Tetrahedron Vol. 45, No. 11, pp. 3429 to 3436, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

REACTION OF ELECTROGENERATED 2-NITROSOBENZOIC ACIDS WITH SULPHINIC ACIDS. A CONVENIENT ROUTE TO N-SULFONYLBENZISOXAZOLONES

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(*Received in Belgium* 6 *March* 1989)

ABSTRACT

A one-pot synthesis of N-sulfonylbenzisoxazolones from 2-nitrobenzoïc acids and sulphinic acids is described ; it successively involves :

- electrosynthesis, in a cell with two consecutive porous electrodes of opposite polarities, of the sodium salt of nitrosobenzoïc acids in aqueous phosphate buffer.

- addition of the sulphinic acid or the corresponding sodium salt to the resulting solution ; the formation of N-sulfonylphenylhydroxylamine takes place to give N-sulfonylbenzisoxazolone by warming after acidification.

INTRODUCTION

Cyclization of phenylhydroxylamines bearing a $-CO_2R$ (R = H, CH_3, C_2H_5) or $-CONH_2$ group in the ortho position is a convenient method for preparing benzisoxazolones[1-3]. The cyclization generally occurs during the chemical or the electrochemical reduction of the starting nitro compound. Some N-substituted benzisoxazolones have been prepared by adding various reagents either directly to the medium during the reduction of the methyl o-nitrobenzoate[4,5] or to the isolated benzisoxazolone[5,6]. Some N-substituted benzisoxazolones were obtained[4-8] by other ways. To our knowledge, only the preparation of one N-sulfonylbenzisoxazolone (1-(methylsulfonyl)-2,1-benzisoxazol-3(1H) one) has been reported from 2,1-benzisoxazol-3(1H) one and methanesulfonylchloride with 28% yield. The present paper is devoted to the one-pot synthesis of N-sulfonylbenzisoxazolones in aqueous medium.

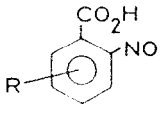
1. ELECTROCHEMICAL SYNTHESIS OF 2-NITROSOBENZOIC ACIDS

We have previously reported[9] the use of a "redox" cell to the direct synthesis of nitrosobenzenes from nitro compounds ; the solution flows through two consecutive porous electrodes of opposite polarities and the following electrochemical reactions occur :

(1) $ArNO_2 \xrightarrow[-\ H_2O]{+\ 4e\ +\ 4H^+} ArNHOH$ (at the porous cathode)

(2) $ArNHOH \xrightarrow{-2e\ -\ 2H^+} ArNO$ (at the porous anode)

By this method, several 2-nitrosobenzoïc acids have been prepared in aqueous phosphate buffer of approximatively pH 7.



b

1b	R = H	4b	R = 5-Cl
2b	R = 5-CH_3	5b	R = 4-CO_2H
3b	R = 4-Cl	6b	R = 6-CO_2H

In this medium, nitro, hydroxylamino and nitroso compounds are soluble ; moreover, the cathodic reduction of the intermediate phenylhydroxylamine does not take place. Because of the high specific area of the electrodes (graphite felt) good yields of nitroso compounds (table I) are obtained after a short contact-time between the flowing solution and the electrodes : the yields are only limited by the cathodic step whereas the anodic step occurs quantitatively ; as a result, formation of azoxy compounds resulting from the reaction between the intermediate hydroxylamine and the nitroso derivative is totally avoided.

Table I - Chemical yields of electrogenerated nitrosobenzoïc acids and of N-sulfonylbenzisoxazolones

2-nitrobenzoïc acids a	2-nitrosobenzoïc acids b chemical yield % (*)		N-sulfonyl(≠)benzisoxazolone c chemical yield %		
			vs. b		vs. a
1a	1b	93	1c1	60	56
			1c2	68	63
			1c3	0	0
2a	2b	93	2c1	80	74
			2c2	71	66
3a	3b	94	3c1	70	66
			3c2	68	64
4a	4b	97	4c1	57	55
			4c2	71	69
5a	5b	87	5c1	70	61
			5c2	78	68
6a	6b	95	6c1	83	79
			6c2	74	70
			6c3	71	67

(*) polarographic analysis

(≠) $R'SO_2$ = c1 R' = C_6H_5 ; c2 R' = 4-$CH_3C_6H_4$; c3 R' = (1S)-(+)-10-camphorsulfonyl.

Generally, as shown by polarographic measurements (figure 1 - curve a), the nitroso compounds exist as monomeric and dimeric forms : the dimeric one being reduced at more cathodic potential ; the ratio between the two forms depends on the nature of the substituents and can be calculated from a polarographic titration.

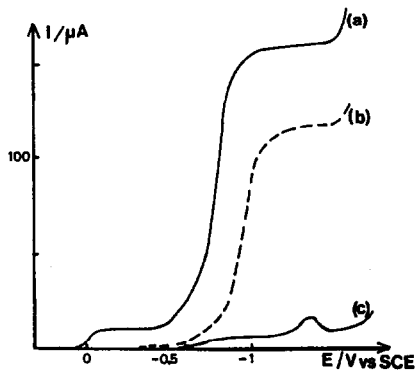


Fig. 1 - Polarograms of the solution recovered after electrolysis of 2-nitrobenzoïc acid 1a ($3.5\ g.l^{-1}$ in phosphate buffer 0.25 M NaH_2PO_4 + 0.25 M Na_2HPO_4) in a "redox" cell (see fig. 2).

a - after electrolysis
b - immediatly after addition of sodium salt of 4-toluene sulphinic acid ($3.8\ g.l^{-1}$)
c - after overnight (wave of unreacted 2-nitrobenzoïc acid)

2. CONDENSATION OF SULPHINIC ACIDS WITH 2-NITROSOBENZOIC ACIDS

The addition of sulphinic acids to nitrosobenzenes, in acidic media, leads to N-sulfonylphenylhydroxylamines ; the opposite reaction is observed in basic media[10] :

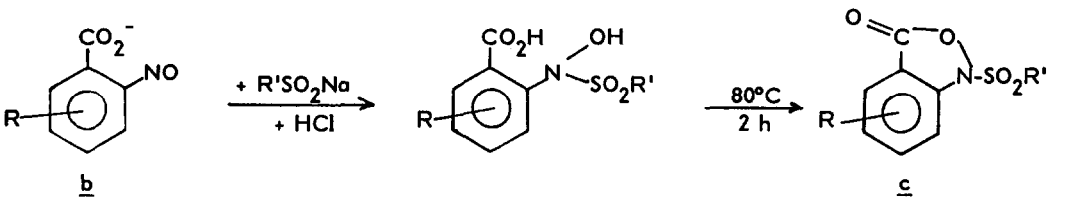
(3) $$ArNO + RSO_2^- \underset{OH^-}{\overset{H^+}{\rightleftharpoons}} ArN(OH)(SO_2R)$$

As shown by polarography (figure 1 - curve b), the monomeric form of the nitroso compound reacts quickly with the sulphinic acid or the corresponding sodium salt (sodium benzene sulfinate or sodium toluene sulfinate, camphor sulphinic acid). In contrast, the dimeric form disappears more slowly (except for chloro compounds 3b and 4b) because of a slow rate of monomerisation ; the rate of disappearance can be increased by heating and by acidification of the medium.

3. CYCLIZATION OF N-SULFONYL 2-HYDROXYLAMINOBENZOIC ACIDS

The cyclization of 2-hydroxylaminobenzoïc acids occurs in hot acidic aqueous medium and yields 2,1-benzisoxazol-3 (1H) one[3] ; however, in some cases, a rearrangement of the hydroxylamino group into aminophenol (Gatterman reaction) takes place instead of the cyclization.

As a general procedure, a slight excess of sulphinic acid (or its sodium salt) and hydrochloric acid are added to the solution of 2-nitrosobenzoïc acid flowing out of the electrolytic cell. Heating the mixture for two hours at 80°C leads to the expected N-sulfonylbenzisoxazolone :



b c

c1 R' = C_6H_5 ; c2 R' = 4-$CH_3C_6H_4$; c3 R' = (1S)-(+)-10 camphorsulfonyl.

The insoluble N-sulfonylbenzisoxazolone is filtered and washed with phosphate buffer to eliminate the residual nitro and nitroso compounds (except for the carboxylic benzisoxazolones 5c and 6c) and then washed with water. The purity of the crude product is generally good ; further crystallization from methanol affords pure products for analysis.

The yield of isolated products (table I) is probably limited by the Gatterman rearrangement.

This is supported by the fact that we normally observed the addition of camphorsulphinic acid to 2-nitrosobenzoïc acid 1b and to nitrosophtalic acid 6b, but only the latter gave ultimately a N-sulfonylbenzisoxazolone. As previously noted by Le Guyader[3], the steric effect of the second carboxylic group favours the cyclization into benzisoxazolone. Moreover, as shown by polarography, nitrosobenzene and p-toluenesulphinic acid condense in acidic medium and the reverse reaction takes place in basic medium, at room temperature (eq. 3), but heating of the acidic solution leads to rearrangement of the corresponding N-sulfonylhydroxylamine which does not regenerate the nitrosobenzene in basic medium.

Note : Physical characteristics of compound 1c2 and of the product resulting from the reaction of 4-toluenesulfonyl chloride with benzisoxazolone (prepared by cyclization of the 2-hydroxylaminobenzoïc acid) are identical.

CONCLUSION

This paper demonstrates the advantage of an electrolysis flow cell with flowing solution to generate some reagents which are then directly used in organic synthesis. Thus, N-sulfonylbenzisoxazolones are cleanly produced in an aqueous medium without organic solvent, directly from 2-nitrobenzoïc acids and sulphinic acids.

This method could be applied to the preparation of similar compounds which have been shown to exhibit antibacterial activity[4,5].

EXPERIMENTAL

1. ELECTROCHEMISTRY

i) Polarography

Polarograms of the solution before and after electrolysis were recorded with a three electrodes TIPOL TACUSSEL polarograph.

ii) Electrolysis

A preparative electrolysis of the 2,1-benzisoxazol-3 (1H) one were carried out at a mercury pool electrode in the cell described by Moinet and Peltier[11]. A TACUSSEL PRT potentiostat was used.

For the continuous two-step preparation of 2-nitrosobenzoïc acids from the corresponding nitro compounds, the cell has been described elsewhere[9]. Its schematic diagram is shown in figure 2.

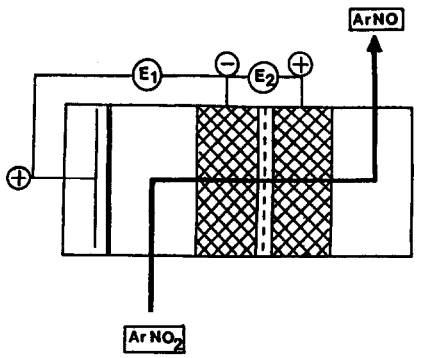


Fig. 2 - Schematic diagram of the cell for the preparation of 2-nitrosobenzoïc acids from the corresponding nitro compounds. E_1 and E_2 : power supplies. ⟶ electrolyte flow circuit.

The two working electrodes (5.2 cm diameter) are made of graphite felt LE CARBONE LORRAINE (12 mm thickness for cathode and 6mm thickness for anode) and are isolated by a thin glass microfibre filter ; an upstream counter-electrode was located in a separated compartment. The cell worked with two power supplies 0-30 V/10 A.

For a typical run, 3.5 to 4.5 g of the nitrobenzoïc acid was dissolved in 1 liter of aqueous phosphate buffer (0.25 M NaH_2PO_4 + 0.25 M Na_2HPO_4). The solution was deoxygenated with nitrogen and pumped through the cell from a reservoir using a peristaltic pump. The electrolyte flow rate (5.8 to 6.2 $cm^3.mn^{-1}$) was measured from the outlet solution. The current intensities were calculated from the Faraday law ; for the same current intensities in the two electrical circuits, the cathodic current intensity is twice the anodic current intensity.

2. SPECTROSCOPY

^1H NMR spectra were obtained on a VARIAN EM 360 A spectrometer (60 MHz). IR spectra were recorded with a PERKIN ELMER 157 G spectrometer.

3. SYNTHESIS OF N-SULFONYLBENZISOXAZOLONES

The starting materials (nitrobenzoïc acids, sodium salt of benzene sulphinic acid and sodium salt of 4-toluene sulphinic acid) were obtained from JANSSEN. Camphorsulphinic acid was prepared from camphorsulfonic acid JANSSEN by the procedure of Smiles and Hilditch[12].

Melting points were determined with a KOFLER apparatus.

i) From sulphinic acids and nitroso intermediates

For the synthesis of N-sulfonylbenzisoxazolones the following procedure described for the 1-(phenylsulfonyl)-2,1-benzisoxazol-3(1H) one 1c1 has been used. The yields are given in table I.

1-(phenylsulfonyl)-2,1-benzisoxazol-3(1H) one (1c1)

Electrolysis of 3.5 g (21 mmol) of 2-nitrobenzoïc acid 1a in phosphate buffer (1 l) was performed as above (the chemical yield in nitroso derivative was determined from polarographic analysis before and after electrolysis).

3.8 g (23 mmol) of the sodium salt of benzene sulphinic acid and 60 cm^3 of hydrochloric acid (d = 1.19) were added to the resulting solution. The solution was stirred at 80°C for 2 h and then cooled and filtered. The precipitate was washed with phosphate buffer and with water. The crude product was dried at 40°C. Crystallization from methanol gave white crystals, m.p. 134°C. Calculated for $C_{13}H_9NO_4S$ (found) : C 56.72 (56.80), H 3.30 (3.25), N 5.09 (5.10), S 11.65 (11.47). IR (CCl_4) : 1800, 1190 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.0-8.0 (m, aromatic H).

1-(4'methylphenylsulfonyl)-2,1-benzisoxazol-3(1H) one (1c2)

Following the procedure for 1c1 on 3.5 g (21 mmol) of 2-nitrobenzoïc acid 1a and 4.1 g (23 mmol) of sodium salt of 4-toluene sulphinic acid, we obtained white cristals (methanol), m.p. 138°C. Calculated for $C_{14}H_{11}NO_4S$ (found) : C 58.12 (57,88), H 3.83 (3.84), N 4.84 (4.84), S 11.08 (10.84). IR (CCl_4) : 1800, 1190 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.35 (3H, s, methyl) 6.9-8.0 (8H, m, aromatic H).

1-(phenylsulfonyl)-5-methyl-2,1-benzisoxazol-3(1H) one (2c1)

Following the procedure for 1c1 on 3.8 g (21 mmol) of 2-nitro-5-methyl-benzoïc acid 2a and 3.8 g (23 mmol) of sodium salt of benzene sulphinic acid, we obtained white crystals (methanol), m.p. 133°C. Calculated for $C_{14}H_{11}NO_4S$ (found) : C 58.12 (57.93), H 3.83 (3.85), N 4.84 (4.60), S 11.08 (11.10). IR (CCl_4) : 1800, 1190 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.4 (3H, s, methyl), 7.2-8.0 (8H, m, aromatic H).

1-(4'methylphenylsulfonyl)-5 methyl-2,1-benzisoxazol-3(1H) one (2c2)

Following the procedure for 1c1 on 3.8 g (21 mmol) of 2-nitro-5-methylbenzoïc acid 2a and 4.1 g (23 mmol) of sodium salt of 4-toluenesulphinic acid, we obtained white crystals (methanol), m.p. 153°C. Calculated for $C_{15}H_{13}NO_4S$ (found) : C 59.39 (59.42), H 4.32 (4.38), N 4.62 (4.62), S 10.57 (10.30). I.R. (CCl_4) : 1800, 1185 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.4 (3H, s, methyl), 2.45 (3H, s, methyl), 7.0-8.0 (7H, m, aromatic H).

1-(phenylsulfonyl)-6-chloro-2,1-benzisoxazol-3(1H) one (3c1)

Following the procedure for 1c1 on 4.23 g (21 mmol) of 2-nitro-4-chlorobenzoïc acid 3a and 3.8 g (23 mmol) of sodium salt of benzene sulphinic acid, we obtained white crystals (methanol), m.p. 154°C. Calculated for $C_{13}H_8ClNO_4S$ (found) : C 50.41 (50.54), H 2.60 (2.53), Cl 11.45 (11.49),

N 4.52 (4.53), S 10.35 (10.37). IR (CCl_4) 1805, 1190 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.2-8.2 (m, aromatic H).

1-(4'methylphenylsulfonyl)-6-chloro-2,1-benzisoxazol-3(1H) one (3c2)

Following the procedure for 1c1 on 4.23 g (21 mmol) of 2-nitro-4-chlorobenzoic acid 3a and 4.1 g (23 mmol) of sodium salt of 4-toluene sulphinic acid, we obtained white crystals (methanol), m.p. 210°C. Calculated for $C_{14}H_{10}ClNO_4S$ (found) : C 51.94 (51.79), H 3.11 (3.21), Cl 10.95 (11.02), N 4.33 (4.22), S 9.90 (9.81). IR (CCl_4) 1800, 1190 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.40 (3H, s, methyl), 7.0-8.0 (7H, m, aromatic H).

1-(phenylsulfonyl)-5-chloro-2,1-benzisoxazol-3(1H) one (4c1)

Following the procedure for 1c1 on 4.23 g (21 mmol) of 2-nitro-5-chlorobenzoic acid 4a and 3.8 g (23 mmol) of sodium salt of benzene sulphinic acid, we obtained white crystals (methanol), m.p. 126°C. Calculated for $C_{13}H_8ClNO_4S$ (found) C 50.41 (50.49), H 2.60 (2.57), Cl 11.45 (11.80), N 4.52 (4.49), S 10.35 (10.27). IR (CCl_4) 1800, 1185 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.4-8.3 (m, aromatic H).

1-(4'methylphenylsulfonyl)-5-chloro-2,1-benzisoxazol-3(1H) one (4c2)

Following the procedure for 1c1 on 4.23 g (21 mmol) of 2-nitro-5-chlorobenzoic acid 4a and 4.1 g (23 mmol) of sodium salt of 4-toluene sulphinic acid, we obtained white crystals (methanol), m.p. 166°C. Calculated for $C_{14}H_{10}ClNO_4S$ (found) : C 51.94 (51.75), H 3.11 (2.97), Cl 10.95 (11.02), N 4.33 (4.31), S 9.90 (9.65). IR (CCl_4) 1800, 1190 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.4 (3H, s, methyl), 7.1-8.1 (7H, m, aromatic H).

1-(phenylsulfonyl)-6-carboxy-2,1-benzisoxazol-3(1H) one (5c1)

The same procedure as for 1c1 was applied starting with 4.48 g (21 mmol) of nitroterephtalic acid 5a and 3.8 g (23 mmol) of sodium salt of benzene sulphinic acid ; however washing of the crude product with phosphate buffer was avoided. We isolated white crystals (methanol), m.p. 200°C. Calculated for $C_{14}H_9NO_6S$ (found) : C 52.66 (52.87), H 2.84 (2.75), N 4.39 (4.36), S 10.04 (9.74). IR (KBr pellets) 1795, 1700, 1185 cm^{-1}. ^1H NMR (CD_3COCD_3) δ 7.1-8.5 (8H, m, aromatic H), 8.8 (1H, br.s, CO_2H).

1-(4'methylphenylsulfonyl)-6-carboxy-2,1-benzisoxazol-3(1H) one (5c2)

The same procedure as for 5c1 was applied starting with 4.48 g (21 mmol) of nitroterephtalic acid 5a and 4.1 g (23 mmol) of sodium salt of 4-toluene sulphinic acid. We obtained white crystals (methanol), m.p. 248°C. Calculated for $C_{15}H_{11}NO_6S$ (found) : C 54.05 (54.30), H 3.33 (3.23), N 4.20 (4.03), S 9.62 (9.56). IR (KBr pellets) 1785, 1695, 1185 cm^{-1}. ^1H NMR (CD_3CODC_3) δ 2.4 (3H, s, methyl), 7.1-8.5 (7H, m, aromatic H), 8.8 (1H, br. s, CO_2H).

1-(phenylsulfonyl)-4-carboxy-2,1-benzisoxazol-3(1H) one (6c1)

Following the procedure for 5c1 on 4.48 g (21 mmol) of 3-nitrophtalic acid 6a and 3.8 g (23 mmol) of sodium salt of benzenesulphinic acid, we obtained white crystals (methanol), m.p. 194°C. Calculated for $C_{14}H_9NO_6S$ (found) C 52.66 (52.72), H 2.84 (2.85), N 4.39 (4.34), S 10.04 (9.74). IR (KBr pellets) 1800, 1700, 1180 cm^{-1}. ^1H NMR (CD_3COCD_3) δ 7.4-8.6 (8H, m, aromatic H), 9.0 (1H, br. s, CO_2H).

1-(4'methylphenylsulfonyl)-4-carboxy-2,1-benzisoxazol-3(1H) one (6c2)

Following the procedure for 5c1 on 4.48 g (21 mmol) of 3-nitrophtalic acid 6a and 3.8 g (23 mmol) of sodium salt of 4-toluene sulphinic acid, we obtained white crystals (methanol), m.p. 212°C. Calculated for $C_{15}H_{11}NO_6S$ (found) C 54.05 (54.01), H 3.33 (3.19), N 4.20 (4.29), S 9.62 (9.91). IR (KBr pellets) 1810, 1700, 1190 cm^{-1}. ^1H NMR (CD_3COCD_3) δ 2.4 (3H, s, methyl) 7.1-8.3 (7H, m, aromatic H), 8.8 (1H, br.s, CO_2H).

1-(1S(+)-10-camphorylsulfonyl)-4-carboxy-2,1-benzisoxazol-3(1H) one (6c3)

Following the procedure for 5c1 on 4.48 g (21 mmol) of 3-nitrophtalic acid 6a and 5 g (23 mmol) of 1 S(+)-10-camphorsulphinic acid, we obtained white crystals (methanol), m.p. 177°C. Calculated for $C_{18}H_{19}NO_7S$ (found) C 54.95 (54.97), H 4.87 (4.85), N 3.56 (3.50), S 8.15 (8.18). IR (KBr pellets) 1800, 1725, 1170 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.9 (3H, s, methyl), 1.1 (3H, s, methyl), 1.4-2.7 (7H, m, camphoryl), 3.5 (2H, AB quartet, J = 14 Hz, CH_2SO_2), 7.9-8.6 (3H, m, aromatic H), 9.0 (1H, br.s, CO_2H). $[\alpha]_D^{17}$ + 15°7 (c = 0.56, acetone).

ii) From 4-toluene sulfonyl chloride and 2,1-benzisoxazol-3(1H) one

Preparation of 2,1-benzisoxazol-3(1H) one was performed according to the procedure of Le Guyader[3]: electroreduction at a mercury cathode at - 0.3 V vs SCE of 1 g (6 mmol) of 2-nitrobenzoïc acid in 1M H_2SO_4, at 60°C, gave 2,1-benzisoxazol-3(1H) one ; the precipitate was filtered after cooling and was washed with water.

To a solution of 0.4 g (3 mmol) of dried crude benzisoxazolone and 0.45 cm^3 (3.1 mmol) of triethylamine in 50 cm^3 of methylene chloride, was added dropwise a solution of 0.8 g (4.2 mmol) of 4-toluene sulfonyl chloride in 20 cm^3 of methylene chloride. The mixture was stirred at room temperature for two hours, then filtered. The filtrate was concentrated to dryness and the residue was crystallized from methanol to give white crystals (0.25 g), m.p. 138°C ; ^1H NMR and IR spectra were identical with those of 1-(4'methylphenylsulfonyl)-2,1-benzisoxazol-3(1H) one 2c2.

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