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Electrosynthesis of nitroso compounds from (1*S*, 2*S*)-2-amino-l-(4-nitrophenyl)-propane-1,3-diol derivatives

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Abstract

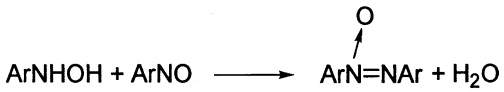
Nitroso compounds were electrogenerated from (1*S*, 2*S*)-2-amino-1-(4-nitrophenyl)-propane-1,3-diol derivatives (derivatives of *p*-nitrophenylserinol) in a "redox" flow cell equipped with two consecutive porous electrodes of opposite polarities. In spite. of the relative instability in methanol-acetate buffer of the hydroxylamine intermediates produced at the first porous electrode (cathode), the nitroso derivatives were prepared in good yields at the second one (anode). A coupling reaction between some nitroso derivatives and *p*-toluenesulphinic acid led to *N*-sulphonylphenylhydroxylamines.

1. Introduction

A direct electrochemical access to nitroso derivatives from the corresponding nitro compounds is not usual. Generally, nitroso compounds are prepared in two consecutive steps as shown in Scheme 1.

Scheme 1

In order to avoid a coupling reaction between the nitroso derivative and the hydroxylamine intermediate giving an azoxy compound (Scheme 2), this intermediate must be quickly and totally oxidized at the anode.



Scheme 2

Over the past few years, an electrochemical "redox" methodology using a flow cell equipped with two consecutive porous electrodes of opposite polarities, has been developped, whereby nitroso compounds can easily be obtained in excellent yields, in protic media, according to Scheme 1 [1–12]. We have used this procedure to prepare nitroso compounds resulting from (1*S*, 2*S*)-2-amino-l-(4-nitrophenyl)-propane-1,3-diol derivatives (derivatives of *p*-nitro-phenylserinol). Considering the electrophilic or dipolar reactivity [13] of nitroso compounds, these species could be key products in the synthesis of more sophisticated molecules having biological potential activities.

2. Experimental

2.1. *Electrochemistry*

All experiments were carried out at room temperature. The solutions were purged with nitrogen.

"Redox" electrolyses were performed in galvanostatic regime using a flow cell as described previously [1, 5]. Two closely consecutive working electrodes (4 cm diameter, 12 mm thickness for cathode and 6 mm thickness for anode) were made of graphite felt (RVG 4000, Le Carbone Lorraine). An upstream counter electrode was placed in a separated compartment. The cell was run with two electrical circuits and two power supplies (Figure 1).

Nitro compounds (about 1 mmol or more) were dissolved in methanol (250 ml) containing acetate buffer (0.5 M CH_3CO_2H + 0.5 M CH_3CO_2Li) as electrolyte. The solution was pumped through the cell from a reservoir using a peristaltic pump. The flow rate (2–5 ml min^{-1}) was measured at the outlet solution.

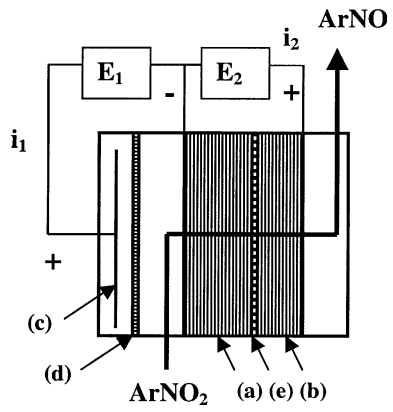


Fig. 1. Schematic diagram of the "redox" flow cell with porous cathode (a) and porous anode (b) (graphite felt) and two electrical circuits; (c) auxilliary counter electrode; (d) diaphragm (cationic membrane) (e) porous insulator; E_1, E_2 power supplies; i_1, i_2 current intensities ($i_1 = i_2$); ⟶ electrode flow circuit.

The current intensities were calculated from Faraday's law according to the quantity of substrate flowing through the porous electrode per second. For the same current intensities in the two electrical circuits ($i_1 = i_2$), the cathodic current ($i_c = i_1 + i_2$) is twice the anodic current ($i_a = i_2 = i_{c/2}$) (i_c = 54 mA and i_a = 27 mA for 4×10^{-3} mol l^{-1} of nitro compounds and a flow rate of 4.2 ml min^{-1}). The efficiencies of the electrolyses were monitored directly by polarography of the outlet solution.

2.2. *Starting compounds*

p-Nitrophenylserinol **1a** and its derivatives **3a–10a** (Scheme 3) were prepared according to the procedure described elsewhere [14–16].

In order to improve the yields of the isolated products, the –OH and $–NH_2$ groups of **1a** Were protected by $N–O^1–O^3$ triple acetylation leading to **2a** [17]. In a similar way, acetic acid 4-nitrobenzyl ester **11a** was prepared from 4-nitrobenzyl alcohol in order to compare the behavior of **2a** with this simpler substrate.

2.3. *Nitroso compounds*

After electrolysis of nitro compounds, the methanolic solution was evaporated under vacuum. The residue was neutralized by a saturated aqueous solution of $NaHCO_3$ to pH 7–8, then extracted with ether. After drying and evaporation of the solvent, the crude nitroso compounds were purified either by column chromatography on silica or by crystallization.

(1S, 2S)-acetic acid 3-acetoxy-2-acetylamino-1-(4-nitrosophenyl)-propyl ester **2b** (ether/light petroleum, 7/3): m.p. 96–98 °C; RMN^{1}H (200 MHz, $CDC1_3$): δ 7.85 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.4 Hz, 2H), 6.15 (d, J = 9.3 Hz, 1H), 5.99 (d, J = 5.4 Hz, 1H), 4.69 (m, 1H), 4.14 (AB, 2H), 2.15 (s, 3H), 2.02 (s, 3H), 1.90 (s, 3H); IR (powder in KBr): 1042.1, 1221.6, 1370.8, 1738.1 (CO), 2921.8 (NH). Anal. Calc.: C, 53.25; H, 5.36; N, 8.28. Found: C, 54.05; H, 5.87; N, 8.72.

3,5-diisopropyl-1-(4-nitrosophenyl)-dihydro-oxazolo [3,4-c] oxazole **3b**: m.p. 119–121 °C; RMN ^{1}H (200 MHz, $CDCl_3$): δ 7.80 (m, 2H), 7.20 (m, 2H), 4.63 RMN ^{1}H (200 MHz, $CDCl_3$): δ 4.45 (d, J = 4.5 Hz, 1H), 4.29 (d, J = 6.3 Hz, 1H), 3.92 (AB, 2H), 3.45 (m, 1H), 1.80 (m, 2H), 1.06 (m, 12H); Anal. Calc.: C, 67.08; H, 7.45; N, 9.20. Found: C, 67.77. H, 7.65; N, 9.28.

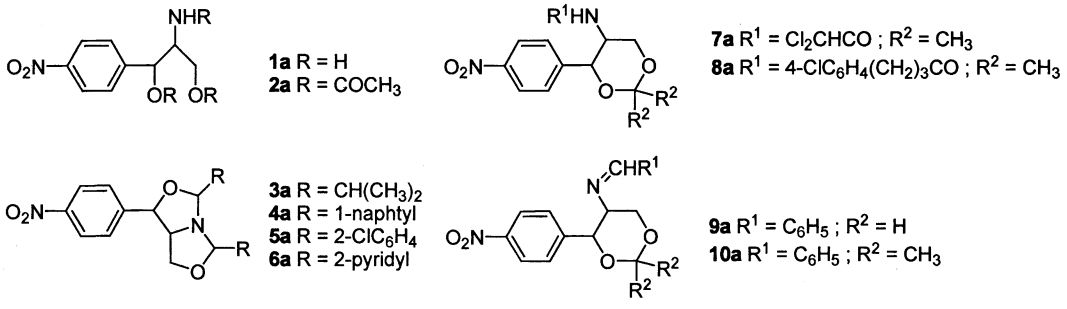
3,5-dinaphtalen-1-yl-1-(4-nitrosophenyl)-dihydro-oxazolo [3,4-c]oxazole **4b**: m.p. 150–152 °C; RMN ^{1}H (200 MHz, $CDCl_3$): δ 8.06 (d, J = 8.1 Hz, 2H), 7.93 (d, J = 7.8 Hz, 2H), 7.71 (m, 14H), 5.81 (s, 1H), 5.71 (s, 1H), 5.06 (d, J = 7.3 Hz, 1H), 4.08(AB, 2H), 3.43 (m, 1H).

3,5-bis-(2-chlorophenyl)-1-(4-nitrosophenyl)-dihydro-oxazolo [3,4-c]oxazole **5b**: m.p, 120–122 °C; RMN ^{1}H (200 MHz, $CDCl_3$): δ 7.83(m, 6H), 7.62 (d, J = 8.3 Hz, 2H), 7.26 (m, 4H), 6.21 (s, 1H), 6.16 (s, 1H), 4.80 (d, J = 7.3 Hz, 1H), 4.32 (AB, 2H), 3.71 (m, 1H).

1-(4-nitrosophenyl)-3,5-dipydidin-2-yl-dihydro-oxazolo[3,4-c]oxazole **6b**: m.p. 108–110 °C; RMN ^{1}H (200 MHz, $CDCl_3$): δ 8.68 (m, 2H), 8.54 (m, 2H), 8.25 (d, J = 8.7 Hz, 1H), 8.20 (d, J = 8.0 Hz,1H), 7.88 (d, J = 8.3 Hz, 2H), 7.57 (m, 2H), 7.49 (d, J = 7.9 Hz, 2H), 5.73 (s,1H), 5.66 (s, 1H), 4.93 (d, J = 6.8 Hz, 1H), 4.14 (m, 1H), 3.79 (AB, 2H).

2,2-dichlora-N-[2,2-dimethyl-4-(4-nitrosophenyl)-[1,3] dioxan-5-yl]-acetamide **7b**: m.p. 117–118 °C; RMN ^{1}H (200 MHz, $CDCl_3$): δ 7.80 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 9.3 Hz, 1H), 5.71 (s, 1H), 5.25 (d, J = 1.5 Hz, 1H), 4.37 (m, 1H), 3.84 (AB, 2H), 1.55 (s, 3H), 1.53 (s, 3H); Anal. Calc.: C, 48.43; H, 4.65; N, 8.07. Found: C, 48.88; H, 4.99; N, 7.96.

4-(4-chlorophenyl)-N-[2,2-dimethyl-4-(4-nitrosophenyl)-[1,3]dioxan-5-y1]-butyramide **8b**; m.p. 110–112 °C; RMN ^{1}H(200 MHz, $CDC1_3$): δ 7.76 (d, J = 8.3 Hz,



Scheme 3

2H), 7.54 (d, $J=8.0$ Hz, 2H), 7.13 (d, $J=8.9$ Hz, 2H), 6.62 (d, $J=7.1$ Hz, 2H), 6.15 (d, $J=9.2$ Hz, 1H), 5.24 (d, $J=10.5$ Hz, 1H), 4.36 (AB, 2H), 3.76 (m, 3H), 2.19 (m, 2H), 1.85 (m, 2H), 1.59 (s, 3H), 1.55 (s, 3H).

Benzylidene-[4-(4-nitrosophenyl)-[1,3]dioxan-5-yl]-amine **9b**: m.p. 168–170 °C; RMN ^{1}H (200 MHz, $CDCi_3$): δ 8.34 (s, 1H), 7.82 (d, $J=7.9$ Hz, 5H), 7.59 (d, $J=8.6$ Hz, 2H), 7.42 (d, $J=8.0$ Hz, 2H), 5.20 (s, 2H), 4.80 (m, 1H), 3.80 (AB, 2H), 3.55 (d, $J=9.0$ Hz, 1H).

Benzylidene-[2,2-dimethyl-4-(4-nitrosophenyl)-[1,3] dioxan-5-yl]-amine **10b**: m.p. 148–150 °C; RMN ^{1}H (200 MHz, $CDC1_3$): δ 7.89 (d, $J=8.1$ Hz, 2H), 7.85 (d, $J=7.9$ Hz, 2H), 7.61 (m, 5H), 7.43 (s, 1H), 5.20 (d, $J=6.3$ Hz, 1H), 4.30 (AB, 2H), 3.20 (m, 1H),1.62, (s, 6H).

Acetic acid 4-nitrosobenzyl ester **11b**: m.p. 128–130 °C; RMN ^{1}H (200 MHz, $CDC1_3$): δ 7.91 (d, $J=8.5$ Hz, 2H), 7.60 (d, $J=8.7$ Hz, 2H), 5.18 (s, 2H), 2.14 (s, 3H); IR (powder in KBr): 1734.1 (CO); 1239.8; 1040.3; 820.7.

2.4. *N-sulphonylated compounds*

N-sulphonylated hydroxylamines were obtained by adding sodium *p*-toluenesulphinate (1 mmol) in 20 ml aqueous H_2SO_4 (0.5 M) to nitroso compounds (0.8 mmol) saturated in methanol. An immediate change of color occurred and, at the same time, a total disappearance of the polarographic wave due to the reduction of the nitroso compound occurred. After filtration of the white precipitate of sodium sulphate, the methanolic solution was evaporated under vacuum and the remaining solution was extracted with ether. After drying and evaporation of the solvent, the crude product was purified by column chromatography on silica.

Acetic acid 3-acetoxy-2-acetylamino-1-{4-[hydroxy-(toluene-4-sulfonyl)-amino]phenyl}-propyl ester **2c**: The physical characteristics are similar to those of the product obtained by adding *p*-toluenesulphonyle chloride to the hydroxylamino derivative electrogenerated from the nitro compound **2a** [17].

2,2-dichloro-N-(4-{4-[hydroxy-(toluene-4-sulfonyle)-amino]-phenyl}-2,2-dimethyl-[1,3]dioxan-5-yl]-acetamide **7c**: m.p. 200–202 °C; RMN ^{1}H (200 MHz, $CDC1_3$): δ 8.30 (s, 1H), 7.54 (d, $J=7.5$ Hz, 2H), 7.38 (d, $J=8.1$ Hz, 2H), 7.31(d, $J=12.2$ Hz, 2H), 7.22 (d, $J=7.9$ Hz, 2H), 5.71 (s, 1H), 5.19 (d, 1H), 4.29 (m, 1H), 3.52 (AB, 2H), 2.35 (s, 3H), 1.41 (s, 3H), 1.24 (s, 3H); IR (powder in KBr); 1682.5 (CO), 1338.8, 1162.1 (SO_2), 1089.5, 812.8, 694.8.

Acetic acid 4-[hydroxy-(toluene-4-sulfonyl)-amino]-benzyl ester **11c**: m.p. 150–152 °C; RMN ^{1}H (200 MHz, $CDC1_3$): δ 7.39 (d, $J=8.2$ Hz, 2H), 7.21 (m, 6H), 5.04 (s, 2H), 3.44 (s, 1H), 2.73 (s, 3H), 2.07 (s, 3H); IR (powder in KBr): 1698.4 (CO), 1161.5 (SO_2), 1039.3, 656.2.

3. Results and discussion

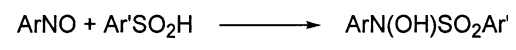
3.1. *Electrosynthesis of nitroso derivatives*

As previously reported [17], the cyclic voltammograms at a hanging mercury electrode or a glassy carbon electrode of nitro compounds **1a–11a** in methanol–acetate buffer were characteristic of nitroarenes in protic media: a reversible system attributed to nitroso-hydroxylamine couple was observed at less cathodic potential after reduction of the nitro group to the hydroxylamino group and scan reversal. Consequently, the hydroxylamine intermediate appeared stable at the time scale (0.1 Vs^{-1}) of the cyclic voltammetry. But, at the long time scale of macroscale electrolysis at a planar electrode (mercury cathode), the phenylhydroxylamines electrogenerated from **1a–11a** were relatively unstable in the presence of a methanolic solution [17].

However, using a "redox" flow cell fitted with two consecutive porous electrodes of large specific area (graphite felt), the hydroxylamine intermediate produced in good yields at the first porous electrode (cathode) can be quickly (few seconds) [1] and totally oxidized into the nitroso derivative at the second porous electrode (anode) avoiding any chemical evolution. In this case, electrosyntheses in a "redox" flow cell of nitroso derivatives from the corresponding nitro compounds were performed in methanol containing acetate buffer (0.5 M CH_3CO_2H + 0.5 M CH_3CO_2Li) as electrolyte. The current intensities at the cathode and at the anode were calculated from Faraday's law (see experimental section).

After "redox" electrolyses, polarographic analyses for all compounds, revealed, on the one hand, a quasi disappearance (up than 90%) of the wave attributed to the reduction of the nitro group before electrolyses ($E_{1/2}$ # −0.5 to −0.6 V*vs*SCE; Table 1), on the other hand, a new cathodic wave ($E_{1/2}$ # −0.03 to −0.06 V*vs*SCE; Table 1) attributed to the reduction of the nitroso group. After work up and purification, the nitroso derivatives were obtained from moderate to good yields (Table 1) and characterized. A secondary electrochemical oxidation of the dihydro oxazolo oxazole moiety could explain the moderate yields obtained from compounds **3a–6a**.

Moreover, the addition of sodium *p*-toluenesulphinate to a part of the electrolyzed solution produced a change of color (green to yellow) and an immediate disappearance of this latter wave. It is well known [4, 5, 18] that nitrosobenzenes and sulphinic acids react according to Scheme 4.

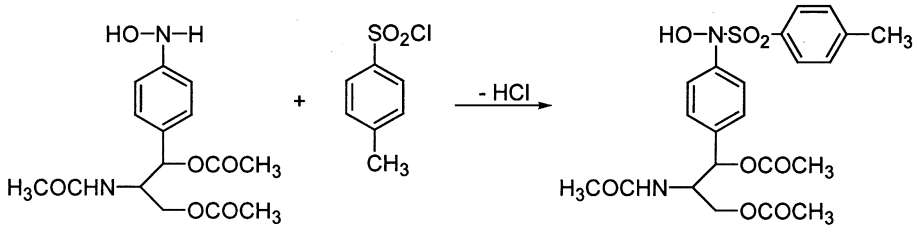


Scheme 4

Table 1. Electrolysis in a "redox" cell of nitro compounds **2a–11a** in methanol containing acetate buffer (0.5 M CH_3CO_2H + 0.5 M CH_3CO_2Li) as electrolyte

Nitro compounds	$E^a_{1/2}$/V$_{vs}$SCE	Nitroso derivatives	$E^b_{1/2}$/V$_{vs}$SCE	Chemical yields /%[c]
2a	−0.60	**2b**	−0.06	80
3a	−0.61	**3b**	−0.07	27
4a	−0.53	**4b**	−0.05	32
5a	−0.58	**5b**	−0.06	43
6a	−0.50	**6b**	−0.03	57
7a	−0.57	**7b**	−0.06	77
8a	−0.54	**8b**	−0.05	68
9a	−0.51	**9b**	−0.04	95
10a	−0.49	**10b**	−0.04	93
11a	−0.61	**11b**	−0.08	78

[a]$E_{1/2}$ for nitro compounds.
[b]$E_{1/2}$ for nitroso derivatives.
[c]After purification.



2c

Scheme 5

3.2. *Synthetic route to N-sulphonylated phenylhydroxylamines*

As reported above (Scheme 4), the addition of sulphinic acids to nitrosobenzenes in acidic media gives *N*-sulphonyiated phenylhydroxylamines. A reverse reaction is observed in basic media with a regeneration of the nitroso compounds. Consequently, arene sulphinic acids can be used as nitroso protecting reagents [18] in order to avoid either an easy reduction of the nitroso group or a coupling reaction (azoxy formation – Scheme 2).

We prepared three *N*-sulphonylated phenylhydroxylamines (table 2) to test their biological properties. After adding sodium *p*-toluene sulphinate in aqueous H_2SO_4 to a methanolic solution of the nitroso compound, we observed an immediate change of the color and a disappearance of the cathodic wave which corresponds to the reduction of the nitroso group. *N*-Sulphonylated hydroxylamine **2c** (scheme 5) was previously prepared by adding *p*-toluenesulphonyl chloride to the hydroxylamino derivative resulting from the cathodic reduction of the nitro compound **2a** at a mercury cathode [17].

Table 2. N-sulphonylated phenylhydroxylamines obtained from nitroso compounds and sodium *p*-toluene sulphinate in aqueous H_2SO_4+ methanol

Nitroso compounds	*N*-sulphonylated phenylhydroxylamines	Chemical yields/%[a]
2b	**2c**	54
7b	**7c**	58
11b	**11c**	59

[a]After purification; calculated vs starting nitroso compound.

4. Conclusion

This work illustrates the advantages of a particular electrochemical procedure for producing molecules, which would be accessible with difficulty by chemical or classical electrochemical methods. Thus, using a "redox" flow cell, new nitroso derivatives were obtained with moderate to good yields. Considering the reactivity of nitrosoarenes [13], these new derivatives are of particular interest as intermediates for organic synthesis of more elaborated molecules. As an example, indoles can be recently produced from the reaction of nitrosoarenes with alkynes [18].

Acknowledgments

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References

1. C. Lamoureux, C. Moinet and A. Tallec, *Electrochim. Acta* **31** (1986a) 1.
2. C. Lamoureux, C. Moinet and A. Tallec, *J. Appl. Electrochem.* **16** (1986b) 819.
3. C. Lamoureux and C. Moinet, *Bull. Soc. Chim. Fr.* (1988) 59.
4. C. Gault and C. Moinet, *Tetrahedron* **45** (1989) 3429.
5. A. Guilbaud-Criqui and C. Moinet, *Bull. Soc. Chim. Fr.* (1992) 295.
6. A. Guilbaud-Criqui and C. Moinet, *Bull. Soc. Chim. Fr.* (1993a) 101.
7. A. Guilbaud-Criqui and C. Moinet, *Bull. Soc. Chim. Fr.* (1993b) 164.
8. C. Moinet, G. Simonneaux, M. Autret, F. Hindré and M. Le Plouzennec, *Electrochim. Acta* **38** (1993) 325.
9. N. Guennec and C. Moinet, *J. Organometal. Chem.* **465** (1994) 233.
10. B.A. Frontana-Uribe and C. Moinet, *Tetrahedron* **54** (1998) 3197.
11. B.A. Frontana-Uribe and C. Moinet, *Eur. J. Org. Chem.* (1999a) 419.
12. B.A. Frontana-Uribe and C. Moinet, *Acta Chem. Scand.* **53** (1999b) 814.

13. P. Zuman and B. Shah, *Chem. Rev.* **94** (1994) 1621.
14. M. Darabantu, G. Plé, S. Mager, E. Cotora, L. Gaina, L. Costas and A. Mates, *Tetrahedron* **53** (1997a) 1873.
15. M. Darabantu, G. Plé, S. Mager, L. Gaina, E. Cotora, A. Mates and L. Costas, *Tetrahedron* **53** (1997b) 1891.
16. M. Darabantu, G. Plé, S. Mager, C. Puscas and E. Cotora, *Tetrahedron* **53** (1997c) 1909.
17. C.V. Cristea, C. Moinet, M. Jitaru and M. Darabantu, *J. Appl. Electrochem.*, In press.
18. A. Darchen and C. Moinet, *J. Chem. Soc. Chem. Commun.* (1976) 820.
19. A. Penoni, J. Volkmann and K.M. Nicholas, *Org. Lett.* **4** (2002) 699.