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

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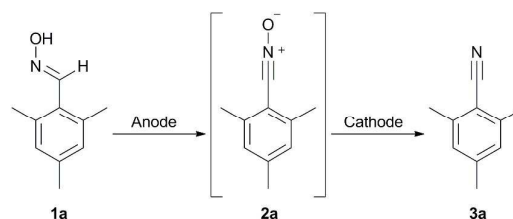
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A direct electroorganic sequence yielding nitriles from oximes in undivided cells is reported. Despite the fact that intermediate nitrile oxides might be formed, the method is viable to prepare benzonitriles without substituents ortho to the aldoxime moiety. This constant current method is easy to perform for a broad scope of substrates and employs common electrodes, such as graphite and lead.

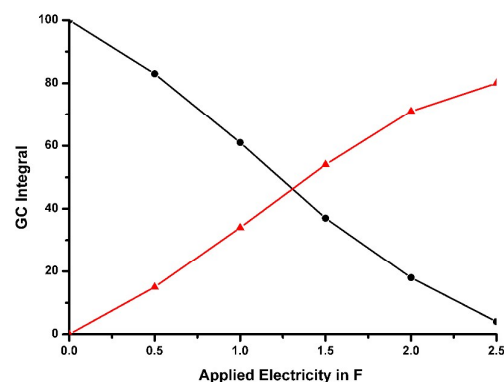
In the past, the formation of nitriles from oximes has been realized by the use of harsh dehydration agents such as phosphorous pentoxide, thionyl chloride, benzenesulfonyl chloride, acetic anhydride, and many others.^{1,2} Unfortunately, these strongly corrosive agents have to be used stoichiometrically or even in excess. This results in unattractive waste generation and considerable safety issues upon work up. Recently, catalytic approaches have emerged which reduce the waste generation significantly.³ However, recycling of the expensive and toxic catalysts still remains an issue. Consequently, new methods for the aldoxime dehydration are highly desired.

Electrochemistry has become an attractive alternative to conventional methods in organic synthesis, since only electricity is applied which might even originate from renewable resources, and therefore no reagent waste is produced.⁴ Shono *et al.* reported an electrochemical protocol to generate nitriles from oximes with halogenides as a mediator.⁵ However, such halogen species cause corrosion at the precious platinum electrodes.^{6,7} Additionally, low current yields make this protocol in particular unattractive. We report a direct, halogen-free procedure to generate nitriles from oximes by the application of inexpensive and easily available electrode materials.



Scheme 1 Transformation of mesitylaldoxime to mesitylnitrile

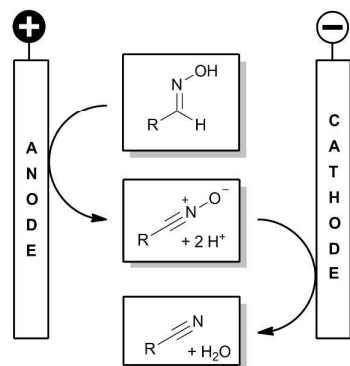
We chose mesitylaldoxime (**1a**) as test substrate. Within the course of transformation we observe stable nitrile oxide as intermediate (**2a**, Scheme 1). Initially, we investigated the anodic reaction using methyltriethyl ammonium methylsulfate (MTES) in acetonitrile as electrolyte. Graphite and glassy carbon were tested as carbon anode materials at room temperature. Glassy carbon served as cathode material in both cases. Graphite turned out to be an excellent anode leading to almost quantitative consumption of the starting material upon application of 2.5 F (Fig. 1).

Fig 1. Transformation of mesitylaldoxime (black curve) at graphite to intermediate nitrile oxide **2a** (red curve) in the course of electrolysis.

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Scheme 2 Domino oxidation-reduction sequence

However, the conversion at glassy carbon electrodes was poor. Only the intermediate nitrile oxide was formed, indicating a possible deactivation of the cathodic surface. It turned out that the deoxygenation is not promoted. As outlined, the intermediate was observed and identified via GC-MS. The anodic conversion leads to nitrile oxide which is the same intermediate as in the halogenide-mediated electrolysis by Shono *et al.* Hence, we consider the transformation as a *domino oxidation-reduction sequence* with respect to the definition of domino reactions, since a stable intermediate is formed which in turn reacts without manipulating the reaction conditions to the final product (Scheme 2).⁸

Nevertheless, the key for the desired reaction sequence seemed to be the deoxygenation of nitrile oxide formed. Having some recent experience with lead electrodes and variations thereof,⁹ we tested lead, stainless steel (A5), nickel, platinum, and boron-doped diamond as cathode materials. Indeed, lead turned out within the screening (see SI for GC-MS data) as an excellent cathode material, whereas the deoxygenation was less favored compared to the other electrode materials. Surprisingly, platinum showed a very poor performance although it is known as the cathode material of choice for this particular deoxygenation reaction.⁵

Subsequently, the influence of temperature and current density was studied (Table 1). Performing the electrolysis at 22 °C proved to be an optimum concerning the temperature, whereas rising (50 °C) or lowering (0 °C) the temperature led to a drop in yield (entries 1 and 5). Investigating the current density rendered the best yields with 10 mA/cm² (entry 3), whereas lower (5 mA/cm²) or higher (20 mA/cm²) current densities resulted in decreased yields and selectivity, respectively (entries 2 and 4).

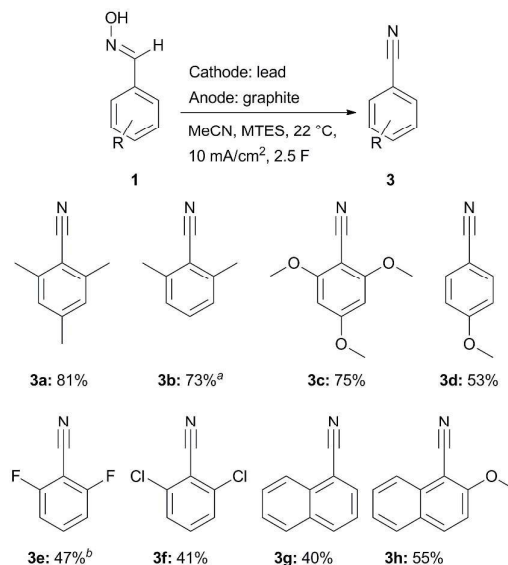
With the optimized electrolysis parameters in hand, we applied the method to a range of substrates in order to elucidate the scope of the reaction (scheme 3). These substrates vary in stability for the intermediately formed nitrile oxides as well as their preference for dimerization. Stabilization of reactive intermediates such as nitrile oxides can be achieved by bulky groups *ortho* to the aldoxime moiety.

Table 1 Optimization of reaction parameters

Entry	T [°C]	j [mA/cm ²]	Q [F]	Isolated yield ^a [%]
1	0	10	2.5	70(4)
2	22	5	2.5	63 (13)
3	22	10	2.5	81 (0)
4	22	20	2	77 (0)
5	50	10	2	66 (0)

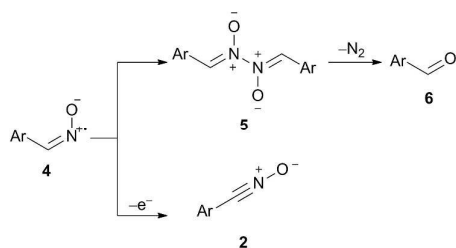
^a Yield of nitrile oxide determined by ¹H NMR in parentheses.

The best results were obtained with mesitylaldoxime (**1a**, 81%), closely followed by 2,4,6-trimethoxybenzaloxime (**1c**, 75%) and 2,6-dimethylbenzaloxime (**1b**, 73%). The unexpectedly low yield of the stabilized 2,6-dichlorobenzaloxime (**1f**, 41%) can be attributed to the competing dechlorination reaction (see SI for GC-MS data). The analogue debromination reaction was even more dominant and disadvantageous for the nitrile formation, whereas 2,6-difluorobenzaloxime (**1e**, 47%) was isolated in a higher yield due to the higher C,F bond strength (Ar-F: 526 kJ/mol; Ar-Cl: 400 kJ/mol; Ar-Br: 336 kJ/mol).¹⁰

Scheme 3 Scope ^a Full conversion after 2.6 F ^b Full conversion after 2.1 F

The stabilized 2-methoxy-1-naphthalaloxime (**1h**) resulted in a yield of 55%, whereas the partially stabilized naphthylaloxime (**1g**) led to a yield of 40%. Surprisingly the non-stabilized 4-methoxybenzonitrile (**3c**) was synthesized in an acceptable yield of 53%.

In general, stabilized substrates result in higher yields than non-stabilized congeners. However, the corresponding aldehyde was detected in all electrolyses by reaction monitoring



Scheme 4: Proposed pathway for the formation of aldehyde and nitrile oxide.

It is noteworthy, that the aldehyde formation was significantly higher for the non-stabilized substrates. It is known that aldioximes are oxidized in a divided cell to iminoxyl radicals which dimerize to aldazine bis-*N*-oxides (**5**, Scheme 4).¹¹

These aldazine bis-*N*-oxides react further to aldehydes by loss of nitrogen. We anticipate that the dimerization takes place prior to the deoxygenation of the intermediate. In contrast, only small amounts of aldehyde have been observed for stabilized substrates. We anticipate that the stability of the iminoxyl radical formed is based on the sterical hindrance and therefore, no or very little dimerization occurs. Hence the formation of nitrile oxide is favored which then undergoes deoxygenation at the cathode leading to the nitrile in high yield.

In conclusion, we developed a direct, halogen-free protocol for the synthesis of nitriles from oximes with yields up to 81% by applying inexpensive and readily available electrode materials such as lead¹² and graphite. This protocol is applicable for a range of substrates under constant current and ambient conditions. Furthermore, some insight into the mechanistic scenery can be deduced confirming a *domino oxidation-reduction sequence*.

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Notes and references

- (a) S. Gabriel and R. Meyer, *Ber. Dtsch. Chem. Ges.*, 1881, **14**, 2332; (b) C. Moureau, *Bull. Soc. Chim. Fr.*, 1894, **11**, 1067; (c) R. Scholl, *Monatsh. Chem.*, 1918, **39**, 231; (d) A. Werner and A. Piguet, *Ber. Dtsch. Chem. Ges.*, 1904, **37**, 4295; (e) L. Claisen and R. Stock, *Ber. Dtsch. Chem. Ges.*, 1891, **24**, 130; (f) O. L. Brady and G. P. McHugh, *J. Chem. Soc., Trans.*, 1923, **123**, 1190; (g) L. Claisen and O. Manasse, *Ber. Dtsch. Chem. Ges.*, 1887, **20**, 2194; (h) H. Metzger, in *Methoden der organischen Chemie*, ed. E. Müller, Thieme Verlag, Stuttgart, 4th edn., 1968, vol. X/4; (i) D. T. Mowry, *Chem. Rev.*, 1948, **42**, 189.
- (a) D. L. J. Clive, *J. Chem. Soc. D*, 1970, 1014; (b) H. G. Foley and D. R. Dalton, *J. Chem. Soc., Chem. Commun.*, 1973, 628; (c) V. P. Kukhar and V. I. Pasternak, *Synthesis*, 1974, **1974**, 563; (d) M. M. Rogic, J. F. Van Peppen, K. P. Klein and T. R.

- Demmin, *J. Org. Chem.*, 1974, **39**, 3424; (e) A. R. Katritzky, G.-F. Zhang and W.-Q. Fan, *Org. Prep. Proced. Int.*, 1993, **25**, 315.
- (a) S. H. Yang and S. Chang, *Org. Lett.*, 2001, **3**, 4209; (b) K. Ishihara, Y. Furuya and H. Yamamoto, *Angew. Chem. Int. Ed.*, 2002, **41**, 2983; *Angew. Chem.* 2002, **114**, 3109. (c) L. Yu, H. Li, X. Zhang, J. Ye, J. Liu, Q. Xu and M. Lautens, *Org. Lett.*, 2014, **16**, 1346.
- (a) H. Lund and O. Hammerich, eds., *Organic electrochemistry*, M. Dekker, New York, NY, 4th edn., 2001; (b) H. J. Schäfer, A. J. Bard and M. Stratmann, eds., *Organic electrochemistry*, Wiley-VCH, Weinheim, 2004, vol. 8; (c) E. Steckhan, T. Arns, W. R. Heineman, G. Hilt, D. Hoormann, J. Jörissen, L. Kröner, B. Lewall and H. Pütter, *Chemosphere*, 2001, **43**, 63; (d) S. R. Waldvogel and B. Elsler, *Electrochimica Acta*, 2012, **82**, 434; (e) R. Francke and R. D. Little, *Chem. Soc. Rev.*, 2014, **43**, 2492; (f) B. A. Frontana-Urbe, R. D. Little, J. G. Ibanez, A. Palma and R. Vasquez-Medrano, *Green Chem.*, 2010, **12**, 2099; (g) H. J. Schäfer, *C. R. Chim.*, 2011, **14**, 745.
- T. Shono, Y. Matsumura, K. Tsubata, T. Kamada and K. Kishi, *J. Org. Chem.*, 1989, **54**, 2249.
- Average pricing at London Metal Exchange (May 2015): 36716 \$/kg
- (a) J. A. Bittles and E. L. Littauer, *Corrosion Science*, 1970, **10**, 29; (b) E. Doná, M. Cordin, C. Deisl, E. Bertel, C. Franchini, R. Zucca and J. Redinger, *J. Am. Chem. Soc.*, 2009, **131**, 2827.
- (a) L. F. Tietze and U. Beifuss, *Angew. Chem. Int. Ed. Engl.*, 1993, **32**, 131; (b) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (c) L.-F. Tietze, G. Brasche and K. M. Gericke, *Domino reactions in organic synthesis*, Wiley-VCH, Weinheim, 2006.
- (a) C. Gütz, M. Selt, M. Bänziger, C. Bucher, C. Römelt, N. Hecken, F. Gallou, T. R. Galvão, S. R. Waldvogel, *Chem. Eur. J.* **2015**, in press, DOI: 10.1002/chem.201502064; (b) C. Edinger, J. Kulisch, S. R. Waldvogel, *Beilstein J. Org. Chem.* 2015, **11**, 294; (c) C. Edinger, S. R. Waldvogel, *Eur. J. Org. Chem.* **2014**, 5144.; (d) C. Edinger, V. Grimaudo, P. Broekmann, S. R. Waldvogel, *ChemElectroChem* 2014, **1**, 1018; J. Kulisch, M. Nieger, F. Stecker, A. Fischer, S. R. Waldvogel, *Angew. Chem. Int. Ed.* 2011, **50**, 5564; *Angew. Chem.* 2011, **123**, 5678.
- D. R. Lide, *CRC handbook of chemistry and physics*, 2006-2007, CRC Press, Boca Raton, FL, 87th edn., 2006.
- (a) V. A. Petrosyan, M. E. Niyazymbetov and E. V. Ul'yanova, *Russ. Chem. Bull.*, 1989, **38**, 1548; (b) V. A. Petrosyan, M. E. Niyazymbetov and E. V. Ul'yanova, *Russ. Chem. Bull.*, 1990, **39**, 546.
- Average pricing at London Metal Exchange (May 2015): 2 \$/kg.