Revisiting the addition of nitriloxides on protoanemonin. A new access to (2*E*)-3-(3′-arylisoxazol-5′-yl)propenoic acids†

Christophe Roussel,[a] Rachid Fihi,[a] Kabula Ciamala,*[a] Pierre Audebert[b] and Joël Vebrel[a]

[a] *Laboratoire de Chimie et Electrochimie Moléculaire, Université de Franche Comté, 16 route de Gray, F-25030 Besançon cedex, France. E-mail: Christophe.Roussel@univ-fcomte.fr*
[b] *Laboratoire de Photophysique et Photochimie Supramoléculaire et Macromoléculaire, Ecole Normale Supérieure de Cachan, 71 Av. du Pdt Wilson, F-94235 Cachan cedex, France. E-mail: audebert@ppsm.ens-cachan.fr*

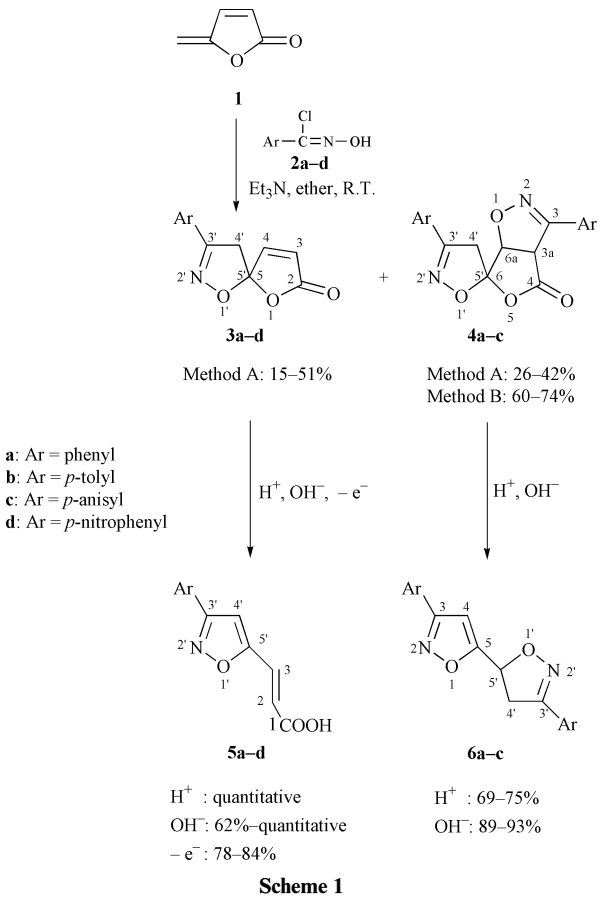
Received* (*in Montpellier, France*) *21st February 2000, Accepted 5th April 2000
Published on the Web 22nd May 2000

Some 4-substituted arylnitriloxides undergo 1,3-dipolar cycloadditions with 5-methylene(5*H*)furan-2-one (protoanemonin) with formation of spiroisoxazolines. These spiroadducts can be opened to the corresponding (2*E*)-3-(3′-arylisoxazol-5′-yl)propenoic acids **5** and 3-aryl-5[4′-(3′-aryl-4′,5′-dihydroisoxazolinyl)]isoxazole **6** by various ways, including acidic and basic treatments, as well as electrooxidation. In the latter case, the electron transfer occurs on the 4,5-dihydroisoxazolic ring and is followed by an internal dissociative electron transfer leading to the opened products.

Réinvestigation de l'addition des nitriloxydes sur la protoanémonine. Nouvelle voie d'accès aux acides (2*E*)-3-(3′-arylisoxazol-5′-yl)propénoïque. Nous avons fait réagir quelques arylnitriloxydes substitués en position 4 sur le cycle aromatique avec la 5-méthylène(5*H*)furan-2-one (protoanémonine) *via* une réaction de cycloaddition [3 + 2]. La réaction conduit à l'obtention d'un mélange de mono et bis-adduits. Ces spiroadduits peuvent se réarranger en acide (2*E*)-3-(3′-arylisoxazol-5′-yl)prop-2-énoïque **5** et en 3-aryl-5[4′-(3′-aryl-4′,5′-dihydroisoxazolinyl)]isoxazole **6** en milieu acide, basique et par électrooxydation. Dans ce dernier cas, l'oxydation intervient sur le cycle isoxazolinique suivi d'un transfert électronique dissociatif conduisant au produit d'ouverture.

In a previous article[1] we showed that the cycloaddition of methylene-γ-butyrolactones with arylnitriloxides is regiospecific. It usually leads to monoadducts, whatever the temperature. However, in the case of 5-methylene(5*H*)furan-2-one **1** (usually called protoanemonin), when this reaction is run in refluxing toluene, an unexpected rearrangment compound is obtained. Since protoanemonin has two reactive sites instead of only one as in the other compounds studied, there was a strong presumption that an intermediate bis-adduct could have been generated in the course of the reaction. Therefore, we decided to search for the reaction conditions that would allow us to isolate this supposed bis-adduct; we succeeded in finding the conditions that allow either monoadducts (**3a–d**) or bis-adducts (**4a–c**) to be isolated. In addition, we submitted the bis-adducts to acidic or basic catalytic reaction conditions (Scheme 1).

Indeed, the expected, previously observed rearrangement leading to 3-aryl-5[4′-(3′-aryl-4′,5′-dihydroisoxazolinyl)]-isoxazole (**6a–c**) was again observed, thus confirming our initial hypothesis. When submitted to the same reaction conditions, the spiroheterocycles (**3a–d**) (the monoadducts of the previous reaction) react giving (2*E*)-3-(3′-arylisoxazol-5′-yl) propenoic acids (**5a-d**). It should be remarked that the homologues of these acids, bearing a halogen or hydroxyl substituent on the 3′ position, are known as synthetic intermediates in the synthesis of natural products belonging to the ibotenic acid [(*R*,*S*)-α-amino-3-hydroxyisoxazole-5-acetic acid] group. Up to now, they were only known as reactional



Scheme 1

† Electronic supplementary information (ESI) available: NOESY 2D NMR spectra of the bis-adduct **4b**. See http://www.rsc.org/suppdata/nj/b0/b001481h/

bioproducts,[2–4] while we propose here a three-step total synthesis.

All the compounds issued from the cycloaddition reactions were submitted to electrochemical oxidation on a platinum electrode. The monoadducts react as previously determined,[5] with the intervention of a catalytic mechanism, leading to the (2*E*)-3-(3′-arylisoxazol-5′-yl)propenoic acids **5a–d**. In contrast, the bis-adducts are extremely stable towards oxidation, remaining unchanged even when submitted to potentials of up to 3 V *vs.* SCE.

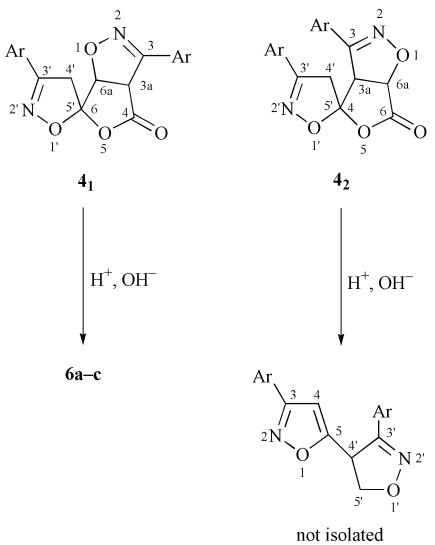
Results and discussion

Cycloadditions

The tuning of the experimental conditions of the cycloaddition of protoanemonin **1** with arylnitriloxides (generated *in situ* from the reaction of **2a–d** with triethylamine) allow the monoadducts, the bis-adducts or a mixture to be produced. In fact, when the reaction is run at room temperature in diethyl ether under classical conditions, with a 1 : 1 stoichiometry, only the monoadducts **3a–d** are obtained (Scheme 1). However, when the reaction is run similarly, but under nitrogen and in the absence of UV light, a mixture of mono and bis-adducts is obtained, the amount of which depends upon the nature of the substituent on the 4 position of the arylnitriloxide (see experimental). It should in addition be recalled that, from the examination of the NMR spectra of the crude reaction products, about 10% of anemonin (dimeric form of protoanemonin) is formed, as previously observed by E. Shaw.[6] The introduction of a catalytic amount of a radical inhibitor such as hydroquinone, nitrobenzene or *p*-nitrophenol leads to the sole formation of bis-adducts **4a–c**, whatever the stoichiometry of the reactants, along with the absence of anemonin.

In all cases, the regiochemistry of the cycloaddition is unique, thus attesting to the regiospecificity of both mechanisms. The regiochemistry of the adducts can be determined by the examination of the ^{13}C NMR displacements of the spiranic junction carbon. In the case of the monoadducts **3a–d**, the observed value of 112.5 ppm *vs.* TMS is in favor of the structure **3** shown on Scheme 1. In the case of the bis-adducts **4a–c**, a straightforward unambiguous determination is not possible, as the observed values of 113–115 ppm are in accordance with both structures $\mathbf{4}_1$ and $\mathbf{4}_2$ (Scheme 2).

Therefore, a NOESY 2D NMR study was realized, which shows that there is a correlation between the protons 4′-H and 6a-H in $\mathbf{4}_1$ or between 4′-H and 3a-H in $\mathbf{4}_2$, therefore close spatially; on the other hand the proton correlated with 4′-H is strongly deshielded (~5.65 ppm *vs.* TMS), showing that it is vicinal to an oxygen. Therefore, the protons 4′-H are close to the most deshielded protons of the structure and the bis-adducts have the structure $\mathbf{4}_1$.



Scheme 2

The regiochemistry thus established has previously been confirmed by an X-ray study[1] of the rearrangement product **6b** issued from the bis-adducts **4b** (Scheme 2).

Chemical opening of the adducts

Bis-adducts. The bis-adducts were submitted to both acidic and basic treatments (trifluoroacetic acid at reflux and ethanolic NaOH at room temperature, respectively), and lead to compounds that are similar to the previously identified compounds in another analogous series of adducts.[1] However, while the acidic treatment directly leads to compounds **6a–c**, the basic treatment first gives an inseparable mixture of two acids, which is attested by the existence in the ^1H NMR spectrum of two different AB systems, as well as several exchangeable protons. However, upon neutralization and further refluxing for 24 h, the expected **6a–c** products are formed quantitatively. For each treatment, we propose the mechanisms shown on Scheme 3. In addition, we have verified that compounds **4a–c** are stable upon 24 h in refluxing toluene, but also yield the expected rearrangement products **6a–c** upon treatment with a catalytic amount of triethylamine. This shows that the base-induced opening is clearly more efficient than the acid-induced one.

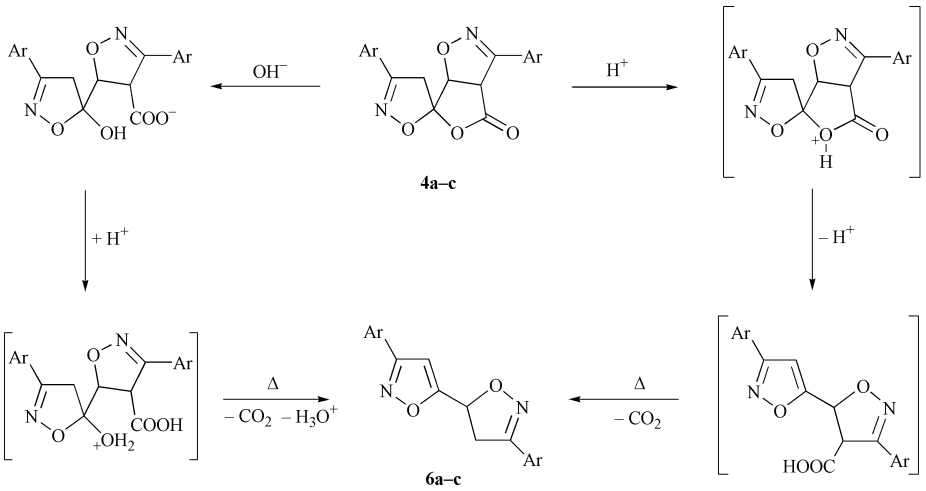
Monoadducts. The monoadducts **3a–d** rearrange into (2*E*)-3-(3′-arylisoxazol-5′-yl)propenoic acids **5a–d** (Scheme 4) upon treatment with HCl in acetonitrile or ethanolic NaOH under much gentler conditions (*e.g.*, 15 min at room temperature in acidic medium). In addition to the IR data, the structure of the rearrangement products is confirmed by the presence of two ethylenic protons with a coupling constant $J = 12.8$ Hz, as well as a D_2O exchangeable proton, while the mass remained unchanged throughout the reaction (*e.g.*, $m/z = 215$ for **5a**).

Electrochemical opening of the adducts

General features. We have submitted the adducts to electrochemical oxidation. In our previous report on related benzocondensed adducts, we had found that an original oxidation took place, leading to the normal open products, the 2-(3-arylisoxazol-5-yl)benzoic acids, through an uncommon electrocatalytic mechanism.[5] However, in the present case, the behavior of the two types of adducts obtained from protoanemonin has been found to differ. The bis-adducts are resistant to oxidation up to 3 V. Despite an oxidation peak discernable in the 2.5–3 V region, using low scan rate cyclic voltammetry, the electrolysis is not possible due to the too high residual solvent oxidation at these elevated potentials, even in dichloromethane. In contrast, the monoadducts can be oxidized around 2 V in dichloromethane or acetonitrile.

Oxidation of the monoadducts. Fig. 1 displays the cyclic voltammograms for the oxidation of the monoadducts **3a–d**. It is clear that, with the exception of **3d**, a single well defined oxidation peak is obtained. Although the oxidation of only three different substituted adducts was investigated, the potentials (see Table 1) correlate well with the Hammett coefficient σ^+ of the substituents on the phenyl ring (Fig. 2). This would suggest a first oxidation process involving electron abstraction from the 4,5-dihydroisoxazolic ring and not from the lactone, while this was not obvious in the case of the benzocondensed adducts (the broadness of the catalytic wave impeded any precise potential correlation). Comparison of the peak currents with a ferrocene standard allows us to determine that the peaks are monoelectronic.

This is in addition corroborated by the fact that one Faraday per mole is exchanged during the electrolyses. It



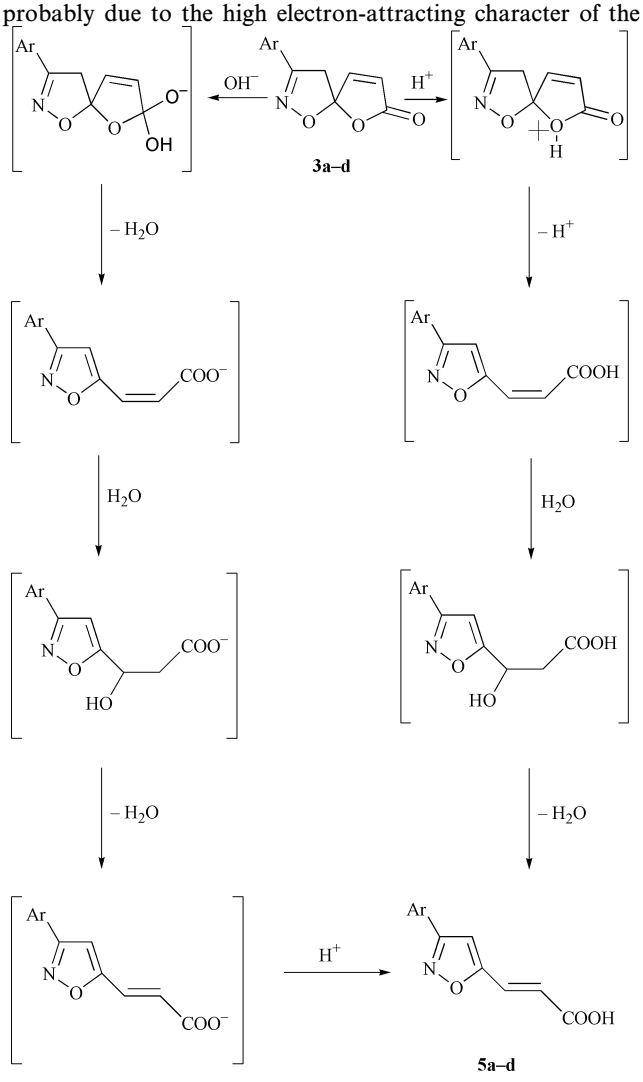
4a–c

6a–c

Scheme 3

should be emphasized that, despite the opened products having the same oxidation state as the monoadducts, the electron exchange results in the production of one proton followed by a solvent oxidation process. The compounds issued from the electrochemical oxidation are the classic ring-opening products, and in all cases very good yields of isolated products are obtained (see Experimental). Coulombic yields are also very fair, on the basis of one Faraday per mole.

Only the adduct **3d** exhibits the catalytic oxidation previously observed with the benzocondensed adducts. This is probably due to the high electron-attracting character of the



3a–d

5a–d

Scheme 4

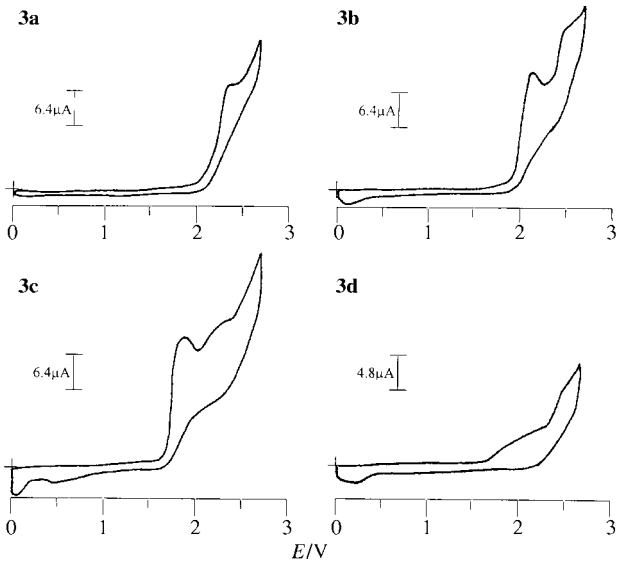


Fig. 1 Electrochemical oxidation of the spiroadducts **3a–d** in CH_3CN + 0.1 M TEAP performed on a 1 mm diameter Pt electrode, scan rate 0.05 V s^{-1}, c = 5 mM.

Table 1 Electrochemical data for spiroadduct **3**

Product	E_p[a]/V	E_v[a]/V	E_w[a]/V	t[b]/min
3a	2.24		2.10	10
3b	2.08		2.00	10
3c	1.83		1.70	10
3d	2.51[c]	1.80–2.35	2.00	10

[a] E_p: peak potential; E_v: catalytic wave potential; E_w: working electrode potential during the electrolysis; all potentials are *vs.* SCE. [b] Electrolysis time. [c] Peak potential of the product **5d**.

Table 2 Electrochemical data for ring-opening product **5**

Product	E_p[a]/V
5a	2.52
5b	2.24
5c	1.90
5d	2.51

[a] E_p: peak potential *vs.* SCE.

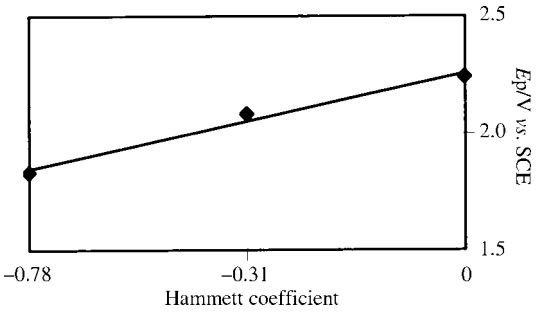


Fig. 2 Correlation between the oxidation peak and the Hammett coefficient σ^+ for products **3a–c**.

nitro group, which impedes the oxidation process on the isoxazoline, therefore oxidation is more liable to occur in this case on the lactone ring. In order to confirm this analysis, we have examined the oxidation of compounds possessing the same lactonic structure as the adducts, namely γ-butyrolactone, 2(5*H*)furanone and 1(3*H*)isobenzofuranone. Only the phthalide is oxidized through the catalytic process previously observed,[5] while the other lactones are not oxidizable in the accessible potential range of the solvent (up to 3 V). This confirms that the monoadduct oxidation process occurs on the unsaturated 4,5-dihydroisoxazolic ring, and involves certainly the unsaturated C=N bond. However, the unreactivity of the bis-adducts towards electrochemical oxidation remains surprising, given that they also contain the same 4,5-dihydroisoxazolic rings, although somewhat deactivated.

From the fact that the bis-adducts are not oxidizable, it is clear that the double bond coming from the precursor protoanemonin ring plays a crucial role in the oxidation process of the monoadducts (certainly of the same kind as that previously played by the benzylic ring in the case of the benzocondensed compounds[5]). However, from the dependence of the peak potentials with the Hammett coefficients, we know that the initial electron transfer should take place on the 4,5-dihydroisoxazolic ring (though this is not completely clear in the case of the weakly reactive **3d** adduct). This apparent contradiction can only be solved by the occurrence of an intramolecular dissociative electron transfer, shown on Scheme 5. The intramolecular electron transfer should be strongly favored by the downhill process of the opening reaction, enhanced by the stabilization of the positive charge by the double bond in the opened cation radical. (One should remark that in the present case, contrary to the benzocondensed adducts, no catalytic mechanism takes place; this is probably due to the inability of the radical produced to reoxidize the substrate; this is not unexpected in regard to the completely conjugated character of this isoxazoloallylic radical.) This phenomenon was previously observed in reduction.[7–10]

To summarize, in light of the previous discussion, we propose the mechanism shown in Scheme 5 for the oxidative one-electron opening of the monoadducts **3a–c**.

Conclusion

We have studied the cycloaddition reaction of several arylnitrile oxides with protoanemonin. We have shown that depending on the reaction conditions, either the monoaddition or the bis-addition products can be obtained selectively. The ring-opening of the adducts has been examined and can occur, in basic and acidic medium, or through an oxidative process in the case of the monoadducts. In this latter case, the oxidation process take place by a one-electron transfer, contrary to the case of the previously examined benzocondensed adducts.

Experimental

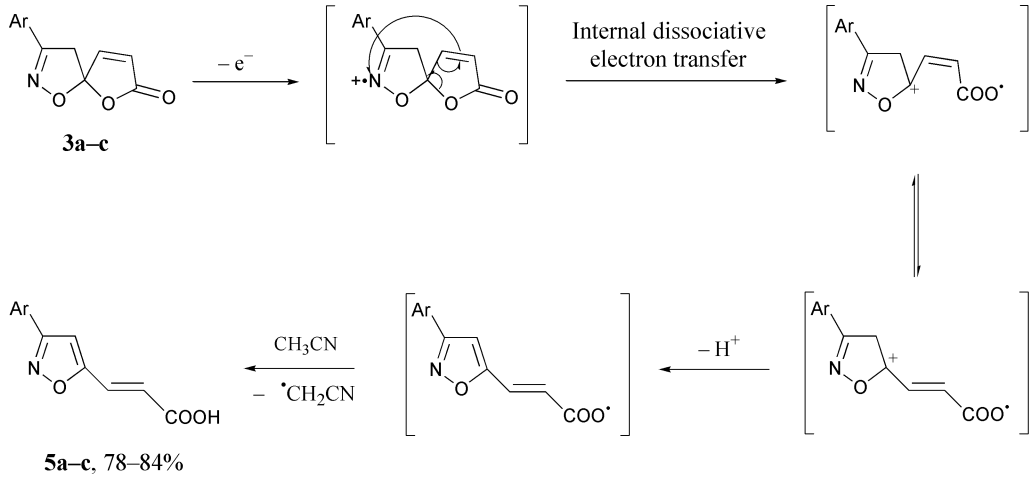
Materials and methods

The starting olefin **1** was synthesized according to the literature procedure[11] (CS_2 was replaced by Et_2O). The arylnitrile-oxides were prepared *in situ* by dehydrohalogenation of the corresponding hydroxyamoyl chlorides **2a–d** according to ref. 12–16. Reactions were carried out under an atmosphere of dry N_2 using a standard Schlenk tube protected from UV. Solvents were purified by standard methods and freshly distilled under nitrogen.

Melting points were obtained on an Electrothermal IA 9200 and are not corrected. IR spectra (KBr) were recorded on a BIO-RAD FTS-7 spectrometer. ^1H, ^{13}C and NOESY NMR spectra were recorded on a Bruker-Spectrospin AC 200 spectrometer operating at 200 MHz for ^1H, 50 MHz for ^{13}C. Chemical shifts were measured relative to TMS in $CDCl_3$ or [D_6]acetone as solvent. Analytical data were obtained by the CNRS (Vernaison, France) and were satisfactory (C, H, N within ±0.30% from theoretical). Mass spectra were recorded on a NERMAG R 1010 H apparatus under electronic impact at 70 eV. Yields are given for isolated products.

Electrochemical setup

Analytical experiments were performed in a three-compartment cell fitted with a saturated calomel reference (SCE), a glassy carbon electrode (diameter 3 mm) or platinum electrode (diameter 1 or 0.5 mm) and a platinum counter electrode. The electrochemical apparatus was a home-made potentiostat[17] (equipped with an ohmic drop compensation system) fitted with 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 tetra-



Scheme 5

ethylamonium perchlorate (Fluka puriss, recrystallized once from acetonitrile–diethyl ether)] as supporting electrolyte. 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.

Synthesis of compounds 3a–d and 4a–c

Method A. Mixture of 2,5-dihydro-3′-arylspiroisoxazolino-[5′,5]furan-2-one 3 and 3,3′-diaryl-3*a*,6*a*-dihydro-4-oxospiro[isoxazolino-5′,6-isoxazolo[3,4-*c*]furanone] 4. To a magnetically stirred solution of protoanemonin **1** (0.48 g, 5 mmol) in dry Et_2O (20 mL) was added the appropriate precursor **2** (7 mmol) and the resulting mixture was stirred at 0 °C under nitrogen for 15 min. Et_3N (1 mL) was then added and the mixture stirred for 24 h at room temperature. The solvent was evaporated under reduced pressure, the residue was dissolved in CH_2Cl_2, and the resulting solution was washed with water (2 × 100 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated to give a crude product identified as a mixture of **3** and **4**. The mixture was taken up in EtOH (20 mL) and irradiated (triturated) by ultrasounds. The beige solid was filtered off to give **4** (**a**, **b** and/or **c**). The filtrate was evaporated *in vacuo* at 30 °C to give **3** (**a**, **b** and/or **c**).

For **3d** (R = NO_2) the crude product was chromatographed on a silica gel column (CH_2Cl_2) to give a yellow solid.

Method B. Pure 3,3′-diaryl-3*a*,6*a*-dihydro-4-oxospiro[isoxazolino-5′,6-isoxazole[3,4-*c*]furanone] 4. The reaction was carried out with 50 mg of hydroquinone, 0.24 g (2.5 mmol) of **1**, 7 mmol of **2** and 1 mL of Et_3N. Under these conditions, only **4** (**a**–**d**) was obtained.

3a: Yield 0.55 g (51%), m.p. 118–120 °C (Et_2O under ultrasonic irradiation at R.T.), white solid, anal. calcd. for $C_{12}H_9NO_3$: C, 66.97; H, 4.21; N, 6.51. Found C, 67.11; H, 4.28; N, 6.48. IR (KBr): *v* 1770, 1590 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 3.45–3.90 (AB system, J = 17.8 Hz, 2H, 4′-H); 6.35 (d, J = 5.4 Hz, 1H, 4-H); 7.35 (d, J = 5.4 Hz, 1H, 3-H); 7.20–7.85 (m, 5H, arom H). ^{13}C NMR ($CDCl_3$, δ): 43.1, 112.5, 125.5–131.1, 148.9, 158.1, 168.6.

3b: Yield 0.57 g (50%), m.p. 150–152 °C (Et_2O under ultrasonic irradiation at R.T.), white solid, anal. calcd. for $C_{13}H_{11}NO_3$: C, 68.12; H, 4.84; N, 6.11. Found C, 68.23; H, 4.91; N, 6.03. IR (KBr): *v* 1785, 1600 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.40 (s, 3H, CH_3); 3.55–3.85 (AB system, J = 17.7 Hz, 2H, 4′-H); 6.35 (d, J = 5.5 Hz, 1H, 4-H); 7.25 (d, J = 7.6 Hz, 2H, arom H); 7.35 (d, J = 5.5 Hz, 1H, 3-H); 7.60 (d, J = 7.6 Hz, 2H, arom H). ^{13}C NMR ($CDCl_3$, δ): 21.3, 43.2, 112.5, 125.4–141.5, 148.9, 158.0, 168.6.

3c: Yield 0.6 g (49%), m.p. 132–134 °C (Et_2O under ultrasonic irradiation at R.T.), white solid, anal. calcd. for $C_{13}H_{11}NO_4$: C, 63.68; H, 4.52; N, 5.71. Found C, 63.96; H, 4.47; N, 5.76. IR (KBr): *v* 1775, 1600 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 3.85 (s, 3H, OCH_3); 3.85–3.55 (AB system, J = 17.7 Hz, 2H, 4′-H); 6.35 (d, J = 5.3 Hz, 1H, 4-H); 7.00 (d, J = 8.7 Hz, 2H, arom H); 7.40 (d, J = 5.3 Hz, 1H, 3-H); 7.65 (d, J = 8.7 Hz, 2H, arom H). ^{13}C NMR ($CDCl_3$, δ): 43.0, 55.2, 112.0, 114.2–164.9, 148.9, 157.2, 168.8.

3d: Yield 0.20 g (15%), m.p. 174–176 °C (Et_2O under ultrasonic irradiation at R.T.), yellow solid, anal. calcd. for $C_{12}H_8N_2O_5$: C, 55.39; H, 3.10; N, 10.77. Found C, 55.65; H, 3.27; N, 10.49. IR (KBr): *v* 1775, 1595 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 3.50–3.80 (AB system, J = 17.8 Hz, 2H, 4′-H); 6.30 (d, J = 5.5 Hz, 1H, 4-H); 7.25 (d, J = 5.5 Hz, 1H, 3-H); 7.80 (d, J = 8.9 Hz, 2H, arom H); 8.25 (d, J = 8.9 Hz, 2H, arom H). ^{13}C NMR ($CDCl_3$, δ): 42.5, 112.7, 124.1–148.3, 148.3, 160.6, 168.9.

4a: Yield 0.43 g (26%) by method A, 1 g (60%) by method B, m.p. 220–222 °C (acetone), colorless solid, anal. calcd. for $C_{19}H_{14}N_2O_4$: C, 68.26; H, 4.22; N, 8.38. Found C, 68.38; H, 4.26; N, 8.41. IR (KBr): *v* 1790 1620, 1600 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 3.50–4.20 (AB system, J = 18.5 Hz, 2H, 4′-H); 4.95 (d, J = 9.0 Hz, 1H, 3a-H); 5.65 (d, J = 9.0 Hz, 1H, 6a-H); 7.35–8.05 (m, 10H, arom H). ^{13}C NMR ($CDCl_3$, δ): 41.8, 55.0, 85.7, 115.5, 126.9–131.1, 153.2, 158.3, 167.5. HRMS *m/z*: 334 (100%).

4b: Yield 0.64 g (35%) by method A, 1.25 g (69%) by method B, m.p. 216–218 °C (acetone), colorless solid, anal. calcd. for $C_{21}H_{18}N_2O_4$: C, 69.62; H, 5.01; N, 7.73. Found C, 69.53; H, 4.91; N, 7.69. IR (KBr): *v* 1785, 1630, 1615 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 2.40 (s, 6H, 2 CH_3); 3.40–4.20 (AB system, J = 18.5 Hz, 2H, 4′-H); 4.90 (d, J = 8.9 Hz, 1H, 3a-H); 5.60 (d, J = 8.9 Hz, 1H, 6a-H); 7.10–8.00 (m, 8H, arom H). ^{13}C NMR ($CDCl_3$, δ): 21.3, 41.9, 55.0, 85.5, 115.4, 126.9–141.6, 153.1, 158.2, 167.6.

4c: Yield 0.83 g (42%) by method A, 1.45 g (74%) by method B, m.p. 223–224 °C (acetone), white solid, anal. calcd. for $C_{21}H_{18}N_2O_6$: C, 63.95; H, 4.60; N, 7.11. Found C, 63.67; H, 4.72; N, 6.79. IR (KBr): *v* 1790, 1630, 1605 cm^{-1}. ^1H NMR ([D_6]acetone, δ): 3.65–4.30 (AB system, J = 18.5 Hz, 2H, 4′-H); 3.85 (s, 6H, 2 CH_3O); 5.40 (d, J = 8.5 Hz, 1H, 3a-H); 5.75 (d, J = 8.5 Hz, 1H, 6a-H), 6.90–8.10 (m, 8H, arom H). ^{13}C NMR ([D_6]acetone, δ): 42.2, 55.6, 56.6, 86.5, 113.3, 115.0–163.0, 153.3, 158.8, 167.0.

Synthesis of (2*E*)-3-[3′-arylisoxazol-5′-yl]propenoic acid 5

Method A: Acidic hydrolysis of the cycloadducts 3a–d (general procedure). To a solution of **3a**–**d** (0.25 mmol) in dry acetonitrile (4.85 mL) was added with stirring 0.15 mL of conc. HCl. The mixture was refluxed for 15 min, and then poured into ice water (100 mL). The precipitate was filtered and the crude product was purified by recrystallization to afford pure **5a**–**d**.

Method B: Basic hydrolysis of the cycloadducts 3a–d (general procedure). To a solution of **3a**–**d** (0.25 mmol) in ethanol (4.1 mL) was added 0.9 mL of 2 M NaOH. The mixture was stirred and refluxed for 15 min. Usual aqueous work up was followed by filtration to leave a product whose spectral and analytical data were consistent with those obtained by method A.

Method C: Electrochemical oxidation of the cycloadducts 3a–d (general procedure). In the anodic compartment of a two-compartment cell fitted with a saturated calomel reference (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 sheet was used as the working electrode, and the electrolyses were performed under argon atmosphere at a constant potential of +2.1 (**3a**), +2.0 (**3b**, **3d**), or +1.7 V (**3c**). 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 **5** were then extracted and purified as before, with thorough washing to eliminate residual traces of the electrolyte salt.

5a: Yield 0.054 g (quantitative) by methods A and B, 0.042 g (78%) by method C, m.p. 212–214 °C (propanol), white solid, anal. calcd. for $C_{12}H_9NO_3$: C, 66.97; H, 4.21; N, 6.51. Found C, 67.15; H, 4.17; N, 6.33. IR (KBr): *v* 3180–2735, 1685, 1650, 1610 cm^{-1}. ^1H NMR ($CDCl_3$, δ): 6.15 (d, J = 12.7 Hz, 1H,

2-H); 7.05 (d, $J = 12.7$ Hz, 1H, 3-H); 7.30–7.60 (m, 3H, arom H); 7.65 (s, 1H, 4′-H); 7.75–7.95 (m, 2H, arom H); 8.95 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, δ): 106.8, 120.6, 126.7–130.0, 162.1, 165.4, 168.5. HRMS *m/z*: 215 (100%).

5b: Yield 0.057 g (quantitative) by methods A and B, 0.048 g (84%) by method C, m.p. 240–241 °C (propanol), beige solid, anal. calcd. for $C_{13}H_{11}NO_3$: calcd. C, 68.12; H, 4.84; N, 6.11. Found C, 68.24; H, 4.79; N, 6.01. IR (KBr): ν 3085–2840, 1685, 1635, 1610 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ): 2.40 (s, 3H, CH_3); 6.20 (d, $J = 12.8$ Hz, 1H, 2-H); 7.05 (d, $J = 12.8$ Hz, 1H, 3-H); 7.30 (d, $J = 7.9$ Hz, 2H, arom H); 7.65 (s, 1H, 4′-H); 7.75 (d, $J = 7.9$ Hz, 2H, arom H); 9.90 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, δ): 21.3, 106.7, 120.8, 126.6–140.2, 163.1, 165.0, 168.5.

5c: Yield 0.061 g (quantitative) by methods A and B, 0.050 g (82%) by method C, m.p. 204–206 °C (propanol), white solid, anal. calcd. for $C_{13}H_{11}NO_4$: calcd. C, 63.68; H, 4.52; N, 5.71. Found C, 68.42; H, 4.60; N 5.62. IR (KBr): ν 3190–2755, 1690, 1645, 1610 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ): 3.85 (s, 3H, OCH_3); 6.15 (d, $J = 12.9$ Hz, 1H, 2-H); 6.95 (d, $J = 8.5$ Hz, 2H, arom H); 7.00 (d, $J = 12.9$ Hz, 1H, 3-H); 7.55 (s, 1H, 4′-H); 7.70 (s, 1H, OH); 7.80 (d, $J = 8.5$ Hz, 2H, arom H). ^{13}C NMR ($CDCl_3$, δ): 55.2, 106.5, 114.2–162.7, 120.6, 161.0, 164.8, 168.6.

5d: Yield 0.065 g (quantitative) by method A, 0.040 g (62%) by method B, 0.053 g (81%) by method C, m.p. 200–201 °C (propanol), yellow solid, anal. calcd. for $C_{12}H_8N_2O_5$: calcd. C, 55.39; H, 3.10; N, 10.77. Found C, 55.46; H, 3.18; N, 10.68. IR (KBr): ν 3145–2795; 1700, 1635, 1610 cm^{-1}. ^{1}H NMR ([D_6]acetone, δ): 3.65 (s, 1H, OH); 6.40 (d, $J = 12.8$ Hz, 1H, 2-H); 7.15 (d, $J = 12.8$ Hz, 1H, 3-H); 7.85 (s, 1H, 4′-H); 8.25 (d, $J = 8.9$ Hz, 2H, arom H); 8.45 (d, $J = 8.9$ Hz, 2H, arom H). ^{13}C NMR ([D_6]acetone, 313 K, δ): 107.5, 125.8–150.0, 162.5, 164.7, 167.1.

Synthesis of 3-aryl-5-[4′-(3′-aryl-4′,5′-dihydroisoxazolinyl)]-isoxazole 6

Method A: Acidic hydrolysis (general procedure). Bis-adduct **4a–c** (0.25 mmol) in trifluoroacetic acid (5 mL) was refluxed for 2 h and then poured into an ice water mixture (100 mL). After extraction with CH_2Cl_2 (3 × 10 mL), the organic phase was washed with water (2 × 20 mL), dried (Na_2SO_4) and evaporated *in vacuo*. The crude products were purified by recrystallization from ethanol.

Method B: Basic hydrolysis (general procedure). To a solution of bis-adduct **4a–c** (0.25 mmol) in ethanol (4.1 mL) was added 2 M NaOH (0.9 mL). The mixture was stirred at room temperature for 2 h. After the usual work up, a crude mixture was dissolved in ethanol (5 mL). Sulfuric acid (1 M, 0.9 mL) was added and the mixture stirred at reflux for 24 h. The reaction was quenched by the addition of ice water (100 mL). After work up in the same manner as in acidic hydrolysis, pure products **6** were obtained.

6a: Yield 0.050 g (69%) by method A, 0.067 g (93%) by method B, m.p. 108–109 °C (ethanol), beige solid, anal. calcd. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found C, 74.53; H, 4.91; N 9.69. IR (KBr): ν 1615 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ): 3.55–3.95 (AB part of ABX system, $J = 16.7$ Hz, $J = 10.7$ Hz, $J = 7.0$ Hz, 2H, 4′-H); 5.90 (X part of ABX system, $J = 10.7$ Hz, $J = 7.0$ Hz, 1H, 5′-H); 6.70 (s, 1H, 4-H); 7.30–7.90 (m, 10H, arom H). ^{13}C NMR ($CDCl_3$, δ): 40.1, 74.1, 100.2, 126.7–130.5, 156.1, 162.4, 170.5.

6b: Yield 0.060 g (75%) by method A, 0.072 g (91%) by method B, m.p. 139–140 °C (ethanol), beige solid, anal. calcd. for $C_{20}H_{18}N_2O_2$: C, 75.47; H, 5.70; N, 7.55. Found C, 75.75; H, 5.68; N, 7.42. IR (KBr): ν 1615 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ): 2.40 (s, 6H, 2 CH_3); 3.50–3.90 (AB part of ABX system, $J = 16.7$ Hz, $J = 10.7$ Hz, $J = 6.9$ Hz, 2H, 4′-H); 5.85 (X part of ABX system, $J = 10.7$ Hz, $J = 6.9$ Hz, 1H, 5′-H); 6.60 (s, 1H, 4-H); 7.10–7.40 (m, 4H, arom H); 7.60 (d, $J = 8.1$ Hz, 2H, arom H); 7.70 (d, $J = 8.1$ Hz, 2H, arom H). ^{13}C NMR ($CDCl_3$, δ): 21.3, 40.2, 74.1, 100.1, 126.6–140.2, 156.1, 162.5, 170.5. HRMS *m/z*: 318 (100%).

6c: Yield 0.065 g (74%) by method A, 0.078 g (89%) by method B, m.p. 165–166 °C (ethanol), beige solid, anal. calcd. for $C_{20}H_{18}N_2O_4$: C, 68.57; H, 5.18; N, 7.99. Found C, 68.43; H, 5.29; N, 8.13. IR (KBr): ν 1615 cm^{-1}. ^{1}H NMR ($CDCl_3$, δ): 3.55–3.85 (AB part of ABX system, $J = 16.6$ Hz, $J = 10.6$ Hz, $J = 6.9$ Hz, 2H, 4′-H); 3.85 (s, 6H, 2 OCH_3); 5.85 (X part of ABX system, $J = 10.6$ Hz, $J = 6.9$ Hz, 1H, 5′-H); 6.65 (s, 1H, 4-H); 6.80–7.10 (m, 4H, arom H); 7.65 (d, $J = 8.5$ Hz, 2H, arom H); 7.75 (d, $J = 8.5$ Hz, 2H, arom H). ^{13}C NMR ($CDCl_3$, δ): 40.3, 55.2, 73.9, 99.9, 114.1–161.2, 155.7, 161.9, 170.4.

Notes and references

1 R. Fihi, K. Ciamala, J. Vebrel and N. Rodier, *Bull. Soc. Chim. Belg.*, 1995, **104**, 55.
2 P. Krogsgaard-Larsen and S. B. Christensen, *Acta. Chem. Scand. Ser. B*, 1976, **30**, 281.
3 J. J. Hansen and P. Krogsgaard-Larsen, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1826.
4 P. Lugosi and J. Schawartz, *Tetrahedron*, 1981, **37**, 3061.
5 C. Roussel, K. Ciamala, P. Audebert and J. Vebrel, *New J. Chem.*, 1999, **23**, 989.
6 E. Schaw, *J. Am. Chem. Soc.*, 1946, **68**, 2510.
7 J. M. Savéant, in *Advances in Electron Transfer Chemistry*, ed. P. S. Mariano, JAI press, Greenwich, CT, USA, 1994, vol. 4, p. 53.
8 M. Robert and J.-M. Savéant, *J. Am. Chem. Soc.*, 2000, **122**, 514.
9 S. Antonello, M. Musumeci, D. D. M. Wayner and F. Maran, *J. Am. Chem. Soc.*, 1997, **119**, 9541.
10 M. S. Workentin, F. Maran and D. D. M. Wayner, *J. Am. Chem. Soc.*, 1995, **117**, 2120.
11 C. Grundmann and E. Kober, *J. Am. Chem. Soc.*, 1955, **77**, 2332.
12 C. Grundmann and R. Richter, *J. Org. Chem.*, 1967, **32**, 2308.
13 R. Huisgen and N. Mack, *Tetrahedron Lett.*, 1961, **17**, 583.
14 K. C. Liu, B. R. Schelton and R. K. Howe, *J. Org. Chem.*, 1980, **45**, 3916.
15 R. H. Wiley and B. J. Wakefield, *J. Org. Chem.*, 1960, **25**, 546.
16 Y. H. Chiang, *J. Org. Chem.*, 1971, **36**, 2146.
17 D. Garreau and J. M. Savéant, *J. Electroanal. Chem.*, 1972, **35**, 309.