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Electrochemical synthesis of 3,5-disubstituted isoxazoles

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ABSTRACT

The electrochemical oxidation of chalcone oximes has been explored using preparative scale electrolysis and cyclic voltammetry (CV). The results show that a constant current electrolysis of chalcone oximes in an undivided cell affords the corresponding isoxazoles in moderate to good yields, using graphite as the working electrode and $NaClO_4/CH_3OH$ as the supporting electrolyte. The cyclic voltammograms for nearly all of the chalcone oximes investigated exhibit only one oxidation peak. On the basis of preparative electrolysis results and CV analysis, a reaction mechanism, involving a combination of electrochemically-generated base and an iminoxy radical intermediate, is proposed.

1. Introduction

Isoxazoles have garnered much attention as a result of their diverse biological activities, including antibacterial [1,2], antimalarial [3], antifungal [4], anticancer [5] and antioxidant [6] behaviors. The fact that the isoxazole framework is a frequent structural motif in natural products coupled with their utility as synthetic building blocks adds to their importance and appeal. By capitalizing on the presence of a comparatively weak N–O bond, for example, isoxazoles can be transformed into such useful structures as those found in α-hydroxy-β-diketones and other β-dicarbonyl compounds [7–10].

Isoxazoles are often synthesized through a [3 + 2] cycloaddition of nitrile oxides with alkynes or alkenes followed by oxidation [11–13]. As van Delft has noted, the thermal [3 + 2] cycloaddition method can suffer from low yields, side-reactions and poor regioselectivity [14]. While transition metal mediated preparations of 3,5-disubstituted and 3,4-disubstituted isoxazoles have been reported to provide satisfactory yields [15,16], a metal-free version of the reaction is environmentally desirable. Toward this end, hypervalent iodine reagents, such as $PhI(OCOCH_3)_2$ [17,18], $PhI(OCOCF_3)_2$ [19] or *t*-BuOI [20] have been employed to facilitate the formation of nitrile oxides from oximes; their subsequent cycloaddition with alkynes leads to a variety of isoxazoles with complete regioselectivity and high yield under mild reaction conditions. Recently, a catalytic oxidative cyclization of aldoximes and alkenes mediated by hypoiodite has also been reported to afford good yields of isoxazolines, although further oxidation to produce isoxazoles was not performed [21,22].

The reaction of hydroxyamine with 1,3-dicarbonyl or α,β-unsaturated carbonyl compounds, followed by an intramolecular oxidative cyclization provides another approach to isoxazoles [23,24]. Since the oximes can be conveniently generated in high yield, the oxidative cyclization of α,β-unsaturated oximes or β-ketooximes constitutes the essential step for the successful construction of the isoxazole framework. Various oxidants such as I_2/KI, NBS, MnO_2 [25] and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) [26] are widely employed to initiate the intramolecular oxidative cyclization. In these cases, the oxidants are used stoichiometrically or in excess; obviously, this can significantly complicate separation of any unused oxidant and isolation of the product. Therefore, the development of catalytic processes involving inexpensive, readily available reagents is highly desirable.

Without a doubt, organic electrochemistry is one of the milder and more environmentally benign tools available to chemists who are interested in the synthesis of heterocyclic compounds [27–30]. In large part, this is due to the fact that it uses electrons as reagents rather than conventional oxidizing and reducing reagents. Encouraged by others [31] as well as our recent studies of coupling processes induced by the reaction of electrochemically-generated base (EGB) with C–H acids [32], we envisaged that an EGB could promote the oxidative cyclization of a chalcone oxime to an isoxazole. This approach would simplify the purification process since no oxidizing reagent would be needed. As detailed below, moderate to good yields of isoxazole derivatives were obtained in this manner. The protocol features mild reaction conditions and the use of a simple electrochemical set-up (undivided cell, constant current).

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2. Experimental

2.1. Instruments and reagents

All melting points were measured with a XT4A Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded using KBr pellets. NMR spectra were recorded with an AV 400 M Bruker spectrometer (400 MHz ^{1}H frequency, 100 MHz ^{13}C frequency). Chemical shifts are given as δ values (internal standard: TMS). Coupling constants are reported in Hz. Compounds **1a–1k** were synthesized according to known procedures [33]. Other chemicals and solvents were obtained from Beijing Chemicals Co. and used without further purification.

2.2. Cyclic voltammetry

Cyclic voltammograms were measured using a Princeton Applied Research 273A Potentiostat/Galvanostat equipped with electrochemical analysis software, using a conventional three-electrode cell. The working electrode was a glassy carbon disk electrode (ca. ϕ = 3 mm). The auxiliary and reference electrodes in these studies consisted of a Pt wire and an Ag/AgCl in 3 M KCl, respectively. Glassy carbon was polished with a polishing cloth before each measurement. All electrodes for CV experiments were obtained from CH Instruments, Inc. USA. The concentration of **1** was 1 mmol L^{-1}, while that of the supporting electrolyte was 0.1 mol L^{-1}.

2.3. General Procedure for the electrosynthesis of isoxazole

A beaker-type undivided cell equipped with a graphite rod anode and an iron rod cathode was maintained in a water bath at room temperature. To the cell was added a solution of 15 mL of 0.1 M $NaClO_4$ supporting electrolyte in MeOH and the α,β-unsaturated ketoxime (0.5 mmol). The solution was electrolyzed at a constant current density of ~3.5 mA cm^{-2} (I = 16 mA). During the electrolysis, a magnetic stirrer was used. The electrolysis was monitored by TLC and was terminated when the ketoxime was consumed. After the electrolysis, the solvent was evaporated. The crude product was purified by column chromatography on silica gel eluted using a mixture of petroleum ether and EtOAc.

Since each of the products corresponds to known substances, a reference to the literature accompanies the characterization data.

3,5-Diphenylisoxazole (2a) [33]. White solid, m.p. 138–139 °C; 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (s, 1H), 7.48–7.54 (m, 6H), 7.86–7.91 (m, 4H).

3-Phenyl-5-(p-tolyl)isoxazole (2b) [34]. White solid, m.p. 110–111 °C; 73% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.45 (s, 3H), 6.80 (s, 1H), 7.30 (d, 2H, J = 8.0 Hz), 7.48–7.52 (m, 3H), 7.56 (d, 2H, J = 8.0 Hz), 7.77–7.90 (m, 2H).

5-(4-Methoxyphenyl)-3-phenylisoxazole (2c) [33]. White solid, m.p. 120–121 °C; 40% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.90 (s, 3H), 6.73 (s, 1H), 7.02 (d, 2H, J = 8.8 Hz), 7.48–7.50 (m, 3H), 7.80 (d, 2H, J = 8.8 Hz), 7.87–7.89 (m, 2H).

3-Phenyl-5-(3,4,5-trimethoxyphenyl)isoxazole (2d) [35]. White solid, m.p. 129–130 °C; 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.93 (s, 3H), 3.97 (s, 6H), 6.80 (s, 1H), 7.08 (s, 2H), 7.49–7.51 (m, 3H), 7.88–7.90 (m, 2H).

5-(4-Bromophenyl)-3-phenylisoxazole (2e) [2]. White solid, m.p. 173–174 °C; 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.86 (s, 1H), 7.49–7.52 (m, 3H), 7.65 (d, 2H, J = 8.8 Hz), 7.73 (d, 2H, J = 8.8 Hz), 7.87–7.89 (m, 2H).

5-(3,4-Difluorophenyl)-3-phenylisoxazole (2f). White solid, m.p. 153–154 °C; 45% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.82 (s, 1H), 7.33 (t, 1H, J = 8.0 Hz), 7.49–7.54 (m, 3H), 7.59–7.62 (m, 1H), 7.66–7.71 (m, 1H), 7.86–7.89 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 98.0, 115.2 (d, J = 19 Hz), 118.2 (d, J = 18 Hz), 122.3–122.4 (m), 124.5–124.6 (m), 126.8, 128.8, 129.0, 129.0, 130.2, 149.8 (dd, J = 81 Hz, 13 Hz), 152.4 (dd, J = 84 Hz, 13 Hz), 163.2, 168.3.

3-(4-Chlorophenyl)-5-phenylisoxazole (2g) [36]. White solid, m.p. 156–157 °C; 51% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (s, 1H), 7.47–7.54 (m, 5H), 7.82–7.87 (m, 4H).

3-(4-Chlorophenyl)-5-(p-tolyl)isoxazole (2h) [37]. White solid, m.p. 136–137 °C; 42% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.38 (s, 3H), 6.84 (s, 1H), 7.48 (d, 2H, J = 8.4 Hz), 7.61(d, 2H, J = 8.0 Hz), 7.83 (d, 2H, J = 8.8 Hz), 7.86 (d, 2H, J = 8.4 Hz).

3-(4-Chlorophenyl)-5-(3,4-dimethoxyphenyl)isoxazole (2i) [36]. White solid, m.p. 143–144 °C; 66% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.97 (s, 3H), 4.00 (s, 3H), 6.72 (s, 1H), 6.98 (d, 1H, J = 8.4 Hz), 7.36 (d, 1H, J = 2.0 Hz), 7.42 (d, 1H, J = 8.4 Hz), 7.47 (d, 2H, J = 9.2 Hz), 7.82 (d, 2H, J = 8.8 Hz).

5-(4-Bromophenyl)-3-(4-chlorophenyl)isoxazole (2j) [38]. White solid, m.p. 193–194 °C; 35% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (s, 1H), 7.48 (d, 2H, J = 8.4 Hz), 7.65 (d, 2H, J = 8.4 Hz), 7.72 (d, 2H, J = 8.4 Hz), 7.81 (d, 2H, J = 8.4 Hz).

3-(4-methoxyphenyl)-5-(p-tolyl)isoxazole (2k) [39]. White solid, m.p. 144–145 °C; 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H), 3.89 (s, 3H), 6.74 (s, 1H), 7.02 (d, 2H, J = 9.2 Hz), 7.31 (d, 2H, J = 8.0 Hz), 7.74 (d, 2H, J = 8.0 Hz), 7.82 (d, 2H, J = 8.0 Hz).

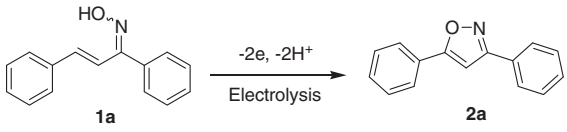
3. Results and discussion

The preparative scale electrolysis was conducted under constant current conditions using a beaker-type undivided cell. Oxime **1a** was chosen as a test substrate to optimize the reaction conditions. The electrolysis was initially performed at a current density of 5.0 mA/cm^{-2} using a Pt plate as the working electrode and an iron rod as the cathode in $NaClO_4$/MeOH supporting electrolyte (Scheme 1), and the desired isoxazole **2a** was obtained in 52% yield (entry 1 of Table 1). Changing to a glassy carbon working electrode gave a slightly higher yield (59%) of **2a** (entry 2 of Table 1). We were pleased to discover that the use of a graphite rod as the working electrode afforded a 77% yield of the desired product, **2a** (entry 3).

We then examined the effect of supporting electrolyte on the oxidative cyclization of oxime **1a**. A moderate yield of **2a** was generated when 0.1 M $NaClO_4$ in EtOH was used as the supporting electrolyte and solvent (entry 4). A change from sodium perchlorate to 0.1 M $LiClO_4$/CH_3OH or 0.1 M Et_4NOTs/CH_3CN led to poor yields (entries 5–6). Thus we conclude that 0.1 M $NaClO_4$/CH_3OH is the preferred supporting electrolyte-solvent combination, although the exact reason is not clear at the present stage (compare, for example, entry 3 with entries 4–6).

Since current density plays an important role in ensuring reaction efficiency in a constant current electrolysis, its influence was also explored. As shown in Table 1, electrolysis at 7.5 mA/cm^{-2} and 3.5 mA/cm^{-2} afforded **2a** in 61% and 66% yield, respectively (entries 7 and 8), each reflecting a substantial reduction when compared to the 77% yield obtained when the current density was 5.0 mA/cm^{-2}.

Finally, we examined the role of charge. As shown in Table 1, the yield of **2a** decreased to 58% (entry 9) and 56% (entry 10) when



Scheme 1. Electrochemical synthesis of isoxazole **2a**.