A Convenient and General Route to 2-Nitro-2,3-dihydrobenzofurans

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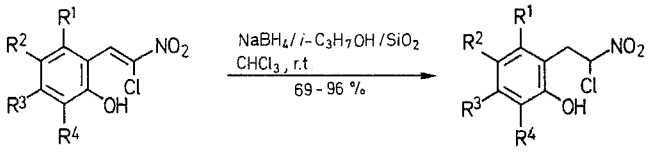
A facile and general two-step preparation of the hitherto unknown title compounds is reported starting from 2-(2-chloro-2-nitroethenyl)phenols. The novel 2-(2-chloro-2-nitroethyl)phenols isolated as intermediates in the synthesis are described.

Benzofurans bearing a nitro group in the 2-position are known to possess a wide range of biological properties[1] and their synthesis has already received considerable attention.[2] However, the corresponding 2,3-dihydro derivatives has remained as yet unexplored in spite of their intrinsic interest in the pharmacological field.

The failures encountered in the previously attempted preparations of these products were fundamentally due to the fact that they always involved a reduction of the double bond of the preformed 2-nitrobenzofurans. In this context, we have carried out many different procedures in our laboratory, which failed because of the delicate nature of the cyclic nitrovinylic system.

We have now circumvented this problem by developing a novel two-step approach to these compounds **3**, which is reported in the present paper. This route which proved to be quite general and efficient is outlined below.



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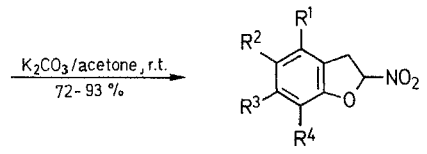

3

1–3	R^1	R^2	R^3	R^4	1–3	R^1	R^2	R^3	R^4
a	H	H	H	H	**h**	OMe	H	H	H
b	H	Cl	H	H	**i**	H	H	OMe	OMe
c	H	Br	H	H	**j**	H	OMe	H	OMe
d	H	Br	H	Br	**k**	OMe	H	H	OMe
e	H	H	H	OMe	**l**	H	Br	H	OMe
f	H	H	OMe	H	**m**	Br	H	H	OMe
g	H	OMe	H	H	**n**	H	NO_2	H	H

Table 1. 2-(2-Chloro-2-nitroethyl)phenols **2** Prepared

Product	Yield[a] (%)	mp[b] (°C) (solvent)	Molecular Formula[c]	MS (70 eV)[d] *m/z* (M^+)	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, *J* (Hz)
2a	94	oil	$C_8H_8ClNO_3$ (201.6)	201, 203	3.30–3.79 (AB part of ABX system, 2H, δ_A = 3.46, J_{AX} = 6.9, J_{AB} = 14.4, δ_B = 3.63, J_{BX} = 7.8); 5.09 (s, 1H, exchangeable with D_2O); 6.09–6.30 (X part of ABX system, 1H); 6.56–7.33 (m, 4H)
2b	75	oil	$C_8H_7Cl_2NO_3$ (236.1)	235, 237, 239	3.25–3.75 (AB part of ABX system, 2H, δ_A = 3.40, J_{AX} = 6.9, J_{AB} = 14.1, δ_B = 3.60, J_{BX} = 7.5); 5.27 (br s, 1H, exchangeable with D_2O); 6.07–6.27 (X part of ABX system, 1H); 6.67 (dd, 1H, *J* = 1.2, 8.0); 7.00–7.32 (m, 2H)
2c	82	50–51 (cyclohexane)	$C_8H_7BrClNO_3$ (280.5)	279, 281, 283	3.25–3.76 (AB part of ABX system, 2H, δ_A = 3.39, J_{AX} = 6.3, J_{AB} = 14.1, δ_B = 3.60, J_{BX} = 7.2); 5.23 (s, 1H, exchangeable with D_2O); 6.07–6.28 (X part of ABX system, 1H); 6.63 (dd, 1H, *J* = 1.4, 7.8); 7.13–7.42 (m, 2H)
2d	81	76–77 (hexane)	$C_8H_6Br_2ClNO_3$ (359.4)	357, 359, 361, 363	3.28–3.82 (AB part of ABX system, 2H, δ_A = 3.43, J_{AX} = 6.6, J_{AB} = 14.0, δ_B = 3.66, J_{BX} = 7.2); 5.76 (s, 1H, exchangeable with D_2O); 6.04–6.22 (X part of ABX system, 1H); 7.22 (br d, 1H, *J* = 2.4); 7.58 (d, 1H, *J* = 2.4)
2e	81	91–92 (hexane)	$C_9H_{10}ClNO_4$ (231.6)	231, 233	3.29–3.80 (AB part of ABX system, 2H, δ_A = 3.46, J_{AX} = 6.9, J_{AB} = 14.1, δ_B = 3.64, J_{BX} = 7.5); 3.88 (s, 3H); 5.82 (s, 1H, exchangeable with D_2O); 6.10–6.30 (X part of ABX system, 1H); 6.60–7.58 (m, 3H)
2f	92	oil	$C_9H_{10}ClNO_4$ (231.6)	231, 233	3.23–3.71 (AB part of ABX system, 2H, δ_A = 3.39, J_{AX} = 5.7, J_{AB} = 13.5, δ_B = 3.55, J_{BX} = 6.9); 3.88 (s, 3H); 5.82 (s, 1H, exchangeable with D_2O); 6.04–6.22 (X part of ABX system, 1H); 6.30 (d, 1H, *J* = 2.4); 6.42 (dd, 1H, *J* = 2.4, 8.4); 6.99 (d, 1H, *J* = 8.4)
2g	92	oil	$C_9H_{10}ClNO_4$ (231.6)	231, 233	3.27–3.76 (AB part of ABX system, 2H, δ_A = 3.43, J_{AX} = 6.6, J_{AB} = 14.1, δ_B = 3.60, J_{BX} = 6.6); 3.75 (s, 3H); 5.03 (br s, 1H exchangeable with D_2O); 6.10–6.29 (X part of ABX system, 1H); 6.55–6.85 (m, 3H)
2h	93	75–76 (hexane)	$C_9H_{10}ClNO_4$ (231.6)	231, 233	3.36–3.91 (AB part of ABX system, 2H, δ_A = 3.52, J_{AX} = 6.0, J_{AB} = 14.0, δ_B = 3.74, J_{BX} = 8.4); 3.82 (s, 3H); 5.04 (s, 1H, exchangeable with D_2O); 6.05–6.25 (X part of ABX system, 1H); 6.40 (d, 1H, *J* = 8.2); 6.49 (d, 1H, *J* = 8.3); 7.12 (dd, 1H, *J* = 8.2, 8.3)
2i	96	95–96 (hexane)	$C_{10}H_{12}ClNO_5$ (261.7)	261, 263	3.24–3.72 (AB part of ABX system, 2H, δ_A = 3.40, J_{AX} = 6.9, J_{AB} = 13.7, δ_B = 3.57, J_{BX} = 6.5); 3.83 (s, 3H); 3.90 (s, 3H); 5.99 (s, 1H, exchangeable with D_2O); 6.05–6.23 (X part of ABX system, 1H); 6.40 (d, 1H, *J* = 8.5); 6.74 (d, 1H, *J* = 8.5)
2j	75	100–102 (cyclohexane)	$C_{10}H_{12}ClNO_5$ (261.7)	261, 263	3.32–3.78 (AB part of ABX system, 2H, δ_A = 3.47, J_{AX} = 6.4, J_{AB} = 12.9, δ_B = 3.64, J_{BX} = 7.4); 3.78 (s, 3H); 3.90 (s, 3H); 5.46 (s, 1H, exchangeable with D_2O); 6.15–6.34 (X part of ABX system, 1H); 6.24 (d, 1H, *J* = 2.7); 6.50 (d, 1H, *J* = 2.7)
2k	89	59–60 (hexane)	$C_{10}H_{12}ClNO_5$ (261.7)	261, 263	3.37–3.92 (AB part of ABX system, 2H, δ_A = 3.53, J_{AX} = 6.5, J_{AB} = 14.2, δ_B = 3.75, J_{BX} = 7.7); 3.77 (s, 3H); 3.85 (s, 3H); 5.83 (s, 1H, exchangeable with D_2O); 6.08–6.28 (X part of ABX system, 1H); 6.33 (d, 1H, *J* = 9.0); 6.73 (d, 1H, *J* = 9.0)
2l	91	93–94 (hexane)	$C_9H_9BrClNO_4$ (310.5)	309, 311, 313	3.23–3.76 (AB part of ABX system, 2H, δ_A = 3.40, J_{AX} = 6.4, J_{AB} = 14.5, δ_B = 3.60, J_{BX} = 7.4); 3.88 (s, 3H); 5.76 (s, 1H, exchangeable with D_2O); 6.06–6.25 (X part of ABX system, 1H); 6.85 (d, 1H, *J* = 2.1); 6.93 (d, 1H, *J* = 2.1)
2m	85	100–101 (cyclohexane)	$C_9H_9BrClNO_4$ (310.5)	309, 311, 313	3.53–4.07 (AB part of ABX system, 2H, δ_A = 3.69, J_{AX} = 6.8, J_{AB} = 14.8, δ_B = 3.91, J_{BX} = 7.0); 3.90 (s, 3H); 5.95 (s, 1H, exchangeable with D_2O); 6.17–6.36 (X part of ABX system, 1H); 6.71 (d, 1H, *J* = 8.7); 7.09 (d, 1H, *J* = 8.7)
2n	69	145–146 (benzene/cyclohexane)	$C_8H_7ClN_2O_5$ (246.6)	246, 248	3.30–3.83 (AB part of ABX system, 2H, δ_A = 3.45, J_{AX} = 7.2, J_{AB} = 14.1, δ_B = 3.68, J_{BX} = 6.6); 6.15–6.34 (X part of ABX system, 1H); 6.88–7.24 (m, 1H); 7.98–8.19 (m, 2H); 10.86 (br s, 1H, exchangeable with D_2O)[f]

[a] Yield of isolated pure product based on **1**.
[b] Melting points are uncorrected.
[c] The microanalyses showed the following maximum deviations from the calculated values: C ±0.28, H ±0.15, N ±0.10, Cl ±0.29.
[d] The mass spectra were obtained on a Nermag Ribermag R10-10C spectrometer.
[e] The ^{1}H-NMR spectra were recorded at 90 MHz using a Varian EM 390 spectrometer.
[f] A mixture $CDCl_3$/DMSO-d_6 (9 : 1) was used for **2n**.

The recently described 2-(2-chloro-2-nitroethenyl)phenols **1**[3] are easily converted into the 2-(2-chloro-2-nitroethyl)phenols **2** by performing a silica gel-assisted reduction with sodium borohydride in a mixture of isopropanol and chloroform.[4] The subsequent heterocyclization of the purified intermediates **2** is then achieved in acetone in the presence of potassium carbonate to furnish the expected 2-nitro-2,3-dihydrobenzofurans **3** in satisfactory overall yields.

The structures of the newly-synthesized compounds **2a–n** and **3a–n** have been unambiguously established by ^{1}H-NMR and mass spectroscopy as well as by elemental analyses (Tables 1 and 2).

2-(2-Chloro-2-nitroethyl)phenols 2a–n; General Procedure:
A solution of the appropriate 2-(2-chloro-2-nitroethenyl)phenol **1**[3] (12 mmol) in a mixture of isopropyl alcohol (25 mL) and $CHCl_3$ (75 mL) is placed in a 250 mL conical flask and efficiently stirred. Silica gel (200–400 mesh ASTM; 6 g) is then added to the suspension followed by powdered sodium borohydride (1.14 g; 30 mmol) in portions over a period of 1 min. The slurry is stirred for an additional 2 h at ambient temperature, acidified dropwise with AcOH (1.8 mL), then allowed to stand for 15 min. The inorganic material is removed by filtration and thoroughly rinsed with several portions of $CHCl_3$. The filtrate is evaporated *in vacuo* to leave a crude product, which is directly chromatographed on a silica gel column [100 g, 200–400 mesh, eluent: CH_2Cl_2 for **2a–m**, CH_2Cl_2/EtOAc (95:5) for **2n**]. For the most part (**2c–e** and **2h–n**), the materials obtained after removal of the solvent under reduced pressure are further purified by recrystallization. In the cases of **2c**, **2d** and **2n**, the chromatographed fractions containing the

Table 2. 2-Nitro-2,3-dihydrobenzofurans **3** Prepared

Product	Yield[a] (%)	mp[b] (°C) (solvent)	Molecular Formula[c]	MS (70 eV)[d] m/z (M^+)	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J(Hz)
3a	75	52–53 (hexane)	$C_8H_7NO_3$ (165.2)	165	3.42–3.99 (AB part of ABX system, 2H, δ_A = 3.59, J_{AX} = 2.1, J_{AB} = 18.0, δ_B = 3.80, J_{BX} = 8.7); 6.09–6.24 (X part of ABX system, 1H); 6.87–7.39 (m, 4H)
3b	83	87.5–90 (hexane)	$C_8H_6ClNO_3$ (199.6)	199, 201	3.43–4.02 (AB part of ABX system, 2H, δ_A = 3.60, J_{AX} = 2.4, J_{AB} = 17.9, δ_B = 3.82, J_{BX} = 8.5); 6.12–6.28 (X part of ABX system, 1H); 6.91–7.42 (m, 3H)
3c	80	92–94 (cyclohexane)	$C_8H_6BrNO_3$ (244.1)	243, 245	3.43–4.00 (AB part of ABX system, 2H, δ_A = 3.59, J_{AX} = 2.2, J_{AB} = 17.0, δ_B = 3.81, J_{BX} = 8.2); 6.09–6.24 (X part of ABX system, 1H); 6.86–7.48 (m, 3H)
3d	86	161.5–162.5 (heptane)	$C_8H_5Br_2NO_3$ (323.0)	321, 323, 325	3.50–4.10 (AB part of ABX system, 2H, δ_A = 3.67, J_{AX} = 2.1, J_{AB} = 17.8, δ_B = 3.91, J_{BX} = 8.1); 6.16–6.30 (X part of ABX system, 1H); 7.16–7.35 (m, 1H); 7.50–7.63 (m, 1H)
3e	84	69–70 (cyclohexane)	$C_9H_9NO_4$ (195.2)	195	3.44–4.03 (AB part of ABX system, 2H, δ_A = 3.61, J_{AX} = 3.0, J_{AB} = 17.7, δ_B = 3.84, J_{BX} = 8.4); 3.93 (s, 3H); 6.14–6.29 (X part of ABX system, 1H); 6.74–7.12 (m, 3H)
3f	87	96–97 (cyclohexane)	$C_9H_9NO_4$ (195.2)	195	3.35–3.92 (AB part of ABX system, 2H, δ_A = 3.51, J_{AX} = 2.0, J_{AB} = 16.8, δ_B = 3.74, J_{BX} = 8.0); 3.77 (s, 3H); 6.08–6.23 (X part of ABX system, 1H); 6.45–6.73 (m, 2H); 7.08 (d, 1H, J = 8.5)
3g	75	53.5–54.5 (cyclohexane)	$C_9H_9NO_4$ (195.2)	195	3.40–3.98 (AB part of ABX system, 2H, δ_A = 3.58, J_{AX} = 2.2, J_{AB} = 17.8, δ_B = 3.79, J_{BX} = 8.7); 3.76 (s, 3H); 6.07–6.22 (X part of ABX system, 1H); 6.67–7.07 (m, 3H)
3h	76	79–80 (hexane)	$C_9H_9NO_4$ (195.2)	195	3.38–3.91 (AB part of ABX system, 2H, δ_A = 3.58, J_{AX} = 1.0, J_{AB} = 18.0, δ_B = 3.69, J_{BX} = 10.5); 3.82 (s, 3H); 6.11–6.25 (X part of ABX system, 1H); 6.54 (d, 1H, J = 8.2); 6.70 (d, 1H, J = 8.4); 7.22 (dd, 1H, J = 8.2, 8.4)
3i	74	82.5–83.5 (heptane)	$C_{10}H_{11}NO_5$ (225.2)	225	3.37–3.96 (AB part of ABX system, 2H, δ_A = 3.53, J_{AX} = 2.1, J_{AB} = 17.3, δ_B = 3.77, J_{BX} = 8.2); 3.86 (s, 3H); 4.06 (s, 3H); 6.12–6.27 (X part of ABX system, 1H); 6.56 (d, 1H, J = 8.3); 6.81 (br d, 1H, J = 8.3)
3j	74	87.5–88.5[f] (cyclohexane)	$C_{10}H_{11}NO_5$ (225.2)	225	3.40–3.99 (AB part of ABX system, 2H, δ_A = 3.57, J_{AX} = 2.4, J_{AB} = 18.0, δ_B = 3.79, J_{BX} = 7.3); 3.75 (s, 3H); 3.91 (s, 3H); 6.09–6.23 (X part of ABX system, 1H); 6.31–6.50 (m, 2H)
3k	93	146–147 (heptane)	$C_{10}H_{11}NO_5$ (225.2)	225	3.40–3.97 (AB part of ABX system, 2H)[g]; 3.77 (s, 3H); 3.90 (s, 3H); 6.11–6.30 (X part of ABX system, 1H); 6.44 (d, 1H, J = 8.7); 6.80 (d, 1H, J = 8.7)
3l	75	110–111 (cyclohexane)	$C_9H_8BrNO_4$ (274.1)	273, 275	3.42–4.00 (AB part of ABX system, 2H, δ_A = 3.59, J_{AX} = 2.2, J_{AB} = 17.9, δ_B = 3.80, J_{BX} = 8.7); 3.93 (s, 3H); 6.11–6.26 (X part of ABX system, 1H); 6.91–7.05 (m, 2H)
3m	75	119.5–121 (heptane)	$C_9H_8BrNO_4$ (274.1)	273, 275	3.43–4.01 (AB part of ABX system, 2H, δ_A = 3.61, J_{AX} = 1.5, J_{AB} = 18.0, δ_B = 3.80, J_{BX} = 8.4); 3.92 (s, 3H); 6.15–6.30 (X part of ABX system, 1H); 6.76 (d, 1H, J = 8.8); 7.10 (d, 1H, J = 8.8)
3n	72	113–114 (benzene/ cyclohexane)	$C_8H_6N_2O_5$ (210.2)	210	3.51–4.12 (AB part of ABX system, 2H, δ_A = 3.70, J_{AX} = 2.0, J_{AB} = 18.1, δ_B = 3.91, J_{BX} = 8.1); 6.25–6.41 (X part of ABX system, 1H); 7.17 (d, 1H, J = 8.6); 8.11–8.38 (m, 2H)

[a] Yield of recrystallized product based on **2**.
[b] Melting points are uncorrected.
[c] The microanalyses showed the following maximum deviations from the calculated values; C ±0.29, H ±0.11, N ±0.14.
[d,e] As in Table 1.
[f] Allotropic change at 76–78 °C.
[g] In this case, the calculation is impracticable because most of the AB lines are overlapped by the signals of the methyl groups.

desired product are stained by a dark impurity. In these instances, it is advisable to stir the relevant solutions with activated charcoal for 2 h. After filtration through a short pad of Celite, the solvent is distilled off to leave a residue, which is recrystallized. With regard to the oily products **2a**, **2b**, **2f** and **2g**, the chromatographed material proved satisfactorily pure as judged by ^{1}H-NMR spectroscopy and microanalyses (Table 1).

2-Nitro-2,3-dihydrobenzofurans 3a–n; General Procedure:
To a solution of **2** (6.5 mmol) in dry acetone (50 mL) is added anhydrous K_2CO_3 (1.8 g; 13 mmol) and the mixture is stirred at room temperature for 4 h (10 h in the case of **3j**). The mineral salts are filtered off by suction and carefully rinsed with small portions of dry acetone. Evaporation of the filtrate to dryness provides a crude material, which is column chromatographed on silica gel (100 g, eluent: CH_2Cl_2). Evaporation of the solvent followed by recrystallization provides analytically pure 2-nitro-2,3-dihydrobenzofurans **3a–n** (Table 2).

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(1) Royer, R. *Ann. Pharm. Fr.* **1983**, *41*, 299.
(2) Tromelin, A., Demerseman, P., Royer, R. *Synthesis* **1985**, 1074, and references cited therein.
(3) Dauzonne, D., Royer, R. *Synthesis* **1987**, 1020.
(4) Sinhababu, A.K., Borchardt, R.T. *Tetrahedron Lett.* **1983**, *24*, 227.