

### A Convenient Synthesis of 2-(2-Nitroethyl)-Phenols

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Although the title compounds can be expected to be valuable and versatile starting materials for synthesizing miscellaneous products of biological interest – such as novel derivatives of benzannellated oxygen-containing heterocycles – a literature survey revealed surprisingly that this class of chemicals is hitherto unknown. The present communication describes a facile and general route to these 2-(2-nitroethyl)-phenols **4**, via the 2-(2-nitroethenyl)-phenols **3**.

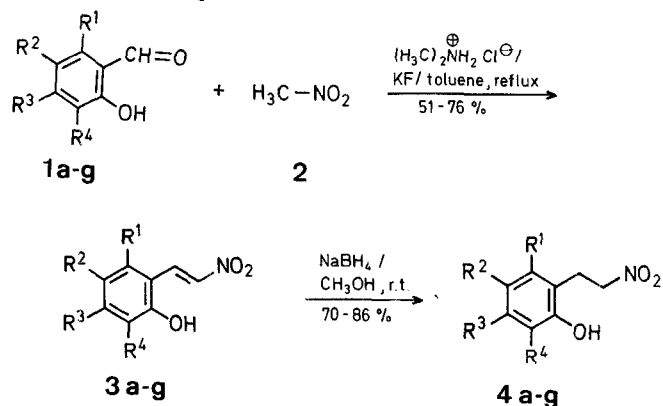
In spite of the numerous works devoted to the  $\beta$ -nitrostyrenes, those dealing with the synthesis of their 2-hydroxy derivatives **3** are few, often occasional, and restricted to a limited number of compounds<sup>1–18</sup>. Furthermore, when they are reported, the yields are rather unsatisfactory in most cases and sometimes refer to non-purified materials. This lack of a general method prompted us to develop a more reliable procedure for compounds **3**. We have found that they

**Table 1.** 2-(2-Nitroethenyl)-phenols **3** prepared

| Prod-<br>uct<br>No. | R <sup>1</sup>          | R <sup>2</sup>   | R <sup>3</sup>   | R <sup>4</sup>   | Reaction<br>time [h] <sup>a</sup> | Yield<br>[%] <sup>b</sup> | m.p. <sup>c</sup> [°C]<br>(solvent)     | Molecular<br>formula <sup>d</sup><br>or Lit. m.p. [°C]                 | <sup>1</sup> H-N.M.R. <sup>e</sup> (DMSO- <i>d</i> <sub>6</sub> /TMS)<br>δ [ppm]   |
|---------------------|-------------------------|------------------|------------------|------------------|-----------------------------------|---------------------------|---|--|--|
| <b>3a</b>           | H                       | H                | H                | H                | 2                                 | 61                        | 134.5–135.5°<br>(benzene)               | 133–134 <sup>e1</sup>  | 6.87 (ddd, 1H, <i>J</i> = 1.2 Hz, 7.2 Hz, 7.5 Hz); 7.03 (dd, 1H, <i>J</i> = 1.2 Hz, 8.1 Hz); 7.35 (ddd, 1H, <i>J</i> = 1.7 Hz, 7.2 Hz, 8.1 Hz); 7.65 (dd, 1H, <i>J</i> = 1.7 Hz, 7.5 Hz); 8.10 (d, 1H, <i>J</i> = 13.5 Hz); 8.18 (d, 1H, <i>J</i> = 13.5 Hz); 10.3–11.1 (1H, exchangeable with D <sub>2</sub> O) |
| <b>3b</b>           | H                       | Br               | H                | H                | 3.5                               | 60                        | 181–182°<br>(toluene)                   | 165–167 <sup>e12</sup>   | 6.92 (d, 1H, <i>J</i> = 8.9 Hz); 7.45 (dd, 1H, <i>J</i> = 2.6 Hz, 8.9 Hz); 7.89 (d, 1H, <i>J</i> = 2.6 Hz); 8.14 (s, 2H); 10.1–11.5 (1H, exchangeable with D <sub>2</sub> O)   |
| <b>3c</b>           | H                       | OCH <sub>3</sub> | H                | H                | 3.5                               | 51                        | 153–153.5°<br>(benzene)                 | 151 <sup>e11</sup>   | 3.73 (s, 3H); 6.80–7.08 (m, 2H); 7.22–7.37 (m, 1H); 8.18 (s, 2H); 9.7–11.0 (1H, exchangeable with D <sub>2</sub> O)  |
| <b>3d</b>           | H                       | H                | OCH <sub>3</sub> | H                | 4                                 | 65                        | 148–149 <sup>e1</sup><br>(toluene)      | C <sub>9</sub> H <sub>9</sub> NO <sub>4</sub><br>(195.2)               | 3.77 (s, 3H); 6.38–6.63 (m, 2H); 7.57 (d, 1H, <i>J</i> = 9.3 Hz); 7.99 (d, 1H, <i>J</i> = 13.5 Hz); 8.13 (d, 1H, <i>J</i> = 13.5 Hz); 10.0–11.5 (1H, exchangeable with D <sub>2</sub> O)   |
| <b>3e</b>           | H                       | H                | H                | OCH <sub>3</sub> | 2.5                               | 76                        | 128–129°<br>(benzene/<br>cyclohexane)   | 129–130 <sup>e5</sup>  | 3.85 (s, 3H); 6.80 (dd, 1H, <i>J</i> = 7.5 Hz, 7.8 Hz); 7.05 (dd, 1H, <i>J</i> = 1.8 Hz, 7.8 Hz); 7.18 (dd, 1H, <i>J</i> = 1.8 Hz, 7.5 Hz); 8.00 (d, 1H, <i>J</i> = 13.5 Hz); 8.17 (d, 1H, <i>J</i> = 13.5 Hz); 9.8–11.3 (1H, exchangeable with D <sub>2</sub> O)  |
| <b>3f</b>           | —(CH=CH) <sub>2</sub> — | H                | H                | H                | 9                                 | 61                        | 224° (dec)<br>(toluene/<br>nitroethane) | C <sub>12</sub> H <sub>9</sub> NO <sub>3</sub> <sup>g</sup><br>(215.2) | 7.23–8.19 (m, 6H); 8.29 (d, 1H, <i>J</i> = 13.5 Hz); 8.78 (d, 1H, <i>J</i> = 13.5 Hz); 10.8–12.1 (1H, exchangeable with D <sub>2</sub> O)  |
| <b>3g</b>           | H                       | H                | OH               | H                | 6.5                               | 56                        | 192° (dec)                              | C <sub>8</sub> H <sub>7</sub> NO <sub>4</sub><br>(181.1)               | 6.34 (dd, 1H, <i>J</i> = 2.3 Hz, 8.4 Hz); 6.42 (d, 1H, <i>J</i> = 2.3 Hz); 7.46 (d, 1H, <i>J</i> = 8.4 Hz); 7.95 (d, 1H, <i>J</i> = 13.5 Hz); 8.13 (d, 1H, <i>J</i> = 13.5 Hz); 10.0–11.0 (2H, exchangeable with D <sub>2</sub> O)   |

<sup>a</sup> Averaged times: the rates of the reactions are somewhat dependent on the vigour of refluxing.<sup>b</sup> Yield of recrystallized product, except for **3g** which has been purified as described in the experimental part.<sup>c</sup> Melting points are uncorrected.<sup>d</sup> Satisfactory microanalyses obtained: C ± 0.23, H ± 0.11, N ± 0.14.<sup>e</sup> The <sup>1</sup>H-N.M.R.-spectra were recorded at 90 MHz using a Varian EM 390 spectrometer.<sup>f</sup> The previously reported melting point: 171–172°C<sup>2</sup> is obviously erroneous.<sup>g</sup> This compound has been recently mentioned<sup>19</sup>, but neither its synthesis nor its physical data have been reported.

are conveniently obtained under mild conditions by the reaction between *o*-hydroxybenzaldehydes **1** and nitromethane (**2**) in the presence of dimethylammonium chloride in refluxing toluene. These condensations are still somewhat slow, but their rates can be greatly enhanced by the addition of a small amount of potassium fluoride to the reaction mixture



(Table 1). The unsaturated compounds **3** are then easily converted into the desired products **4** in good yields by treatment with sodium borohydride in methanol at room temperature (Table 2).

The preparation of the  $\beta$ -nitrostyrene derivatives **3** is also achievable by using primary amine hydrochlorides or other secondary amine hydrochlorides such as *n*-propylammonium chloride or diethylammonium chloride. However, in both cases, longer reaction times are required without noticeable improvements in the yield. In addition, the use of *n*-propylammonium chloride provides in variable amounts the corresponding *N*-*n*-propylsalicylaldimines as side-products. In another connection, we have ascertained that potassium fluoride alone is unsuited for carrying out these condensations because it leads to intractable mixtures.

The optimum proportions of the reagents involved have been experimentally determined. The new products **4a-g** as well as the intermediates **3a-g** have been fully characterized on the basis of their microanalytical and spectral data.

**Table 2.** 2-(2-Nitroethyl)-phenols **4** prepared

| Product No. | R <sup>1</sup>          | R <sup>2</sup>   | R <sup>3</sup>   | R <sup>4</sup>   | Yield [%] <sup>a</sup> | m.p. [°C] <sup>b</sup> (solvent) or b.p./torr [°C] | Molecular formula <sup>c</sup>                          | <sup>1</sup> H-N.M.R. <sup>d,e</sup> (CDCl <sub>3</sub> /TMS) δ [ppm]   |
|-------------|-------------------------|------------------|------------------|------------------|------------------------|--|---|---|
| <b>4a</b>   | H                       | H                | H                | H                | 76                     | 124–126°/0.06                                      | C <sub>8</sub> H <sub>9</sub> NO <sub>3</sub> (167.2)   | 3.32 (t, 2H, <i>J</i> = 7.5 Hz); 4.67 (t, 2H, <i>J</i> = 7.5 Hz); 5.0–5.3 (1H, exchangeable with D <sub>2</sub> O); 6.67–7.32 (m, 4H)   |
| <b>4b</b>   | H                       | Br               | H                | H                | 86                     | 55–56° (benzene/hexane); 180–183°/0.3              | C <sub>8</sub> H <sub>8</sub> BrNO <sub>3</sub> (246.1) | 3.28 (t, 2H, <i>J</i> = 7.5 Hz); 4.66 (t, 2H, <i>J</i> = 7.5 Hz); 5.24 (s, 1H, exchangeable with D <sub>2</sub> O); 6.64 (d, 1H, <i>J</i> = 9.3 Hz); 7.13–7.42 (m, 2H)  |
| <b>4c</b>   | H                       | OCH <sub>3</sub> | H                | H                | 78                     | 168–171°/0.15                                      | C <sub>9</sub> H <sub>11</sub> NO <sub>4</sub> (197.2)  | 3.28 (t, 2H, <i>J</i> = 7.5 Hz); 3.75 (s, 3H); 4.65 (t, 2H, <i>J</i> = 7.5 Hz); 4.9–5.3 (1H, exchangeable with D <sub>2</sub> O); 6.58–6.82 (m, 3H)   |
| <b>4d</b>   | H                       | H                | OCH <sub>3</sub> | H                | 80                     | 80–81° (benzene/cyclohexane)                       | C <sub>9</sub> H <sub>11</sub> NO <sub>4</sub> (197.2)  | 3.25 (t, 2H, <i>J</i> = 7.5 Hz); 3.76 (s, 3H); 4.63 (t, 2H, <i>J</i> = 7.5 Hz); 5.43 (s, 1H, exchangeable with D <sub>2</sub> O); 6.33 (d, 1H, <i>J</i> = 2.4 Hz); 6.44 (dd, 1H, <i>J</i> = 2.4 Hz, 8.4 Hz); 7.04 (d, 1H, <i>J</i> = 8.4 Hz)  |
| <b>4e</b>   | H                       | H                | H                | OCH <sub>3</sub> | 85                     | 118–120°/0.02                                      | C <sub>9</sub> H <sub>11</sub> NO <sub>4</sub> (197.2)  | 3.33 (t, 2H, <i>J</i> = 7.5 Hz); 3.88 (s, 3H); 4.65 (t, 2H, <i>J</i> = 7.5 Hz); 5.82 (s, 1H, exchangeable with D <sub>2</sub> O); 6.70–6.96 (m, 3H)   |
| <b>4f</b>   | —(CH=CH) <sub>2</sub> — | H                | H                | H                | 73                     | 95–95.5° (benzene/cyclohexane)                     | C <sub>12</sub> H <sub>11</sub> NO <sub>3</sub> (217.2) | 3.79 (t, 2H, <i>J</i> = 7.5 Hz); 4.68 (t, 2H, <i>J</i> = 7.5 Hz); 5.3–5.5 (1H, exchangeable with D <sub>2</sub> O); 7.03 (d, 1H, <i>J</i> = 9 Hz); 7.26–8.05 (m, 5H)  |
| <b>4g</b>   | H                       | H                | OH               | H                | 70                     | 75–76.5°   | C <sub>8</sub> H <sub>9</sub> NO <sub>4</sub> (183.2)   | 3.03 (t, 2H, <i>J</i> = 7.5 Hz); 4.63 (t, 2H, <i>J</i> = 7.5 Hz); 6.13 (dd, 1H, <i>J</i> = 2.3 Hz, 8.2 Hz); 6.30 (d, 1H, <i>J</i> = 2.3 Hz); 6.81 (d, 1H, <i>J</i> = 8.2 Hz); 9.09 (s, 1H, exchangeable with D <sub>2</sub> O); 9.40 (s, 1H, exchangeable with D <sub>2</sub> O) <sup>f</sup> |

<sup>a</sup> Yield of distilled or recrystallized product except for **4g** which has been purified by chromatography.<sup>b</sup> Melting points are uncorrected.<sup>c</sup> Satisfactory microanalyses obtained: C ± 0.22, H ± 0.16, N ± 0.19.<sup>d</sup> The <sup>1</sup>H-N.M.R.-spectra were recorded at 90 MHz using a Varian EM 390 spectrometer.<sup>e</sup> The CH<sub>2</sub> triplets are more or less broadened because of asymmetry induced through restricted rotation about the C—C bond.<sup>f</sup> In DMSO-*d*<sub>6</sub>.**2-(2-Nitroethenyl)-phenols (3a–f); General Procedure:**

Dimethylammonium chloride (20.4 g, 0.25 mol), commercial *o*-hydroxybenzaldehyde (**1a–f**; 0.125 mol), toluene (75 ml), nitromethane (**2**; 75 ml), and potassium fluoride (1.09 g, 18.75 mmol) are placed in a one-necked 500 ml conical flask fitted with a Dean-Stark water separator (capacity about 20 ml). The mixture is vigorously refluxed with stirring until the theoretical amount of water (2.25 ml) has decanted off. The volatiles are then thoroughly removed from the reaction vessel using a rotary evaporator by heating gradually from 50°C to 100°C to afford a crude material which is allowed to cool to about 50°C. Chloroform (20 ml in the case of **3a**, 50 ml in the other cases) and 0.2 normal hydrochloric acid (100 ml) are added to this lukewarm residue. The mixture obtained is heated in the water-bath at 60°C for 1–2 min using the rotary evaporator and is afterwards let to stand overnight in a refrigerator (–5°C). A crystalline solid is isolated by suction, carefully rinsed with several portions of water, and dried in a vacuum-desiccator. The chloroform layer is separated, and the aqueous layer is extracted with dichloromethane (3 × 30 ml). The combined extracts are evaporated under reduced pressure to yield a material which is chromatographed on a silica gel column (150 g, eluent dichloromethane/ethyl acetate, 95:5). After removal of the volatiles, the resulting product and the previously filtered solid are recrystallized together.

In the case of **3a**, the recrystallization is hindered by the presence of a scarcely soluble impurity and the following work up is to be recommended. The filtered and chromatographed materials are combined and covered with isopropyl ether (100 ml). The mixture is gently refluxed with stirring for 10 min and allowed to stand overnight at

–5°C. A white precipitate is filtered out, then thoroughly washed with small amounts of cold isopropyl ether. Evaporation of the solvent gives a solid which is recrystallized from benzene to afford **3a** as yellow crystals; yield: 12.6 g (61%); m.p. 134.5–135.5°C.

This drawback does not occur when the reaction is performed without potassium fluoride, but it takes about 40 h in this case for the reaction to go to completion and the yield is not markedly better (69%).

**5-Hydroxy-2-(2-nitroethenyl)-phenol (3g):**

This compound is readily soluble in water and the above-described work up is unsuitable. In this instance, using identical amounts of reagents, the crude oily material obtained after evaporation of the solvents from the reaction vessel is homogeneously triturated with Celite (25 g) whilst hot, then allowed to cool to room temperature. This mixture is gently refluxed with diethyl ether (200 ml) on the rotary evaporator. The sticky residue is filtered out and washed with diethyl ether (6 × 100 ml). This solid is placed in a porous thimble and extracted for 8 h with a Soxhlet apparatus (capacity about 400 ml) using the combined ether washings as solvent. After cooling, the solid is ground in a mortar and extracted for 8 additional h (this operation is repeated twice). Removal of the ether yields a red solid (17.2 g) which is crushed and covered with a mixture dichloromethane/methanol, 95:5 (50 ml). This suspension is smoothly refluxed with stirring for 10 min and allowed to cool in a refrigerator. Filtration of the solid affords pure **3g** as a red powder; yield: 12.7 g (56%); m.p. 190–192°C (dec.).

|   |       |         |        |        |
|---|-------|---------|--------|--------|
| C <sub>8</sub> H <sub>7</sub> NO <sub>4</sub> | calc. | C 53.04 | H 3.89 | N 7.73 |
| (181.1)                                       | found | 53.27   | 3.95   | 7.63   |

**2-(2-Nitroethyl)-phenols (4a–g); General Procedure:**

The 2-(2-nitroethyl)-phenol **3a–g** (0.125 mol) is covered with methanol (600 ml) in a wide-necked 2 l conical flask. Sodium borohydride (8.3 g, 0.22 mol) is added portionwise in 15 min to the stirred mixture. The solution is stirred for 30 min after the addition of sodium borohydride is completed, then acidified with the theoretical amount of 12 normal hydrochloric acid (~ 18.4 ml) and smoothly concentrated under vacuum. The residue is diluted with water (100 ml) and extracted with dichloromethane (**4a–f**) or ethyl acetate (**4g**) (300 ml, then 3 × 50 ml). The organic extracts are combined, dried with magnesium sulfate, filtered, and evaporated to dryness. The residue is chromatographed on a silica gel column (250 g, eluent dichloromethane/ethyl acetate, 95:5 for **4a–f**, 75:25 for **4g**). Removal of the solvents followed by recrystallization or distillation yields pure **4a–f**.

With regard to **4g**, these latter purification techniques have failed as an attempted distillation ended in an explosive decomposition and the attempted recrystallizations were unsuccessful on account of the extremely slow solidification of this product. However, the chromatographed material is satisfactorily pure as judged by N.M.R. spectroscopy and microanalytical results.

$C_8H_9NO_4$  calc. C 52.46 H 4.95 N 7.65  
(183.2) found 52.41 4.85 7.57

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