Cycloaddition of some arylnitriloxides with 3-methylenephthalide: electrocatalytic opening of the adducts

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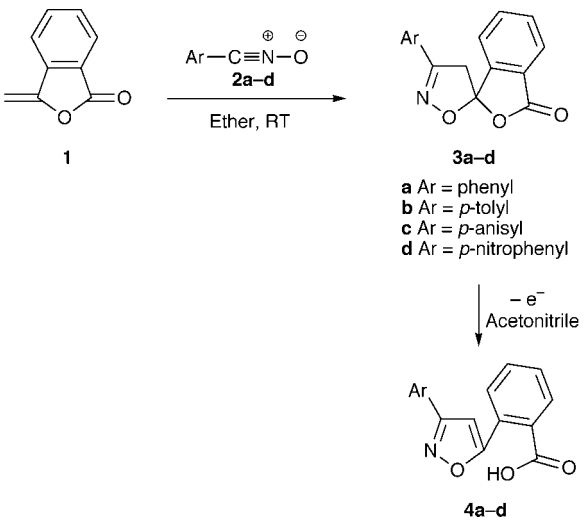
Some 4-substituted arylnitriloxides undergo 1,3 dipolar cycloadditions with 3-methylenephthalide with formation of spirodihydroisoxazoles. These spiroadducts can be opened to the corresponding 2-(3-arylisoxazol-5-yl)benzoic acid by various methods, including thermal and acidic treatments, as well as electrooxidation. In the latter case, the ring-opening mechanism is shown to involve a catalytic electron exchange between the substrate and an intermediate $ArCO_2^{\cdot}$ radical.

Cycloaddition de quelques arylnitiloxydes avec le 3-méthylènephthalate: ouverture électrocatalytique des adduits. Nous avons fait réagir quelques arylnitriloxydes substitués en position 4 sur le cycle aromatique avec le 3-méthylènephthalide *via* une réaction de cycloaddition [3 + 2]. La réaction conduit à l'obtention d'un spirohétérocycle unique. Ces spiroadduits peuvent se réarranger en acide 2-(3-arylisoxazol-5-yl)benzoïque en milieu acide ou basique, par thermolyse et par électrooxydation. Dans ce dernier cas, l'ouverture s'effectue par un échange électronique catalytique entre le substrat et un radical de type $ArCO_2^{\cdot}$ produit intermédiairement.

The recurrent interest in bicyclic molecules with a spirannic junction leads us to reinvestigate the reactivity of some α-methylene- and γ-methylene-γ-butyrolactones with selected 1,3-dipoles.[1] We present here the reaction of 3-methylenephthalide with various 4-substituted arylnitriloxides. This reaction was previously investigated by Liu and Howe[2] with differently substituted substrates; it is shown here that their conclusion can be generalized, whatever the electronic effect of the substituent in the 4 position of the aromatic ring of the dipole, with the same regio- and stereochemistry.

In addition, we investigated extensively the opening of the cycloadducts. We show that acid catalysed opening takes place much more easily in polar solvents like acetonitrile at room temperature. It is also possible to electrooxidize the resulting spiroisoxazoles, which occur in high yields with ring opening of the benzocondensed ring and formation of the same benzoic acid as that produced by thermal or acid treatment of the adducts (Scheme 1).



Scheme 1

Moreover, we suggest that an original electrocatalytic mechanism is responsible in this particular case, through the formation of an $ArCO_2^{\cdot}$ intermediate that undergoes an electron transfer reaction rather than the classical Kolbe decarboxylation, which is known to be disfavoured in the case of aromatic acids.[3,4]

Results and discussion

Cycloadditions

We have submitted to cycloaddition reactions with 3-methylenephthalide **1** the arylnitriloxides **2a–d**, respectively unsubstituted or bearing a methyl, methoxy or nitro group on the *para* position of the ring, according to Scheme 1. In each case the conclusion of Liu and Howe was verified; the regio- and stereochemistry of the cycloadduct are in favour of the sole formation of the adduct **3** (Scheme 1). This is proved unambiguously by the ^{13}C NMR displacement of the spirannic C, which is observed at 112 ppm, while in the case of the formation of the other isomer (with inversion of the spirannic carbon) it would have been observed at 60–70 ppm.

Chemical opening of the adducts

As was observed by Liu and Howe[2] in the case of **3a** only the adducts can be opened by thermal (200–230 °C) treatment, as well as by the action of a diluted acid (chlorhydric acid) or alkali (NaOH), giving the benzoic acids **4a–d**. This reaction is general and insensitive to the substituent on the phenyl ring, which is not unexpected in this case given that the most probable mechanism involves an attack on the lactone, and not on the isoxazole ring. However, we found that acetonitrile was a much better solvent for acidic opening of the adducts. In fact,

the ring-opening reaction was complete with a catalytic amount of chlorhydric acid at room temperature in 15–20 min instead of 1 h at reflux in dioxane as previously described.[2]

Electrochemical opening of the adducts

Although chemical oxidation of some isoxazolines has been described in the literature,[5–9] the electrooxidation of rings such as the adducts **3** is unknown to date.

The cyclic voltammograms (CVs) of the adducts **3** have been performed and are relatively similar, as exemplified by the case of **3a** (Fig. 1, curves a–d). The voltammograms feature two irreversible peaks, the first being in the 1.1–1.2 V region and the second towards 1.8 V (except for **3d**); the potentials are reported in Table 1. In addition, the first peak displays an anomalous behaviour since it vanishes at low scan rates, while it grows in at higher scan rates to reach an intensity approximately equal to that of the second peak. By simple comparison with the CVs of the resulting acids **4** (Fig. 2), it is clear that the second peak must be ascribed to the irreversible oxidation of the isoxazolic ring (Table 2). Electrolyses have been performed, at potentials given in Table 1. The electrolyses are complete after *ca.* 5% of the theoretical amount of charge has been passed (on the basis of one electron per mol). The results of the constant potential electrolyses are independent of the applied potential in the 1.2–2.0 V range.

On the basis of these results, we propose the electrocatalytic mechanism pictured in Scheme 2. Since the Kolbe reaction is known not to occur with aromatic acids,[4] the $ArCO_2^{\cdot}$ radical is likely to undergo further electron transfer to the substrate.

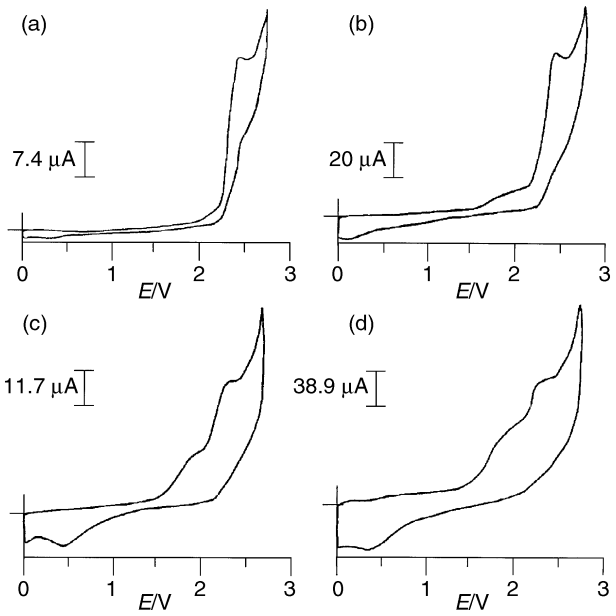


Fig. 1 Electrochemical oxidation of the spiroadduct **3a** in CH_3CN with 0.1 M NEt_4ClO_4. (*a*) Scan rate 0.05 V s^{-1}, $C = 5$ mM, on a 1 mm diameter Pt electrode. (*b*) Scan rate 0.27 V s^{-1}, $C = 5$ mM, on a 1 mm diameter Pt electrode. (*c*) Scan rate 2.70 V s^{-1}, $C = 1$ mM, on a 0.5 mm diameter Pt electrode. (*d*) Scan rate 27.0 V s^{-1}, $C = 1$ mM, on a 0.5 mm diameter Pt electrode.

Table 1 Electrochemical data for the spiroadducts **3**[a]

Product	E_v[b]/V	E_w[b]/V
3a	1.15–1.55	1.40
3b	1.15–1.60	1.40
3c	1.15–1.55	1.40
3d	1.80–2.35	2.10

[a] Electrolysis time of 10 min. [b] E_v and E_w are the catalytic wave potential and working electrode potential during the electrolysis, respectively, *vs.* SCE.

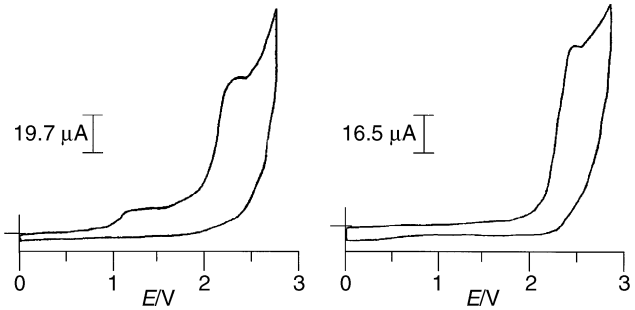
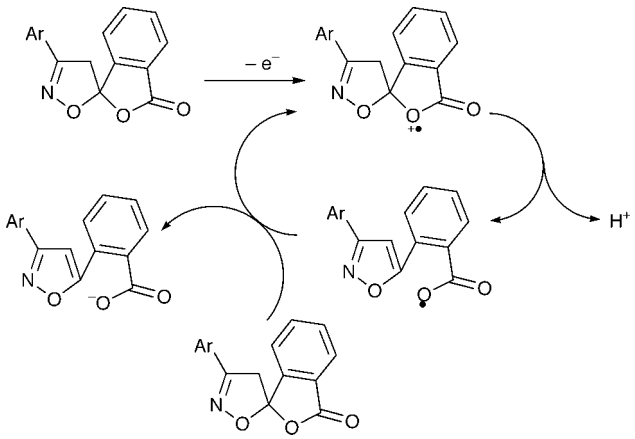


Fig. 2 Electrochemical oxidation of the spiroadduct **3a** (left) and resulting acid **4a** (right) in CH_3CN with 0.1 M NEt_4ClO_4 performed on a 3 mm diameter carbon electrode, scan rate 0.05 V s^{-1}, $C = 1$ mM.

There is no data on the formal redox potentials of the $RCO_2^-/RCO_2^{\cdot}$ couple (its determination is almost impossible due to the fast follow-up reactions). However, the peak potential for the oxidation of benzylic acids is in the +1.0 V range; therefore, it is likely that the formal potential E° in our case lies quite above 1.1 V, which is high enough to allow the oxidation of the substrate by the $ArCO_2^{\cdot}$ radical.



Scheme 2

Another possible explanation could be that the opening is catalysed by protons coming from the first oxidation reaction; however, in the case of acidic treatment the reaction requires a longer time and much more acidic conditions to reach completion. TLC monitoring shows that the ring-opening reactions in acetonitrile with HCl require 20 min with a *ca.* five-fold excess of hydrochloric acid, while the electrochemical opening of the adducts is complete within 10 min. A further explanation could involve hydrogen atom abstraction (on the isoxazolinic ring) from substrates **3** by the electrogenerated radical, followed by reoxidation and aromatization. In order to rule out this hypothesis, we have refluxed compounds **3** in methanol in the presence of benzoyl peroxide, which is known to form phenyl radicals under these conditions. Compounds **3** are insensitive to such treatment, since they are recovered unchanged after the refluxing treatment. Therefore, it can be concluded that the substrates do not react with Ph$^{\cdot}$ radicals, which therefore rules out any radical based H atom abstraction by the intermediate.

Table 2 Electrochemical data for the ring opening products **4**

Product	E_p[a]/V
4a	2.33
4b	2.31
4c	2.29
4d	2.60

[a] E_p is the peak potential *vs.* SCE.

Experimental

Melting points were determined with a digital Electrothermal IA 9200 apparatus and are uncorrected. IR spectra (KBr) were recorded on a Bio-Rad FTS-7 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Spectrospin AC 200 spectrometer operating at 200 MHz for ^{1}H and at 50 MHz for ^{13}C spectra. Chemical shifts were measured relative to TMS. Analytical data were obtained by the CNRS Vernaison (France) and were satisfactory (C, H, N $\pm$0.30% from theoretical).

Synthesis of compounds 1, 2a–d and 3a–d

The 3-methylenephthalide **1** and arylnitriloxides **2** were prepared according to literature procedures.[2,10–14] The cycloadditions giving **3** were realized in diethyl oxide at room temperature, under nitrogen atmosphere with 50 mg of hydroquinone added in order to prevent polymerization of the dipolarophile, according to our previously published procedure.[1]

3a. Yield: 1 g (76%), mp 131 °C (ethanol), green solid, mp lit 120–122 °C. Anal. Calcd. % for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28; Found C, 72.31; H, 4.20; N, 5.34. IR (KBr) $\tilde{\nu}$ 1595, 1770 cm^{-1}; H NMR (d_6-DMSO) δ 4.10–4.50 (AB system, $J = 18.5$), 7.45–8.15 (m, 9H, arom); ^{13}C NMR (d_6-DMSO) δ 44.3, 112.3, 123.9–143.3, 159.1, 166.4.

3b. Yield: 0.71 g (51%), mp 135 °C (ethanol), white solid. Anal. Calcd. % for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.06; Found C, 73.03; H, 4.74; N, 5.12. IR (KBr) $\tilde{\nu}$ 1595, 1770 cm^{-1}; ^{1}H NMR (d_6-DMSO) δ 2.40 (s, 3H, CH_3), 4.10–4.50 (AB system, $J = 18.5$), 6.95–8.25 (m, 8H, arom); ^{13}C NMR (d_6-DMSO) δ 20.8, 44.4, 112.1, 123.8–143.3, 158.9, 166.4

3c. Yield: 0.93 g (63%), mp 168–169 °C (ethanol), beige solid. Anal. Calcd. % for $C_{17}H_{13}NO_4$: C, 69.14; H, 4.44; N, 4.74; Found C, 69.22; H, 4.51; N, 4.79. IR (KBr) $\tilde{\nu}$ 1595, 1770 cm^{-1}; ^{1}H NMR (d_6-DMSO) δ 3.85 (s, 3H, OCH_3), 4.10–4.50 (AB system, $J = 18.6$), 6.95–8.25 (m, 8H, arom); ^{13}C NMR (d_6-DMSO) δ 44.6, 55.2, 112.2, 114.4–161.4, 158.5, 166.4

3d. Yield: 0.34 g (22%), mp 181–183 °C (ethanol), yellow solid. Anal. Calcd. % for $C_{16}H_{10}N_2O_5$: C, 61.94; H, 3.25; N, 9.03; Found C, 62.06; H, 3.29; N, 9.06. IR (KBr) $\tilde{\nu}$ 1590, 1770 cm^{-1}; ^{1}H NMR (d_6-DMSO) δ 4.20–4.60 (AB system, $J = 18.6$), 7.70–8.60 (m, 8H, arom); ^{13}C NMR (d_6-DMSO) δ 43.8, 112.6, 124.2–148.7, 158.3, 167.3.

Ring-opening reactions

Opening through acidic treatment. To a stirred solution of spiroadducts **3** (0.25 mmol) in acetonitrile (4.85 mL) was added slowly, at room temperature, 0.15 mL of concentrated HCl. Stirring was continued for 15–20 min, the solvent was removed *in vacuo* and the obtained residue **4** was recrystallized from carbon tetrachloride. Yields were quantitative.

Opening through electrochemical oxidations. In the anodic compartment of a two-compartment cell fitted with a saturated calomel reference electrode (SCE), was placed a spiroadduct **3** (0.25 mmol) dissolved in acetonitrile (10 mL) and 0.1 M of tetraethylammonium perchlorate. The cathodic compartment was filled with 10 mL of pure electrolyte. A 3.5 cm^2 platinum plate was used as the working electrode, and the electrolyses were performed under argon atmosphere at a constant potential of +1.4 V (+2.1 in the case of **3d**). The electrolyses were stopped when the current reached 1.5 times the background current of the cell (separately measured with no substrate added). After the end of the electrolysis, acetonitrile was evaporated *in vacuo* and the compounds **4** were then extracted and purified as before, with thorough washing to eliminate residual traces of the electrolyte salt.

4a. Yield: 0.050 g (75%), mp 190–191 °C (CCl_4), white solid. Anal. Calcd. % for $C_{16}H_{11}NO_3$: C, 72.44; H, 4.18; N, 5.28; Found C, 72.31; H, 4.20; N, 5.34. IR (KBr) $\tilde{\nu}$ 3095–2885, 1690, 1610 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 4.65 (s, 1H, OH), 6.80 (s, 1H, H isoxazole), 7.15–8.10 (m, 9H, arom); ^{13}C NMR ($CDCl_3$) δ 101.2, 126.8–132.1, 159.9, 167.5, 169.9.

4b. Yield: 0.055 g (78%), mp 160–162 °C (CCl_4), orange solid. Anal. Calcd. % for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.06; Found C, 73.03; H, 4.74; N, 5.12. IR (KBr) $\tilde{\nu}$ 3100–2865, 1690, 1605 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H, CH_3), 3.65 (s, 1H, OH), 6.80 (s, 1H, H isoxazole), 7.15–8.10 (m, 8H, arom); ^{13}C NMR ($CDCl_3$) δ 21.2, 101.0, 125.9–139.9, 162.4, 169.1, 171.1. HRMS (*m/z*): 279, 278, 188, 158, 77.

4c. Yield: 0.055 g (74%), mp 151–152 °C (CCl_4), beige solid. Anal. Calcd. % for $C_{17}H_{13}NO_4$: C, 69.14; H, 4.44; N, 4.74; Found C, 62.22; H, 4.51; N, 4.79. IR (KBr) $\tilde{\nu}$ 3100–2870, 1695, 1615 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.90 (s, 1H, OH), 3.85 (s, 3H, OCH_3), 6.75 (s, 1H, H isoxazole), 7.15–8.10 (m, 8H, arom); ^{13}C NMR ($CDCl_3$) δ 55.2, 100.9, 114.1–161.8, 160.8, 169.0, 170.7.

4d. Yield: 0.060 g (77%), mp 199–200 °C (CCl_4), yellow solid. Anal. Calcd. % for $C_{16}H_{10}N_2O_5$: C, 61.94; H, 3.25; N, 9.03; Found C, 62.06; H, 3.29; N, 9.06. IR (KBr) $\tilde{\nu}$ 3115–2840, 1690, 1600 cm^{-1}. ^{1}H NMR (d_6-acetone) δ 2.90 (s, 1H, OH), 7.30 (s, 1H, H isoxazole), 7.60–8.50 (m, 8H, arom); ^{13}C NMR (d_6-acetone) δ 101.8, 124.8–149.4, 161.8, 167.9, 171.7.

Electrochemical setup

Analytical experiments were performed in a three-compartment cell fitted with an SCE, a glassy carbon (diameter 3 mm) or platinum (diameter 1 or 0.5 mm) electrode and a platinum counter electrode. The electrochemical apparatus was composed of a home-made potentiostat[15] (equipped with an ohmic drop compensation system), a PAR 173 Universal programmer, a Nicolet digital oscilloscope and a Sefram 164 plotter. The solvent was spectroscopic grade acetonitrile [distilled over $CaCl_2$ and stored on 3 Å molecular sieves with 0.1 M tetraethylamonium perchlorate (Fluka puriss, recrystallized once in acetonitrile–diethyl oxide)] as supporting electrolyte. The concentration of product **3** or **4** was usually 1 or 5×10^{-3} M and the cell was flushed with argon throughout the experiment. Ohmic compensation was used when necessary (*i.e.*, for scan rates over 1 V s^{-1}).

Electrosyntheses were performed in a two-compartment cell fitted with a SCE as reference electrode, a platinum work electrode (diameter 15 mm) and platinum wire counter electrode. The electrochemical apparatus was a radiometer PGP 201 potentiostat.

Conclusion

The 1,3 dipolar cycloadditions of 4-substituted arylnitriloxides with 3-methylenephthalide occurs according to a classical scheme. However, an original feature of the adducts is their electrooxidative conversion, which occurs according to an electrocatalytic mechanism. Further investigations are currently being done in this area.

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