Microwave-Assisted Synthesis of Isonitriles: A General Simple Methodology

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Supporting Information

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Experimental Protocols

All reagents and solvents were obtained from Aldrich. All conventional reactions were run under dry nitrogen in flame-dried glassware using standard techniques unless otherwise stated. Thin-layer chromatography (TLC) analysis was performed with Merck Kieselgel 60 F254 plates and visualized using UV light, KMnO_4 staining. Melting points were determined in open capillary tubes on a Buchi apparatus (Buchi B-540) and are uncorrected. The experiments were performed using using a flask equipped with a reflux condenser mounted outside the apparatus. FT-IR spectra were recorded as KBr pellets on Bruker Equinox 55 spectrometer (value in cm^{-1}). Analytical HPLC analysis was performed with a Shimadzu analytical instrument (Shimadzu LC-2010), equipped with UV diode-array detector (Shimadzu SPD-M10AVP). Analytical HPLC was performed using a reversed phase Nucleosil C18 (5 μm) column (250 x 2 mm) (Grom, Herremberg, Germany). Solvents used for HPLC elution were (A) H_2O containing 0.1% TFA, (B) methanol. Elution was performed in the isocratic condition of 20% A and 80% B over the course of 40 min at a flow rate of 0.8 mL/min (220 nm detection). ^1H NMR (300 MHz) and proton-decoupled ^{13}C NMR (75.4 MHz) Fourier transform spectra were obtained with Varian VXR-300 spectrometer in CDCl_3 using CDCl_3 solutions and TMS as an internal standard. Chemical shifts are expressed in (δ) ppm values, and coupling constants are expressed in Hertz (Hz). The following abbreviations are used: s (singlet), d (doublet), m (multiplet) and further qualified as a (apparent), br (broad), brs (broad singlet), c (complex). Elemental analyses were performed on a Perkin-Elmer 420 B analyzer.

Some products, in particular, 1-isocyanopentane, *tert*-butylisocyanide,¹ 1-isocyanocyclohex-1-ene, and benzylisocyanide¹ were identified by comparison with commercial products (Aldrich).

General Procedure

Method A. The procedure for the preparation of (S)-methyl 2-isocyano-3-methylbutanoate (entry **9**, Table 1) is representative for all aliphatic cases. In a CEM designed 10 mL pressure-rated reaction vial equipped with a magnetic stirrer, pyridine (120 μ L, 1.52 mmol), CH₂Cl₂ (5.0 mL), (S)-methyl 2-formamido-3-methylbutanoate² [0.12 g, 0.76 mmol, $\{[\alpha]_D^{25} -27.5$ (c 1.7, EtOH)³}, and TCT, (0.14 g, 0.76 mmol) were added sequentially at 0 °C while stirring. The vial was sealed and immediately irradiated at 100 °C (by modulation of the power) for 10 min in a self-tuning single mode CEM DiscoverTM Focused Synthesizer. The solution was cooled rapidly at room temperature by passing compressed air through the microwave cavity for 1 min, then diluted with CH₂Cl₂ and washed with a saturated solution of KHSO₄. Removal of the solvent in vacuo, gave chemically pure (S)-methyl 2-isocyano-3-methylbutanoate **9** (0.086 g, 0.61 mmol, 80% yield).

(1) Walborsky, H. M.; Niznik, G. E. *J. Org. Chem.* **1972**, 37, 187.

(2) De Luca, L.; Giacomelli, G.; Porcheddu, A.; Salaris, M. *Synlett*, **2004**, 2570.

(3) Chancellor, T.; Morton, C. *Synthesis* **1994**, 1023; Giard, T.; Bénard, D.; Plaquevent, J. C. *Synthesis* **1998**, 297.

Method B. The preparation of 1-isocyano-4-methoxybenzene is representative for the aromatic isonitriles. To *N*-(4-methoxyphenyl)formamide (0.08 g, 0.53 mmol) contained in a CEM 10 mL pressure-rated vial equipped with a magnetic stirrer, TEA (240 μ L, 1.75 mmol), TCT (0.29 g, 1.59 mmol), and CH_2Cl_2 (5.0 mL) were added sequentially at 0°C. The vial was sealed, immediately irradiated at 50 °C (by modulation of the power) for 3 min. The solution was cooled rapidly at room temperature by passing compressed air through the microwave cavity for 1 min, then diluted with CH_2Cl_2 and washed with a saturated solution of KHSO_4 . Removal of the solvent under vacuum, gave 0.053 g of chemically pure 1-isocyano-4-methoxybenzene **12** (75% yield).⁴

(4) Hammick, D. L.; New, R. C. A.; Sidgwick, N. V.; Sutton, L. E. *J. Chem. Soc* **1930**, 1876.

Characterization Data

2

2: 80% yield. ^1H NMR (CDCl_3): δ (ppm) 3.48-3.40 (m, 1H), 3.30-3.23 (m, 1H), 1.59-1.53 (m, 2H), 1.30-1.22 (m, 8H), 0.86 (m, 3H). ^{13}C NMR (CDCl_3): δ (ppm) 161.2, 41.0, 31.5, 29.4, 28.8, 26.7, 22.4, 13.8. Anal. Calcd for $\text{C}_8\text{H}_{15}\text{N}$: C, 76.74; H, 12.07; N, 11.19. Found: C, 76.71; H, 12.19; N, 11.30.

6

6: 95% yield. IR 3061, 3026, 2929, 2859, 2148 (NC), 1663, 1539, 747. ^1H NMR (CDCl_3): δ (ppm) 7.28-7.13 (m, 5H), 3.31-3.24 (m, 1H), 3.19-3.13 (m, 1H), 2.66-2.59 (m, 2H), 1.87-1.80 (m, 2H). ^{13}C NMR (CDCl_3): δ (ppm) 161.43, 141.08, 128.4, 128.2, 125.9, 37.6, 32.9, 30.9. (ESI + ve ion). Calcd for $\text{C}_{10}\text{H}_{11}\text{N}$: 145.1 [(M+H) $^+$]. Found: 146.3. Anal. Calcd for $\text{C}_{10}\text{H}_{11}\text{N}$: C, 82.72; H, 7.64; N, 9.65. Found: C, 82.81; H, 7.69; N, 9.53.

7

7¹: 90% yield. Bp 93-95°C (0.05 mm).⁵ ¹H NMR (CDCl₃): δ (ppm) 7.28-7.12 (m, 2H), 6.82-6.77 (m, 2H), 4.61 (m, 2H), 3.72 (s, 3H). ¹³C NMR (CDCl₃): δ (ppm) 163.9, 161.0, 131.9, 130.1, 114.2, 55.5, 46.2. IR (neat) 3038, 3004, 2956, 2932, 2149, 1666, 1513, 1249, 818. Anal. Calcd for C₉H₉NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.41; H, 6.25; N, 9.43.

8

8: 90% yield. IR: (neat) 2999, 2924, 2850, 2147, 1674, 1590, 1516, 1261, 1025. ¹H NMR (CDCl₃): δ (ppm) 6.72 (m, 3H), 3.84 (s, 6H), 3.63 (t, J = 7 Hz, 2H), 2.71 (t, J = 7 Hz, 2H). ¹³C NMR (CDCl₃): δ (ppm) 156.5, 150.1, 146.5, 132.9, 122.2, 115.7, 113.1, 56.8, 56.1, 45.7, 37.1. Anal. Calcd for C₁₁H₁₃NO₂: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.01; H, 6.89; N, 7.24.

(5) 90-95°C (0.05 mm) (Ugi, I.; Fetzer, U.; Eholzer, U.; Knapfer, H.; Offermann, K. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 472).

9

9: $[\alpha]_D^{20} +5.36$ (*c* 1.7, CHCl₃), [lit.⁶ $[\alpha]_D^{20} +5.5$ (*c* 3.4, CHCl₃); IR (neat) 2985, 2145, 1750. ¹H NMR (CDCl₃): δ (ppm) 4.27 (d, 1H), 3.93 (s, 3H), 2.03-2.74 (m, 1H), 1.09 (dd, 6H). ¹³C NMR (CDCl₃): δ (ppm) 172.5, 160.8, 62.8, 53.2, 26.4, 18.9. Anal. Calcd for C₇H₁₁NO₂: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.50; H, 7.90; N, 9.81.

10

10: 86% yield. Bp 85-87°C (50 mm). IR (neat): 2130 (NC), 1745. ¹H NMR (CDCl₃): δ (ppm) 7.40 (m, 1H), 6.31 (m, 1H), 5.90 (s, 1H), 4.45 (s, 2H). ¹³C NMR (CDCl₃): δ (ppm) 161.4, 151.1, 142.1, 110.3, 107.4, 44.5. Anal. Calcd for C₆H₅NO: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.35; H, 4.79; N, 13.01.

(6) Kamer, P. C. J.; Cleij, M. C.; Nolte, R. J. M.; Harada, T.; Hezemans, A.; Drenth, W. *J. Am. Chem. Soc.* **1988**, *110*, 1581.

11

11: 1190% yield. Bp 50-52°C (11 mm).⁷ ¹H NMR (CDCl₃): δ (ppm) 7.40-7.32 (m, 2H), 7.20-7.08 (m, 3H). Anal. Calcd for C₇H₅N: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.60; H, 4.92; N, 13.44.

12

12: 75% yield. Bp 114-116° (5 mm), mp 30°C.⁸ IR (neat) 3051, 2988, 2123, 1616, 1635, 1613, 1487, 1245, 1111, 1028. ¹H NMR (CDCl₃): δ (ppm) 7.55-7.52 (ad, 2H), 6.90-6.87 (ad, 2H), 3.82 (s, 3H). ¹³C NMR (CDCl₃): δ (ppm) 166.6, 163.3, 129.0, 122.9, 116.3, 55.7.

(7) Bp: 50-52 (11 mm). Weber, W. P.; Gokel, G *Tetrahedron Lett.* **1972**, 1637.

(8) Hammick, D. L.; New, R. C. A.; Sidgwick, N. V.; Sutton, L. E. J. Chem, Soc 1930, 1876.

13

13: 90% yield. IR (neat) 2148 (NC). ^1H NMR (CDCl_3): δ (ppm) 7.95-7.92 (ad, 2H), 7.50-7.47 (ad, 2H). ^{13}C NMR (CDCl_3): δ (ppm) 163.2, 140.6, 127.8, 126.4, 119.7, 118.1. Anal. Calcd for $\text{C}_8\text{H}_4\text{F}_3\text{N}$: C, 56.15; H, 2.36; N, 8.19. Found: C, 56.22; H, 2.43; N, 8.09.

14

14: 92% yield. IR (neat): 2143. ^1H NMR (CDCl_3): δ (ppm) 8.3 (d, 2H), 6.78 (d, 2H). ^{13}C NMR (CDCl_3): δ (ppm) 164.7, 155.8, 135.3, 130.1, 122.5. Anal. Calcd for $\text{C}_7\text{H}_4\text{N}_2\text{O}_2$: C, 56.76; H, 2.72; N, 18.91. Found: C, 56.62; H, 2.83; N, 18.88.

15

15: 90% yield. ^1H NMR (CDCl_3): δ (ppm) 8.48 (as, 1H), 7.80-7.74 (ad, 2H), 7.23-7.20 (ad, 2H), 2.49 (s, 3H). ^{13}C NMR (CDCl_3): δ (ppm) 163.3, 148.6, 137.3, 132.3, 127.5, 124.6, 116.4, 13.5. Anal. Calcd for $\text{C}_8\text{H}_6\text{N}_2\text{O}_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.14; H, 3.79; N, 19.81.