A General and Unexpected Synthesis of 2-(2-Chloro-2-nitroethenyl)phenols

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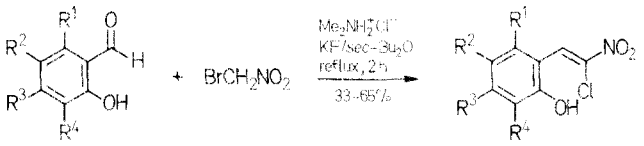
A convenient preparation of the previously unknown title compounds from 2-hydroxybenzaldehydes and bromonitromethane is described.

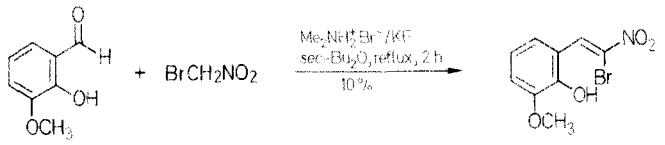
In continuation of our investigations on the use of the system dimethylammonium chloride/potassium fluoride as reagent for the condensation of active methylene compounds with aromatic aldehydes,[1-3] we became interested in examining the behavior of the versatile[4,5] bromonitromethane (**2**).

Preliminary attempts with *o*-vanillin (**1e**) and bromonitromethane (**2**) in toluene led to an inseparable mixture of 2-(2-bromo-2-nitroethenyl)-6-methoxyphenol (**4**) and 2-(2-chloro-2-nitroethenyl)-6-methoxyphenol (**3e**). The unforeseen presence of this latter compound in appreciable amounts prompted us to modify the experimental conditions in order to prepare a sole product. We thus found that the use of higher-boiling solvents such as butyl acetate, diisobutyl ether, or di-*sec*-butyl ether provides the chloro compound **3e** free from bromo derivative in 59, 58, and 61% yield, respectively, under similar conditions. The slightly better yield obtained in the latter case lead us to investigate the reaction in di-*sec*-butyl ether systematically.



1a-n **2** **3a-n**

No bromo compound was formed in any of the fourteen cases herein examined (Table). However, it must be pointed out that the use of dimethylammonium bromide instead of dimethylammonium chloride allows one to obtain the pure bromo derivative, although in poor yield. Thus, in the case of **1e**, the product **4** was isolated only in 10% yield.



1e **2** **4**

This unsatisfactory result is mainly due to the fact that the reaction stops far from completion. Unfortunately, several trials carried out to improve the yield were unsuccessful. Thus, we have established that:

- prolongation of the reaction time is useless since it rather lowers the yield;
- the use of larger amounts of reagents does not markedly influence the result.

A likely explanation for the unexpected formation of the title chloro compounds is that chloronitromethane produced *in situ* reacts with the aldehyde, instead of bromonitromethane. We have found that nucleophilic substitution of bromide by chloride ion present in the medium takes place when bromonitromethane alone is submitted to the same conditions. The transformation is complete and the chloronitromethane thus obtained was unam-

Table. 2-(2-Chloro-2-nitroethenyl)phenols **3** from 2-Hydroxybenzaldehydes **1**[a]

Product	R^1	R^2	R^3	R^4	Yield (%)[b]	m.p.[c] [°C] (solvent)	Molecular Formula[d]	MS (70 eV)[e] *m/e* (M^+)	^{1}H-NMR[f] ($CDCl_3$/TMS)[g] δ, *J*(Hz)
3a	H	H	H	H	38	115–115.5° (benzene/hexane)	$C_8H_6ClNO_3$ (199.6)	199, 201	5.70 (br. s, 1H exchangeable with D_2O); 6.86 (dd, 1H, *J* = 1.3, 8.0); 7.01 (ddd, 1H, *J* = 1.3, 7.6, 8.0); 7.36 (ddd, 1H, *J* = 1.8, 7.6, 8.0); 8.04 (dd, 1H, *J* = 1.8, 8.0); 8.80 (s, 1H)
3b	H	Cl	H	H	43	154–154.5° (benzene/cyclohexane)	$C_8H_5Cl_2NO_3$ (234.0)	233, 235, 237	5.66 (br. s, 1H, exchangeable with D_2O); 6.81 (d, 1H, *J* = 8.7); 7.31 (dd, 1H, *J* = 2.5, 8.7); 8.0 (d, 1H, *J* = 2.5); 8.68 (s, 1H)
3c	H	Br	H	H	45	135–136° (benzene/cyclohexane)	$C_8H_5BrClNO_3$ (278.5)	277, 279, 281	5.72 (br. s, 1H, exchangeable with D_2O); 6.75 (d, 1H, *J* = 8.7); 7.44 (dd, 1H, *J* = 2.4, 8.7); 8.13 (d, 1H, *J* = 2.4); 8.67 (s, 1H)
3d	H	Br	H	Br	42	152–154.5° (benzene/hexane)	$C_8H_4Br_2ClNO_3$ (357.4)	355, 357, 359, 361	5.99 (br. s, 1H, exchangeable with D_2O); 7.72 (d, 1H, *J* = 2.2); 8.06 (d, 1H, *J* = 2.2); 8.62 (s, 1H)
3e	H	H	H	OCH_3	61	137–138.5° (benzene/cyclohexane)	$C_9H_8ClNO_4$ (229.6)	229, 231	3.93 (s, 3H); 6.20 (s, 1H, exchangeable with D_2O); 6.80–7.02 (m, 2H); 7.55–7.81 (m, 1H); 8.80 (s, 1H)
3f	H	H	OCH_3	H	33	132–133° (trichloroethylene)	$C_9H_8ClNO_4$ (229.6)	229, 231	3.82 (s, 3H); 6.38–6.61 (m, 2H); 7.96–8.29 (m, 1H); 8.89 (s, 1H); 10.20 (br. s, 1H, exchangeable with D_2O)
3g	H	OCH_3	H	H	36	160–162° (benzene/hexane)	$C_9H_8ClNO_4$ (229.6)	229, 231	3.78 (s, 3H); 6.85–6.98 (m, 2H); 7.53–7.66 (m, 1H); 8.87 (s, 1H); 9.48 (s, 1H, exchangeable with D_2O)
3h	OCH_3	H	H	H	33	107–108° (benzene/cyclohexane)	$C_9H_8ClNO_4$ (229.6)	229, 231	3.87 (s, 3H); 5.32 (br. s, 1H exchangeable with D_2O); 6.38–6.63 (m, 2H); 7.27 (dd, 1H, *J* = 8.1, 8.4); 8.37 (s, 1H)
3i	H	H	OCH_3	OCH_3	58	163–163.5° (benzene/cyclohexane)	$C_{10}H_{10}ClNO_5$ (259.7)	259, 261	3.95 (s, 6H); 6.38 (s, 1H, exchangeable with D_2O); 6.58 (d, 1H, *J* = 9.1); 7.91 (d, 1H, *J* = 9.1); 8.79 (s, 1H)
3j	H	OCH_3	H	OCH_3	34	170–170.5° (trichloroethylene/cyclohexane)	$C_{10}H_{10}ClNO_5$ (259.7)	259, 261	3.80 (s, 3H); 3.91 (s, 3H); 5.82 (s, 1H, exchangeable with D_2O); 6.62 (d, 1H, *J* = 2.7); 7.18 (d, 1H, *J* = 2.7); 8.82 (s, 1H)
3k	OCH_3	H	H	OCH_3	55	119.5–120.5° (benzene/cyclohexane)	$C_{10}H_{10}ClNO_5$ (259.7)	259, 261	3.80 (s, 3H); 3.88 (s, 3H); 6.16 (s, 1H, exchangeable with D_2O); 6.37 (d, 1H, *J* = 9.0); 6.87 (d, 1H, *J* = 9.0); 8.33 (s, 1H)
3l	H	Br	H	OCH_3	62	138–139° (benzene/cyclohexane)	$C_9H_7BrClNO_4$ (308.5)	307, 309, 311	3.93 (s, 3H); 6.14 (s, 1H, exchangeable with D_2O); 7.05 (d, 1H, *J* = 2.0); 7.76 (d, 1H, *J* = 2.0); 8.67 (s, 1H)
3m	Br	H	H	OCH_3	65	123–124° (cyclohexane)	$C_9H_7BrClNO_4$ (308.5)	307, 309, 311	3.93 (s, 3H); 6.12 (s, 1H, exchangeable with D_2O); 6.79 (d, 1H, *J* = 8.7); 7.13 (d, 1H, *J* = 8.7); 8.18 (s, 1H)
3n	H	NO_2	H	H	39	156–159°	$C_8H_5ClN_2O_5$ (244.6)	244, 246	7.12 (d, 1H, *J* = 9.0); 8.19 (dd, 1H, *J* = 2.7, 9.0); 8.74 (s, 1H); 8.93 (d, 1H, *J* = 2.7); 11.40 (br. s, 1H, exchangeable with D_2O)

[a] Aldehydes **1a–g, n** are commercially available. Compound **1h** was prepared according to Ref. 12–13.
Aldehydes **1i–m** were synthesized according to Ref. 14–18, respectively.

[b] Yield of recrystallized product except for **3n** which was purified as described in the experimental part.

[c] Melting points are uncorrected.

[d] Satisfactory microanalyses obtained: C ±0.30, H ±0.15, N ±0.19, Cl ±0.29.

[e] The mass spectra were obtained on a Nermag Ribermag R 10-10C spectrometer.

[f] The ^{1}H-NMR spectra were recorded at 90 MHz using a Varian EM 390 spectrometer.

[g] A mixture $CDCl_3$/DMSO-d_6 (9 : 1) was used for **3f**, **3g**, and **3n**.

biguously characterized by comparison of its spectral data[6] with those of a sample prepared by an alternative method.[7] In this context, we have further established that in the reactions of **1e** or **1f** no significant improvement in yield is observed when chloronitromethane is used in place of bromonitromethane under comparable conditions.

We have also ascertained that in the case of the bromo derivative **4**, no halogen exchange occurs when this product is treated in a similar way, the only product obtained (besides unreacted material) being the dehalogenated compound which proved identical with authentic 6-methoxy-2-(2-nitroethenyl)phenol.[1]

Although the yields are moderate in certein cases, the facile synthesis described here leads to new products which are interesting in several respects:

From a pharmacological viewpoint, they represent a novel class of compounds worthy of an investigation for possible cytotoxic effects.[8-10]

With regard to organic synthesis, they are attractive chemicals insofar as their structure predisposes them to be useful intermediates for the preparation of benzo-annelated heterocycles.

The structures of 2-(2-chloro-2-nitroethenyl)phenols **3a–n** as well as that of 2-(2-bromo-2-nitroethenyl)-6-methoxyphenol **(4)** were elucidated on the basis of microanalysis, mass spectroscopy, and ^{1}H-NMR. The low field observed for the resonance of the ethylenic protons unequivocally proves that these compounds are obtained as pure *Z* isomers (the aromatic ring and the nitro group are located on the opposite sides of the double bond) on the basis of theoretical work on the ^{1}H-NMR spectra of the related (*Z*)- and (*E*)-β-bromo-β-nitrostyrene.[11]

2-(2-Chloro-2-nitroethenyl)phenols (3a–n); General Procedure:
In a 250 mL Erlenmeyer flask fitted with a Dean-Stark water trap (capacity ~ 20 mL) are placed the 2-hydroxybenzaldehyde (**1a–n**; 40 mmol), dimethylammonium chloride (9.8 g, 0.12 mol), bromonitromethane[19,20] (**2**; 10.5 g, 75 mmol), di-*sec*-butyl ether (110 mL), and potassium fluoride (350 mg, 6 mmol). The mixture is heated to reflux with vigorous stirring for 2 h, then allowed to cool to room temperature. Rotary evaporation of the volatiles from the reaction vessel yields a residue which is taken up with H_2O (50 mL) and CH_2Cl_2 (200 mL). After filtration through a short pad of Celite, the organic layer is separated and the aqueous phase is extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts are dried ($MgSO_4$), filtered, then evaporated under reduced pressure. The crude product is directly chromatographed on a silica gel column [200 g, 200–400 mesh, eluent CH_2Cl_2 for **3a–e** and **3h–m**, CH_2Cl_2/EtOAc (95:5) for **3f, g, n**]. Evaporation of the solvents *in vacuo* followed by recrystallization provides the analytically pure compounds **3a–m** (Table).

With product **3n**, several attempted recrystallizations failed due to partial decomposition. In this case, a second silica gel chromatography (150 g, 200–400 mesh, eluent $CHCl_3$) proved efficient to give the compound in satisfactory purity.

$C_8H_5ClN_2O_5$	calc.	C 39.29	H 2.06	Cl 14.49	N 11.45
(244.6)	found	39.10	2.24	14.32	11.26

2-(2-Bromo-2-nitroethenyl)-6-methoxy-phenol (4):
The procedure is performed with 2-hydroxy-3-methoxybenzaldehyde (**1e**; 6.09 g, 40 mmol) as described above except that dimethylammonium chloride is replaced by dimethylammonium bromide (15.1 g, 0.12 mol). After extraction, removal of the solvent affords a crude material (8.9 g) which is column-chromatographed on silica gel (250 g, 200–400 mesh, eluent CH_2Cl_2). Evaporation to dryness followed by recrystallization from benzene/cyclohexane furnishes pure **4** as bright-yellow crystals; yield: 0.98 g (10%); m.p. 155–156 °C.

$C_9H_8BrNO_4$	calc.	C 39.44	H 2.94	Br 29.16	N 5.11
(274.1)	found	39.40	2.98	28.86	5.24

MS (70 eV): *m/e* = 273, 275 (M^+).

IR (KBr): ν = 3500, 1606, 1525, 1365 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.94 (s, 3H); 6.17 (s, 1H, exchangeable with D_2O); 6.80–7.05 (m, 2H); 7.60–7.85 (m, 1H); 9.01 (s, 1H).

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