ratio pyrazole:**2a** = 1:1, without a solvent, room temperature, 20 h.

†† **5**: *E*/*Z* ≈ 4:1 (ref. 7). ^{13}C NMR ($CDCl_3$) δ: (*E*)-isomer: –0.68 and –0.45 (2$SiMe_3$), 11.54 (Me), 64.86 (CH_2), 160.82 (C=N); (*Z*)-isomer: –0.45 and –0.17 (2$SiMe_3$), 16.50 (Me), 58.72 (CH_2), 163.4 (C=N).

We can conclude that the reactivity of azoles in the N,C-cross-coupling reactions with BSENA is similar to the reactivity of *N*-nitramines in analogous reactions.[5]

Thus, a convenient preparative method for synthesis of 2-azolyl-substituted oximes from available aliphatic nitro compounds and azoles was developed. Oximes **4** are promising synthetic building blocks for drug and plant protection research.[10,11]

This work was performed at the Scientific Educational Centre for Young Scientists and supported by the Russian Foundation for Basic Research (grant nos. 99-03-32015 and 00-15-97455) and by the Federal Programme ‘Integration’ (grant no. A0082).

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Received: 1st March 2000; Com. 00/1619