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Supplementary Information

Electroorganic Synthesis of Nitriles via Halogen-free Domino Oxidation-Reduction Sequence

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General remarks

All electrolyses were carried out in an undivided 25 mL-beaker type cell. The anode was made of isostatic graphite (SGL Carbon, Bonn, Germany), the cathode was made of lead. The oximes and methyltriethylammonium sulfate (MTES) were synthesized according to procedures previously described.¹ All other chemicals were obtained from commercial sources and were used without further purification. The yields refer to isolated compounds and purity was determined by ¹H NMR. The column chromatography was performed on silica gel 60 (0.04–0.063 mm, Macherey-Nagel & Co GmbH, Düren, Germany). ¹H NMR and ¹³C NMR spectra were recorded at 22 °C (±1 °C) by using AV 300 and AV II 400 instruments (both Bruker Analytik GmbH, Karlsruhe, Germany). The chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as external standard and traces of CHCl₃ in the corresponding solvent, respectively. Gaschromatographic measurements were carried out with a GC-2010 instrument (Shimadzu, Japan) using a HP-5 column (Agilent Technologies, USA; length: 30 m, inner diameter: 0.25 mm, carrier gas: hydrogen). GC-MS were performed using a GC-2010 (Shimadzu, Japan) with a HP-1 column (Agilent Technologies, USA; length: 30 m, inner diameter: 0.25 mm, carrier gas: hydrogen) connected to a GCMS-QP2010 instrument (Shimadzu, Japan). Melting points were determined using a Stuart Melting Point Apparatus SMP3 (Bibby Sterilin, Stone, United Kingdom). FD-MS spectra were recorded with a MAT 95 instrument, 70 eV (Thermo Finnigan, Bremen, Germany). High resolution mass spectrometry (HRMS) was performed with a QTof Ultima 3 instrument (Waters Micromass, Milford, Massachusetts, USA).

Experimental section

Electrolysis protocol A

A solution of 2,4,6-trimethylbenzaldoxime (0.163 g, 0.999 mmol) and MTES (0.116 g, 0.510 mmol) in acetonitrile (5 mL) was electrolyzed at ambient temperature applying a current density of 10 mA/cm². After the application of 1 F of charge, a sample of the reaction mixture (50-100 μ L) was filtered through silica and washed with EtOAc and the resulting solution was analyzed by GC and GC-MS, respectively. The described procedure was performed until the desired amount of charge in total has been applied.

Electrolysis protocol B

A solution of 2,4,6-trimethylbenzaldoxime (1.029 g, 6.305 mmol) and MTES (0.576 g, 2.534 mmol) in acetonitrile (25 mL) was electrolyzed at 22 °C with a current density of 10 mA/cm^2 . After the application of 2.5 F of charge, an excess of p-toluenesulfonyl hydrazide (0.128 g, 0.687 mmol) was added until no aldehyde appeared anymore on TLC detected by staining with 2,4-dinitrophenylhydrazine. The solution was evaporated and the crude product was purified by column chromatography (cyclohexane/EtOAc 20:1) to yield a white crystalline solid (M.p.: 52 °C) as product (0.740 g, 5.096 mmol, 81%).



2,4,6-Trimethylbenzonitrile² (3a): ¹H NMR (300 MHz, CDCl₃): $\delta = 6.93$ (s, 2H), 2.47 (s, 6H), 2.32 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): $\delta = 142.9$, 142.1, 128.3, 117.8, 110.4, 21.7, 20.7. HR-MS (ESI): m/z calcd for C₁₀H₁₁N+Na⁺ 168.0789, found 168.0803.



2,6-Dimethylbenzonitrile³ (**3b**): The electrolysis protocol B was followed using 2,6-dimethylbenzaldoxime (1.038 g, 6.957 mmol) as substrate applying 2.6 F of charge. Purification by column chromatography (cyclohexane/EtOAc 20:1) yielded the product (0.663 g, 73%) as white crystalline solid (M.p.: 89 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.34 (t, *J* = 7.7, 2H), 7.11 (d, *J* = 7.7, 3H), 2.53 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ = 142.2, 132.2, 127.4, 117.4, 113.4, 20.9. MS (FD): *m*/*z* = 131 (100), 132 (10). HR-MS (ESI): *m*/*z* calcd for C₉H₁₀N 132.0813, found 132.0835.



2,4,6-Trimethoxybenzonitrile⁴ (3c): The electrolysis protocol B was followed using 2,4,6-trimethoxybenzaldoxime as substrate. Purification after column chromatography (2:1 \rightarrow 3:2) yielded the product (0.710 g, 75%) as yellow crystalline solid (M.p.: 144 °C). ¹H NMR (300 MHz, CDCl₃): $\delta = 6.05$ (s, 2H), 3.87 (s, 6H), 3.85 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): $\delta = 165.4$, 163.9, 114.7, 90.4, 84.1, 56.2, 55.8. MS (FD): m/z = 193 (100), 194 (9). HR-MS (ESI): m/z calcd for C₁₀H₁₁NO₃+Na⁺ 216.0637, found 216.041.



4-Methoxybenzonitrile⁴ (**3d**): The electrolysis protocol B was followed using 4-methoxybenzaldoxime (1.025 g, 6.779 mmol) as substrate. Purification by column chromatography (cyclohexane/EtOAc 10:1 \rightarrow 7:1) yielded the product (0.482 g, 53%) as white crystalline solid (M.p.: 56 °C). ¹H NMR (300 MHz, CDCl₃): δ = 7.57 (d, 2H, *J* = 9.0), 6.94 (d, 2H, *J* = 9.0), 3.85 (s, 3H). ¹³C NMR (75 MHz, CDCl₃): δ = 162.9, 134.1, 119.3, 114.8, 104.0, 55.6. HR-MS (ESI): *m/z* calcd for C₈H₇NO+Na⁺ 156.0245, found 156.0433.



2,6-Difluorobenzonitrile⁵ (**3e**): The electrolysis protocol B was followed using 2,6-difluorobenzaldoxime (1.038 g, 6.607 mmol) as substrate applying 2.1 F. The solvent was removed and the residue filtered through silica (cyclohexane/EtOAc 3:1). After evaporation, the crude product was purified by bulb-to-bulb distillation (20 mbar, 100 °C) to yield the product as a yellow oil (0.435 g, 47%). ¹H NMR (300 MHz, CDCl₃): δ = 7.61 (tt, *J* = 8.6, 6.4, 1H), 7.12 - 7.01 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ = 163.5 (d, *J* = 261.8), 135.7 (t, *J* = 10.1), 112.3 (d, *J* = 23.2), 109.3, 92.7 (t, *J* = 19.0). MS (FD): *m*/*z* = 139 (100), 140 (7). HR-MS (ESI): *m*/*z* calcd for C₇H₃NF₂+Na⁺ 162.0131, found 162.0150.



2,6-Dichlorobenzonitrile⁶ (**3f**): The electrolysis protocol B was followed using 2,6-dichlorobenzaldoxime (1.027 g, 5.405 mmol) as substrate. After purification by column

chromatography, the crude product was recrystallized from EtOH to yield the product (0.383 g, 41%) as white crystalline solid (M.p.: 143 °C). ¹H NMR (300 MHz, CDCl₃) $\delta = 7.52 - 7.40$ (m, 3H). ¹³C NMR (75 MHz, CDCl₃) $\delta = 138.6$, 134.0, 128.3, 114.5, 113.5. MS (FD): m/z = 171 (100), 172 (7), 173 (63), 174 (4), 175 (9). HR-MS (ESI): m/z calcd for C₇H₃N³⁵Cl₂+Na⁺ 193.9540, found 193.9535.



1-Naphthonitrile⁷ (**3g**): The electrolysis protocol B was followed using 1-naphthaldoxime (1.034 g, 6.040 mmol) as substrate. Purification by column chromatography (cylcohexane/EtOAc 10:1) yielded the product (0.369 g, 40%) as yellow solid. ¹H NMR (400 MHz, CDCl₃): δ = 8.23 (dd, *J* = 8.3, 1.1, 1H), 8.07 (d, *J* = 8.3, 1H), 7.94 – 7.88 (m, 2H), 7.69 (ddd, *J* = 8.3, 6.9, 1.3, 1H), 7.62 (ddd, *J* = 8.2, 6.9, 1.3, 1H), 7.52 (dd, *J* = 8.4, 7.2, 1H). ¹³C NMR (101 MHz, CDCl₃): δ = 133.4, 133.0, 132.7, 132.4, 128.8, 128.7, 127.6, 125.2, 125.0, 117.9, 110.3. HR-MS (ESI): *m/z* calcd for C₁₁H₇N+Na⁺ 176.0476, found 176.0468.



2-Methoxy-1-naphthonitrile⁸ (**3h**): The electrolysis protocol B was followed using 2-Methoxy-1-naphthaldehyde oxime (1.009 g, 5.015 mmol), except instead of pure acetonitrile, acetonitrile/DMSO 9:1 (v:v) was used as solvent. Purification by column chromatography (cyclohexane/EtOAc 5:1) yielded the product (0.505 g, 55%) as orange crystalline solid (M.p.: 98 °C). ¹H NMR (400 MHz, CDCl₃): δ = 8.08 (dd, *J* = 8.4, 0.9, 1H), 8.02 (d, *J* = 9.2, 1H), 7.82 (d, *J* = 8.2, 1H), 7.63 (ddd, *J* = 8.3, 6.9, 1.3, 1H), 7.44 (ddd, *J* = 8.1, 6.9, 1.1, 1H), 7.26 (d, *J* = 9.2, 1H), 4.06 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ = 161.7,

135.1, 133.7, 129.3, 128.6, 128.1, 125.2, 124.1, 115.8, 112.1, 95.3, 56.7. HR-MS (ESI): m/z calcd for $C_{12}H_9NO+H^+$ 184.0762, found 184.0775.

Formation of nitrile oxide



The electrolysis protocol A was followed.

GC-MS









Screening on cathode material



The electrolysis protocol A was followed. The gas chromatograms are depicted using different cathode materials (lead, stainless steel (A5), nickel, platinum, and boron-doped diamond). Lead turned out as an excellent cathode showing the highest selectivity with regard to the nitrile. In presence of the other electrode materials, the reaction mixtures consisted mainly of unconsumed nitrile oxide and only a small amount of the desired nitrile. Additionally, undefined side-products were formed which implies that the deoxygenation is hindered at stainless steel (A5), nickel, platinum, and boron-doped diamond.

Cathode: lead



Cathode: stainless steel (A5)



Cathode: nickel



Cathode: platinum



Cathode: boron-doped diamond



Dehalogenation reaction

The electrolysis protocol A was followed applying 3 F of charge for 2,6dichlorobenzaldoxime and 2 F of charge for 2,6-dibromobenzaldoxime.



GC-MS



Spectrum

Line#:1 R.Time:6.5(Scan#:303) MassPeaks:17 RawMode:Single 6.5(303) BasePeak:137(7295) BG Mode:None m/z Line#:2 R.Time:8.2(Scan#:503) MassPeaks:32 RawMode:Single 8.2(503) BasePeak:171(14278) BG Mode:None

m/z



GC-MS



NMR spectra



¹H NMR (300 MHz, CDCl₃)







¹H NMR (300 MHz, CDCl₃)









References

- (a) L. F. Fieser and J. L. Hartwell, J. Am. Chem. Soc., 1938, 60, 2555; (b) M. L. McIntosh, M. R. Naffziger, B. O. Ashburn, L. N. Zakharov and R. G. Carter, Org. & Biomol. Chem., 2012, 10, 9204; (c) B. Elsler, D. Schollmeyer, K. M. Dyballa, R. Franke and S. R. Waldvogel, Angew. Chem. Int. Ed., 2014, 53, 4979.
- 2. W. Zhou, J. Xu, L. Zhang and N. Jiao, Org. Lett., 2010, 12, 2888.
- 3. P. Y. Yeung, C. M. So, C. P. Lau and F. Y. Kwong, Org. Lett., 2011, 13, 648.
- 4. W. Zhou, L. Zhang and N. Jiao, Angew. Chem. Int. Ed., 2009, 48, 7094.
- 5. S. Ushijima, K. Moriyama and H. Togo, Tetrahedron, 2011, 67, 958.
- 6. P. Anbarasan, H. Neumann and M. Beller, *Chem. Eur. J.*, 2011, **17**, 4217.
- 7. M. Hatsuda and M. Seki, *Tetrahedron*, 2005, **61**, 9908.
- 8. S. Ushijima, K. Moriyama and H. Togo, Tetrahedron, 2012, 68, 4588.