Triphenylbismuth carbonate-mediated oxidation of hydroxylamines to nitrones and \textit{in situ} 1,3-dipolar cycloaddition

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1. General

2. Gram-scale synthesis of compound 2a

3. Gram-scale synthesis of compound 3a

4. Analytical data

5. References

6. Copies of $^1$H and $^{13}$C NMR Spectra

S2

S2

S2

S3

S6

S7
1. **General**

Reactions were carried out using dry solvents. TLC was performed on silica gel plates visualized either with a UV lamp (254 nm/365 nm), or using solutions of phosphomolybdic acid in EtOH or KMnO$_4$–K$_2$CO$_3$ in water followed by heating. Flash chromatography was performed on Kieselgel 60 (230–240 mesh, Merck). NMR spectra were recorded on a Bruker AVANCE DPX 400 spectrometer. $^1$H NMR spectra were recorded at 400 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane as internal standard, multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet), coupling constant ($J$) in Hz, integration. $^{13}$C NMR spectra were recorded at 100 MHz and data are reported as follows: chemical shift in ppm from tetramethylsilane with the deuterated solvent signal(s) used for calibration, multiplicity with respect to proton (deduced from DEPT experiments, s = quaternary carbon (C), d = CH, t = CH$_2$, q = CH$_3$). Mass spectra were recorded using a Waters Micromass ZQ 2000 ESI spectrometer. IR-spectra were recorded using a Perkin-Elmer 2000 FT-IR. Wavenumbers are given in cm$^{-1}$ at their maximum intensity.

2. **Gram-scale synthesis of compound 2a.**

At room temperature, to a solution of N,N-dibenzyl hydroxylamine 1a (1.02 g, 4.78 mmol, 1 equiv.) in CH$_2$Cl$_2$ (50 mL) was added portionwise Ph$_3$BiCO$_3$ (2.63 g, 1.1 equiv.). The white slurry was stirred at room temperature for 2 h. The mixture was then filtered over a pad of celite, rinsed with CH$_2$Cl$_2$, and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography over silica (Pentane/EtOAc, 1:0 to 1:1) to afford 0.98 g of compound 2a (97%, white solid).

3. **Gram-scale synthesis of compound 3a.**

At room temperature, to a solution of N,N-dibenzyl hydroxylamine 1a (1 g, 4.68 mmol, 1 equiv.) and benzannulated cyclooctyne 4 (0.96 g, 1 equiv.) in CH$_2$Cl$_2$ (70 mL) was added portionwise Ph$_3$BiCO$_3$ (2.57 g, 1.1 equiv.). The white slurry was stirred at room temperature for 2 h. The mixture was then filtered over a pad of celite, rinsed with CH$_2$Cl$_2$, and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography over silica (Pentane/EtOAc, 1:0 to 9:1) to afford 1.47 g of compound 3a (76%, white solid).
4. Analytical data

**Compound 2a.** Flash chromatography (Pentane/EtOAc, from 1:0 to 1:1). \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.23-8.18 (m, 2H), 7.52-7.26 (m, 9H), 5.06 (s, 2H) ppm. \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 134.2 (d), 133.1 (s), 130.4 (d), 130.3 (d), 129.2 (d), 128.9 (d), 128.5 (d), 128.4 (d), 71.1 (t) ppm. IR (neat) 1580, 1457, 1147, 903, 724 cm\(^{-1}\). MS (ES\(^+\))\(^+\): 212 [M+H]\(^+\).

**Compound 2b.** Flash chromatography (Pentane/EtOAc, from 1:0 to 8:2). \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.41-8.39 (m, 2H), 7.92 (s, 1H), 7.79-7.77 (m, 2H), 7.51-7.46 (m, 6H) ppm. \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 149.0 (s), 134.5 (d), 130.9 (s), 129.9 (d), 129.1 (d), 128.9 (d), 128.6 (d), 121.7 (d) ppm. IR (neat) 1549, 1484, 1444, 1065, 919, 764 cm\(^{-1}\). MS (ES\(^+\))\(^+\): 198 [M+H]\(^+\).

**Compound 2c.** Flash chromatography (CH\(_2\)Cl\(_2\)/MeOH from 1:0 to 98:2). \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 6.64 (t, J = 5.8 Hz, 1H), 3.73 (t, J = 7.0 Hz, 2H), 2.48 (q, J = 6.8 Hz, 2H), 1.89 (qt, J = 7.2 Hz, 2H), 1.51 (qt, J = 7.2 Hz, 2H), 1.35-1.24 (m, 18H), 0.87 (t, J = 6.7 Hz, 1H) ppm. \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 139.2 (d), 65.3 (t), 31.6 (t, x2), 29.3 (t), 29.0 (t, x2), 28.9 (t), 27.3 (t), 26.5 (t), 26.4 (t), 25.5 (t), 22.5 (t), 14.0 (q) ppm. IR (neat) 1600, 1463, 904, 724 cm\(^{-1}\). MS (ES\(^+\))\(^+\): 256 [M+H]\(^+\).

**Compound 2d.** Compound 2d was isolated from compound 2d’ by flash chromatography (Pentane/EtOAc, from 1:0 to 7:3 to 0:1, then CH\(_2\)Cl\(_2\)/MeOH 95:5). \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.25-8.23 (m, 2H), 7.45-7.41 (m, 3H), 7.37 (s, 1H), 3.92 (t, J = 7.14 Hz, 2H), 2.00 (quint, J = 7.5 Hz, 2H), 1.40-1.24 (m, 18H), 0.87 (t, J = 6.39 Hz, 3H) ppm. \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 134.1 (s), 130.4 (s), 130.2 (d), 128.4 (d), 121.7 (d), 67.3 (t), 31.8 (t), 29.5 (t), 29.4 (t), 29.3 (t), 29.2 (t), 29.1 (t), 27.7 (t), 26.4 (t), 22.6 (t), 14.0 (q) ppm. IR (neat) 1457, 1153, 903, 724 cm\(^{-1}\). MS (ES\(^+\))\(^+\): 290 [M+H]\(^+\).

**Compound 2d’.** \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 7.40-7.33 (m, 5H), 6.62 (t, J = 5.6 Hz, 1H), 4.84 (s, 2H), 2.45 (dd, J = 13.8, 6.94 Hz, 2H), 1.48-1.40 (m, 2H), 1.31-1.19 (m, 16H), 0.87 (t, J = 6.44 Hz, 3H). \(^13\)C NMR (CDCl\(_3\)) \(\delta\) 137.5 (s), 130.4 (d), 129.3 (d), 128.9 (d), 128.2 (d), 85.8 (t), 31.8 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.2 (t), 22.6 (t), 14.0 (q) ppm. IR (neat) 1777, 1456, 1214, 908, 750 cm\(^{-1}\). MS (ES\(^+\))\(^+\): 290 [M+H]\(^+\).

S3
**Compound 2e.** Flash chromatography (Pentane/EtOAc, from 1:0 to 8:2). $^1$H NMR (CDCl$_3$) $\delta$ 8.24-8.22 (m, 2H), 7.49 (s, 1H), 7.43-7.37 (m, 3H), 4.48-4.41 (m, 1H), 2.33-2.24 (m, 2H), 2.05-1.90 (m, 4H), 1.70-1.60 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$) $\delta$ 132.8 (d), 130.6 (s), 128.5 (d, x2), 76.3 (d), 31.4 (t), 25.5 (t) ppm. IR (neat) 1572, 1451, 1328, 140, 903, 726, 695 cm$^{-1}$. MS (ES$^+$): 190 [M+H]$^+$. HRMS calcd for C$_{12}$H$_{16}$NO $[M+H]^+$ 190.1232, found 190.1244.

**Compound 2f.** Flash chromatography (Pentane/EtOAc, from 1:0 to 7:3). $^1$H NMR (CDCl$_3$) $\delta$ 8.29-8.26 (m, 2H), 7.49-7.37 (m, 4H), 3.61-3.55 (m, 1H), 2.12-2.00 (m, 2H), 1.67-1.57 (m, 2H), 0.93 (td, $J$ = 7.5, 1.4, Hz, 6H) ppm. $^{13}$C NMR (CDCl$_3$) $\delta$ 134.0 (d), 130.3 (s), 130.0 (d), 128.5 (d), 128.4 (d), 80.7 (d), 25.9 (t), 10.7 (q) ppm. IR (neat) 1572, 1455, 1337, 1150 cm$^{-1}$. MS (ES$^+$): 192 [M+H]$^+$. HRMS calcd for C$_{12}$H$_{18}$NO $[M+H]^+$ 192.1388, found 192.1401.

**Compounds 2g and 2g'.** Flash chromatography (Pentane/EtOAc, from 1:0 to 6:4), 1:1 ratio of 2g and 2g'. $^1$H NMR (CDCl$_3$) $\delta$ 8.27-8.18 (m, 4H), 7.47-7.32 (m, 11H), 7.12-7.04 (m, 3H), 5.02 (s, 2H), 4.99 (s, 1.4 Hz) ppm. $^{13}$C NMR (CDCl$_3$) $\delta$ 163.3 (s, $^1J_{CF}$ = 253 Hz), 163.0 (s, $^1J_{CF}$ = 253 Hz), 137.4 (d), 137.0 (d), 134.4 (d), 133.3 (d), 132.8 (s), 131.6 (d), 131.1 (d, $^1J_{CF}$ = 9 Hz), 130.9 (d, $^1J_{CF}$ = 9 Hz), 130.6 (d), 130.4 (d), 130.1 (s), 126.6 (s, $^4J_{CF}$ = 3 Hz), 115.8 (d, $^3J_{CF}$ = 21 Hz), 115.5 (d, $^3J_{CF}$ = 21 Hz), 71.0 (t), 70.2 (t) ppm. IR (neat) 1597, 1503, 1231, 1147, 846, 703 cm$^{-1}$. MS (ES$^+$): 230 [M+H]$^+$. HRMS calcd for C$_{14}$H$_{13}$FN = 230.0981, found 230.0965.

**Compounds 2h and 2h'.** Flash chromatography (Pentane/EtOAc, 1:0 to 6:4), 1:1 ratio of 2h and 2h'. $^1$H NMR (CDCl$_3$) $\delta$ 8.22-8.18 (m, 4H), 7.47 (dd, $J$ = 7.9, 2.0 Hz, 2H), 7.43-7.37 (m, 7H), 7.32 (d, $J$ = 8.7 Hz, 2H), 6.95-6.89 (m, 4H), 5.04 (d, $J$ = 14.0 Hz, 2H), 4.97 (d, $J$ = 14.0 Hz, 2H), 3.83 (s, 3H), 3.82 (s, 3H) ppm. $^{13}$C NMR (CDCl$_3$) $\delta$ 161.0 (s), 160.0 (s), 133.9 (d), 133.97(d), 133.3 (s), 130.8 (d), 130.5 (d), 130.3 (d), 129.1 (d), 128.9 (d), 128.8 (d), 128.5 (d), 128.3 (d), 125.1 (s), 123.3 (s), 114.3 (d), 113.7 (d), 70.6 (t, x2), 55.2 (q) ppm. IR (neat) 1611, 1513, 1303, 1250, 1176, 1030, 903, 724 cm$^{-1}$. MS (ES$^+$): 242 [M+H]$^+$. HRMS calcd for C$_{15}$H$_{16}$NO$_2$ [M+H]$^+$ 242.1181, found 242.1171.
**Compound 2i.** Flash chromatography (CH$_2$Cl$_2$/MeOH, from 1:0 96:4, silica deactivated with aqueous NH$_4$OH). $^1$H NMR (CDCl$_3$) $\delta$ 7.97 (dd, $J = 7.3$, 1.6 Hz, 2H), 7.49-7.38 (m, 3H), 7.30-7.22 (m, 3H), 7.06 (dd, $J = 7.9$, 1.6 Hz, 1H), 5.06 (d, $J = 15.5$ Hz, 1H), 4.60 (d, $J = 15.5$ Hz, 1H), 4.17-4.11 (m, 1H), 3.79-3.66 (m, 2H), 2.84 (dt, $J = 16.4$, 5.0 Hz, 1H) ppm. $^{13}$C NMR (CDCl$_3$) $\delta$ 131.1 (s), 129.9 (s), 129.1 (d), 129.0 (d), 128.5 (d), 127.5 (d), 126.7 (d), 126.2 (d), 120.5 (d), 71.3 (t), 65.5 (t), 26.2 (t) ppm. IR (neat) 1489, 903, 726 cm$^{-1}$. MS (ES$^+$): 226 [M+H]$^+$. 

**Compound 2j.** Could not be purified by chromatography, NMR provided for the crude. $^1$H NMR (CDCl$_3$) $\delta$ 7.86 (d, $J = 8.0$ Hz, 2H), 7.48 (t, $J = 7.8$ Hz, 2H), 7.31-7.21 (m, 4H), 7.14 (d, $J = 8.0$ Hz, 2H), 4.07 (t, $J = 11.0$ Hz, 2H), 3.35-3.30 (m, 2H), 2.67 (d, $J = 8.4$ Hz, 2H), 2.56-2.47 (m, 2H), 2.15 (m, 1H), 1.50-1.43 (m, 2H) ppm. MS (ES$^+$): 268 [M+H]$^+$. HRMS calcld for C$_{18}$H$_{22}$NO [M+H]$^+$ 268.1701, found 268.1699.

**Compound 3a.** Flash chromatography (Pentane/EtOAc from 1:0 to 9:1). $^1$H NMR (CDCl$_3$) $\delta$ 7.53-7.50 (m, 3H), 7.39-7.35 (m, 2H), 7.33-7.23 (m, 7H), 7.18-7.11 (m, 4H), 7.09 (td, $J = 7.5$, 1.5 Hz, 1H), 7.03 (td, $J = 7.5$, 1.5 Hz, 1H), 6.97 (dd, $J = 7.5$, 1.5 Hz, 1H), 5.24 (s, 1H), 4.65 (d, $J = 13.0$ Hz, 1H), 4.31 (d, $J = 13.0$ Hz, 1H), 3.43-3.35 (m, 1H), 3.22-3.15 (m, 1H), 3.12-3.05 (m, 1H), 2.97-2.90 (m, 1H) ppm. $^{13}$C NMR (CDCl$_3$) $\delta$ 147.8 (s), 141.3 (s), 140.9 (s), 138.9 (s), 136.1 (s), 132.4 (s), 130.9 (s), 129.9 (d), 129.6 (d), 129.3 (d), 128.5 (d), 128.4 (d, x2), 127.8 (d), 127.6 (d), 127.4 (d), 126.9 (d), 126.8 (d), 125.6 (d), 125.4 (d), 110.3 (s), 63.0 (s), 36.8 (t), 32.9 (t) ppm. IR (neat) 1502, 1382, 872, 735 cm$^{-1}$. MS (ES$^+$): 416 [M+H]$^+$. 

**Compound 3e.** Flash chromatography (eluent Pentane/EtOAc from 1:0 to 94:6). $^1$H NMR (CDCl$_3$) $\delta$ 7.42 (dd, $J = 6.9$, 1.8 Hz, 2H), 7.30 (t, $J = 7.7$ Hz, 2H), 7.27-7.22 (m, 1H), 7.17-7.13 (m, 4H), 7.08 (dd, $J = 7.3$, 1.6 Hz, 1H), 7.05 (dd, $J = 3.3$, 1.7 Hz, 1H), 7.01 (dd, $J = 7.3$, 1.7 Hz, 1H), 6.97 (dd, $J = 7.6$, 1.9 Hz, 1H), 5.26 (s, 1H), 3.83 (quint, $J = 6.6$ Hz, 1H), 3.45-3.38 (m, 1H), 3.23-3.09 (m, 2H), 3.02-2.95 (m, 1H), 2.16-2.03 (m, 2H), 1.97-1.74 (m, 4H), 1.70-1.61 (m, 2H) ppm. $^{13}$C NMR (CDCl$_3$) $\delta$ 147.6 (s), 142.1 (s), 140.9 (s), 138.8 (s), 132.6 (s), 130.9 (d), 129.9 (d), 129.5 (d), 128.5 (d), 128.4 (d), 127.7 (d), 127.3 (d), 126.9 (d), 126.7 (d), 125.6 (d), 125.4 (d), 110.2 (s), 77.7 (d), 68.0 (d), 36.9 (t), 33.0 (t), 31.2 (t), 30.3 (t), 24.8 (t), 24.7 (t) ppm. IR (neat) 1674, 1493, 1451, 1029, 905, 729 cm$^{-1}$. MS (ES$^+$): 394 [M+H]$^+$. HRMS calcld for C$_{28}$H$_{32}$NO [M+H]$^+$ 394.2171, found 394.2183.
5. References


6. Copies of \(^1\)H and \(^{13}\)C NMR Spectra

[Image of NMR spectrum for Compound 2a]