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Electrochemical synthesis of nitriles from aldehydes using TEMPO as a mediator

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Abstract

A novel electrochemical route to generate nitriles from aldehydes under mild conditions using a catalytic amount of TEMPO (2,2,6,6-tetramethylpiperidinyl-l-oxy) as the mediator and hexamethyldisilazane as the nitrogen source in the presence of acetic acid has been developed. A variety of aromatic, heteroaromatic and aliphatic aldehydes have been converted to their corresponding nitriles in good to excellent yields. A plausible reaction mechanism is proposed based on the cyclic voltammetry, in situ FTIR and the identification of intermediates.

Keywords: Electrosynthsis; Nitriles; TEMPO; Aldehydes; Hexamethyldisilazane

1. Introduction

Nitriles are widely present in dyes, herbicides, agrochemicals and electronic materials. The nitrile group serves as an important intermediate in the organic synthesis of many pharmaceuticals [1-2]. Representative methods for the preparation of nitriles, such as Rosenmund–von Braun reaction [3], Sandmeyer reaction [4], and other approaches [5-9] involve reactions of halide/CN exchange. Dehydration of amides is another commonly used method. However, different dehydrating agents and high temperature are needed [10,11], and sometimes the scope of reaction is limited [12]. The synthesis of nitriles from aldoximes has also received much attention during the past decades and several methods have been reported [13,14]. Again, these methods suffer from the disadvantages of low yields and excess use of toxic reagents. Considering the accessibility of starting materials, the oxidations to nitriles from aldehydes, alcohols or acids have emerged as alternative synthetic strategies. Various nitrogen sources such as urea, ammonium and hydroxylamine have been employed [15-19]. Yet in most existing methods, transition metals are always needed. Therefore, there is a growing demand for a mild, efficient and versatile method for synthesis of nitriles from cheap substrates with commercially available oxidants or catalysts. During the compilation of the present work, Jinho Kim et al reported a nitroxyl/NOx catalyst system for the aerobic oxidative conversion of aromatic aldehydes to nitriles at 50° C [20].

Very recently, a successful attempt has been made to generate nitriles from aldehydes and hexamethyldisilazane (HMDS) mediated by an oxoammonium salt (4-acetylamino-2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate) [21]. However, 2.5 equiv. of oxoammonium salt are used as the oxidant and a stoichiometric amount of pyridine is

needed in this route. Additionally, the reaction is carried out in the solvent dichloromethane, which is considered to be environment-unfriendly [22]. 2,2,6,6-Tetramethylpiperidinyl-l-oxy (TEMPO), which can be easily oxidized to TEMPO⁺ (oxoammonium ion) via one-electron oxidation, is widely utilized in the oxidation of alcohols into their corresponding carbonyl compounds [23,24]. In our previous studies of alcohols oxidation, TEMPO was employed as the catalyst with oxygen [25,26] or electric current [27-30] as the terminal oxidant. Especially, electrochemical routes offer remarkable advantages such as good atom economy and non-pollution [31,32]. Chiba and Okimoto prepared nitriles from aldehydes by means of indirect electrooxidation using potassium iodide as the redox catalyst [33]. Unfortunately, when aldehydes such as nitrobenzaldehydes some and furan-2-carbaldehyde were used as substrates, no desired products could be obtained. Herein we report a novel electrochemical route to generate nitriles using a catalytic amount of TEMPO as the mediator and HMDS as the nitrogen source without toxic reagents under mild conditions (Scheme 1).



Scheme 1. Synthesis of nitriles from aldehydes

2. Experimental

Adamantane-1-carbaldehyde and benzofuran-2-carbaldehyde were prepared in our laboratory. Other chemicals were purchased from supplier and used without purification. Cyclic voltammetry was carried out using CHI6208 electrochemical workstation (CH Instrument, Inc. USA.) on an L-type platinum electrode in 0.1 M NaClO₄-CH₃CN at room temperature. A platinum sheet (3.0 cm^2) was employed as the counter electrode and Ag/Ag⁺ electrode (0.1 M AgNO₃ in acetonitrile) as the reference one.

Preparative electrolysis experiments were performed using 263A Potentiostat/Galvanostat (Princeton Applied Research). 0.1 M NaClO₄-CH₃CN solution (10 mL) containing aldehydes (1 mmol), TEMPO (0.1 mmol), HMDS (2.5 mmol) and AcOH (2.5 mmol) was electrolyzed with stirring in an undivided cell (30 mL) equipped with two platinum sheets as anode (1.5 cm²) and cathode (3.0 cm²) respectively at a constant potential of 1.5 V *vs* Ag/Ag⁺ (0.1 M AgNO₃ in acetonitrile). The electrode separation was 1 cm. When the reaction was finished, 10 mL of saturated Na₂SO₃ solution was added into the reaction mixture and stirred for 15 minutes. Then the mixture was extracted with CH₂Cl₂ (20 mL x 3). The organic layer was dried with anhydrous Na₂SO₄ and concentrated in a rotary evaporator. The products were obtained via purification of column chromatography and their structures were confirmed by ¹H NMR, ¹³C NMR and MS. NMR was performed on a Bruker Avance III spectrometer. GC-MS was performed on Thermo Trace ISQ instrument with TG 5MS capillary column.

In situ FTIR spectroscopic experiments were carried out on a Nicolet 670 FTIR spectrometer equipped with a MCT-A detector cooled by liquid nitrogen. The disk electrode of Pt (5 mm in diameter) was used as the working electrode. Two hundred interferograms with the resolution of 8 cm⁻¹ were collected and co-added into a single-beam spectrum.

N,N'-dibenzylidene-1-phenylmethanediamine

and

N,N'-bis(4-fluorobenzylidene)-1-(4-fluorophenyl)methanediamine (**B**) were prepared according to the literature [34]. A suspension of benzaldehydes (20 mmol), HMDS (40 mmol) and dried ZnCl₂ (10 mmol) in 60 mL CH₂Cl₂ was stirred for 12 h at room temperature. The reaction mixture was poured into 50 mL H₂O and extracted with CH₂Cl₂ (30 mL x 3). The extract was dried by anhydrous Na₂SO₄ and concentrated under reduced pressure. The resulting mixture was recrystallized with 20 mL hexane to give the desired products. The characterization data of **A** were in agreement with the reported values [34]. **B** was obtained as a white solid, mp: 75-76 °C. ¹H NMR (500 MHz, CDCl₃): δ =8.52 (2H, s), 7.85-7.88 (4H, m), 7.48-7.51 (2H, m), 7.06-7.15 (6H, m), 5.92 (1H, s). ¹³ C NMR (125 MHz, CDCl₃): 164.6 (d, *J*=250.3 Hz), 162.5 (d, *J*=244.8 Hz), 159.4, 137.5 (d, *J*=2.4 Hz), 132.1 (d, *J*=3.2 Hz), 130.7 (d, *J*=9.0 Hz), 128.8 (d, *J*=8.1 Hz), 115.8 (d, *J*=21.8 Hz), 115.4 (d, *J*=21.1 Hz), 91.8. HRMS (ESI), m/z, 353.1259, [MH⁺], calcd for C₂₁H₁₆F₃N₂, 353.1266.

3. Results and discussion

3.1. Cyclic voltammetry

Fig.1a shows the cyclic voltammogram of 0.01 M TEMPO dissolved in 0.1 M NaClO₄-CH₃CN solution, in which a typical redox couple is observed at 0.337 V and 0.180 V vs. Ag/Ag^+ . It corresponds to the one-electron redox reaction of nitroxyl radical and oxoammonium ion [31]. When

benzaldehyde was added to the solution, almost the same peak currents were observed in Fig. 1b which revealed benzaldehyde showed only a little voltammtric response on the bare Pt. When HMDS and AcOH were added, the oxoammonium ion reduction current disappeared and the anodic peak current was greatly enhanced as shown in Fig.1c. It demonstrated that TEMPO⁺ has reacted with benzaldehyde/HMDS/AcOH and been reduced to the hydroxylamine (TEMPOH) which could be oxidized in the following cycle.



Fig.1. Cyclic voltammograms of TEMPO (0.01 M) recorded at 50 mV s⁻¹ in 0.1M NaClO₄-CH₃CN solution (a) in the presence of (b) 0.1 M benzaldehyde and (c) 0.1 M benzaldehyde+ 0.25 M HMDS +0.25 M AcOH.

3.2. Preparative electrolysis

Inspired by cyclic voltammetric experiments, we were interested in developing an electrochemical method for the synthesis of benzonitrile from benzaldehyde. The optimized loading of HMDS was 2.5 equiv. according to a series of experiments. The requirement for excess HMDS might be due to the hydrolysis of HMDS. To avoid the unwanted oxidation of aldehydes to

carboxylic acids and the decomposition of acetonitrile on the bare Pt electrode [35], electrolysis experiments were carried out at different low potentials in our initial investigation. But a long reaction time was required. Thus the electrolysis was performed at a moderate potential (1.5 V *vs* Ag/Ag^+) to promote the reaction rate. Although the amount of TEMPO employed in the reaction should be as less as possible, the increase of the loading of TEMPO led to a shorter reaction time. It was proved that 0.1 equiv. of TEMPO could provide a reasonable conversion and an acceptable reaction rate.

As shown in Table 1, the scope of the electrochemical reaction was surveyed. Aromatic aldehydes could be converted smoothly to aromatic nitriles. Benzaldehyde readily reacted to form benzonitrile, and the GC yield of benzonitrile was high (99%, entry 1). The isolated yield of benzonitrile was relatively low (78%) because, due to its volatility, part of it was lost during the work up. Indeed, benzonitrile was detected in the solvent removed by rotary evaporation. The same applies to o- and p-fluorobenzonitriles (entries 8 and 9). In agreement with this observation, the isolated yield of non-volatile solid nitriles was very high (92-94%, entries 2, 14, and 17). Benzaldehydes bearing electron-withdrawing substituents 4-nitrobenzaldehyde, such as chlorobenzaldehyde (o-, m- and p-) and fluorobenzonitrile (o- and p-) underwent oxidative conversion to produce the corresponding nitriles in good to excellent yields (entries 2-5, 8 and 9), while it was difficult to fully convert bromobenzaldehydes (o- and m-) into bromobenzonitriles with 10 mol% of TEMPO (entrie 6 and 7). When a variety of tolualdehydes (o-, m- and p-) were submitted to this electrochemical transformation, the conversions were higher than 99%, and yields methylbenzonitriles of higher than 83% (entries 10-12). The reaction of were 4-(tert-butyl)benzaldehyde required a longer reaction time (15 h), and 4-(tert-butyl)benzonitrile

could be obtained in 87% yield (entry 13). However, 4-methoxybenzaldehyde needed an increased TEMPO loading and extended reaction time. A 98% conversion of 4-methoxybenzaldehyde with 92% isolated yield of 4-methoxybenzonitrile was achieved in 25 h by increasing the loading of TEMPO to 20 mol% (entry 14).

The successful conversion of 5-bromofuran-2-carbaldehyde and benzofuran-2-carbaldehyde to 5-bromofuran-2-carbonitrile and benzofuran-2-carbonitrile showed that this reaction could tolerate heteroaromatic substrates (entries 15 and 16). Aliphatic aldehydes were also investigated. The oxidation of adamantane-1-carbaldehyde generated adamantane-1-carbonitrile in 94% isolated yield (entry 17). When undecanal was used as the substrate, acceptable conversion could be achieved under our initial reaction conditions, but the yield of undecanenitrile was very poor. It was due to the self-aldol reaction of undecanal in the presence of HMDS [36]. Adding HMDS dropwise slowly into the reaction solution actually led to a higher yield, though the self-aldol reaction could not be completely avoided (entriey 18). For allylic aldehydes, such as cinnamaldehyde, this electrocatalytic oxidation system could provide 94% conversion with 64% isolated yield of cinnamonitrile (entry 19).

Entry	Substrate	Product	Time/h	Conversion/%	Yield ^[b] /%
1	С Н		15	>99	78 (99)
2	O O ₂ N H	O ₂ N	12	>99	92
3	CI O H	CI N	12	96	86

Table 1. Electrochemical synthesis of nitriles from aldehydes^[a]

4	CIH	CI	12	>99	86
5	CI H	CI N	12	>99	87
6	Br O H	Br	12	86	79
7	Br	Br	12	92	79
8	F H	F	12	>99	78 (92)
9	F O H	F	12	>99	77 (90)
10	ОН	N	12	>99	92
11	O H	N	12	>99	83
12	о Н	N	12	>99	90
13	Y H	N	15	95	87
14 ^[c]	мео	Meo	25	98	92
15	Br O CHO	Br	15	90	82
16	СНО	CN CN	15	91	80
17	онс	N	10	97	94
18 ^[d]	∽∽∽∽∽→ H O	N N	15	90	59
19 ^[d]	СНО	N	15	92	64

^[a] Reaction conditions: substrates (1 mmol), HMDS (2.5 equiv.), AcOH (2.5 equiv.), TEMPO (10 mol%) and NaClO₄ (0.1 M) in CH₃CN (10 mL). ^[b] Isolated yield. Values in parentheses were determined by GC internal standard method. ^[e]TEMPO (20 mol%). ^[d] HMDS was slowly added into the solution.

3.3. In situ FTIR investigation

Fig. 2 shows the in situ FTIR spectra of 0.1 M NaClO₄-CH₃CN solution containing 0.1 M benzaldehyde, 0.25 M HMDS and 0.01 M TEMPO. The reference potential was set at 0 mV and the potential was varied stepwise from 0 mV to 800 mV. At potentials of 200 mV and higher, positive and negative bands can be clearly seen.



Fig.2. In situ FTIR spectra collected on Pt electrode during the oxidation of 0.1 M benzaldehyde with 0.01 M TEMPO and 0.25 M HMDS in 0.1 M NaClO₄-CH₃CN solution.

The positive bands at 1703 cm⁻¹ and 1204 cm⁻¹ were ascribed to the C=O and C-C stretching vibrations of benzaldehyde respectively thus showing the consumption of benzaldehyde [37]. The negative band at 1626 cm⁻¹ was attributed to the N⁺=O stretching vibration of TEMPO⁺ [38]. Moreover, the C=N vibration of acetonitrile was found at 2260 cm⁻¹. ClO₄⁻ exhibited a characteristic absorption peak at 1119 cm⁻¹. In addition, another important signal, the negative-band at 2226 cm⁻¹, was detected as the C=N vibration of the major product benzonitrile. The negative bands at 1076 cm⁻¹ and 1261 cm⁻¹ were ascribed to asymmetric stretching of Si-O-Si and Si-CH₃ respectively [39,40].

3.4. Mechanism investigation

In an effort to gain insight into the plausible reaction mechanism, the reaction mixture was directly subjected to ¹H NMR analysis. It was found that besides protons of benzaldehyde and benzonitrile, several protons belonging to another compound could be observed within an hour. After comparison with the authentic product synthesized by reaction of benzaldehyde with HMDS catalysed ZnCl₂ [34], confirmed by that this compound we was N,N'-dibenzylidene-1-phenylmethanediamine (A). In addition, when 4-fluorobenzaldehyde was used the substrate, ¹H NMR analysis showed it was almost completely converted to as N,N'-bis(4-fluorobenzylidene)-1-(4-fluorophenyl)methanediamine (**B**) in an hour (Scheme 2a). **B** also synthesized (see Experimental section) and its electrooxidation did afford was 4-fluorobenzonitrile and 4-fluorobenzaldehyde. Thus, we infer that the N,N'-disubstituted methanediamines are the crucial intermediates for the current synthesis of benzonitriles.

With benzaldehyde as the model molecule, the overall reaction mechanism for the electrochemical synthesis of benzonitrile from benzaldehyde using TEMPO as the mediator is shown in Scheme 2b. Three benzaldehyde molecules can react with two HMDS molecules to give a N,N'-dibenzylidene-1-phenylmethanediamine molecule, which is oxidized by two TEMPO⁺ ions to give a benzaldehyde and two benzonitrile molecules in the presence of H_2O . At the same time TEMPO⁺ is reduced to TEMPOH, which can be regenerated by electro-oxidation.



Scheme 2. (a) ¹H NMR spectra of (1) 4-fluorobenzaldehyde, (2) N,N'-bis(4-fluorobenzylidene)-1-(4-fluorobenzaldehyde after reaction mixture of oxidative conversion of 4-fluorobenzaldehyde after reaction time of 1 h. (b) Plausible reaction mechanism.

4. Conclusion

In summary, we have reported an efficient electrochemical method to generate nitriles from aldehydes under mild conditions using a catalytic amount of TEMPO as the mediator and HMDS as

the nitrogen source. Both aromatic aldehydes and aliphatic aldehydes give very good yields of nitriles. According identification to the results of in situ FTIR and the of N,N'-dibenzylidene-1-arylmethanediamine intermediates, a plausible reaction mechanism is proposed.

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Highlights

- (1) A novel electrochemical route to generate nitriles from aldehydes under mild conditions using a catalytic amount of TEMPO as the mediator and hexamethyldisilazane as the nitrogen source in the presence of acetic acid has been developed.
- (2) A plausible reaction mechanism is proposed based on the cyclic voltammetry, in situ FTIR and the confirmed intermediates.

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