A Convenient Synthesis of 2-Nitrophenols from 1,2-Dichlorobenzenes

Joseph Zilberman,* David Ioffe, Igal Gozlan
IMI (TAMI) Institute for Research and Development, Haifa Bay 26111, P.O.B. 10140 Haifa, Israel

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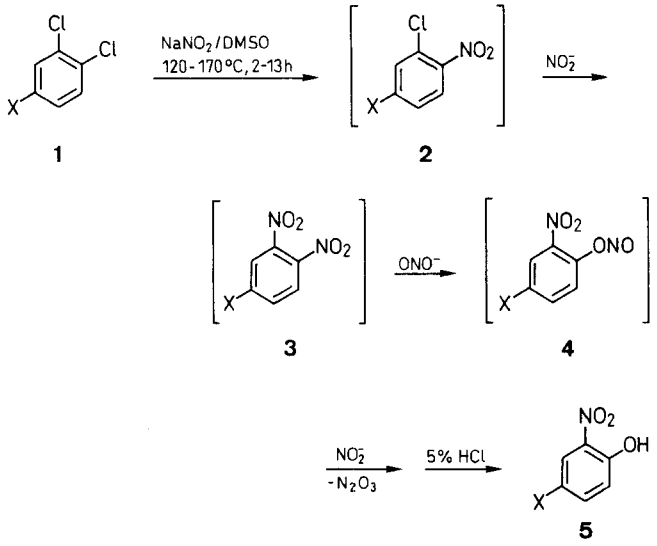
Aromatic nucleophilic substitution of 1,2-dichlorobenzenes **1** possessing a strong electron-withdrawing group in the 4-position with a nitrite ion give the corresponding 2-nitrophenols **5**.

The reaction of haloaliphatic compounds with a nitrite ion is a convenient method for the synthesis of the corresponding nitro compounds.[1] However, such a displacement of halogen atom of monohaloaromatics with the nitro group has no synthetic potential for preparing aromatic nitro compounds.[2,3] The end product of this reaction is usually the phenoxide (ArO^-).[2]

As for polyhaloaromatics, the only reported reaction is that of anthraquinones having two and more chlorine (bromine) atoms in certain positions with sodium nitrite in dimethylformamide, which leads to mixtures of hydroxynitroanthraquinones.[4-6] The reaction mechanism was not discussed.

We investigated the reaction of substituted 1,2-dichlorobenzenes **1a–e** with sodium nitrite and found that the presence of an electron-withdrawing substituent in the 4-position enables us to obtain 2-nitrophenols **5a–e** in good yields. This reaction can therefore be used as a convenient and simple method for the preparation of 2-nitrophenol derivatives. We presume that the formation of nitrophenols **5** proceeds according to Scheme 1.

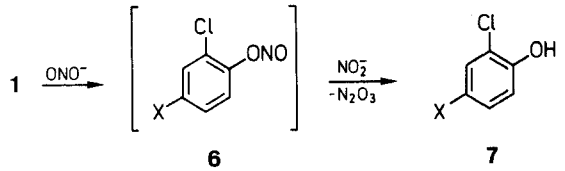


1–5	X	d	$PhSO_2$
a	NO_2	e	4-$MeC_6H_4SO_2$
b	PhCO	f	CF_3
c	3,4-$Cl_2C_6H_3SO_2$	g	MeCO

Scheme 1

The substituent, being an electron-withdrawing group and located in the 4-position, promotes a nucleophilic substitution of the chlorine atom by the nitrite ion (*N*-attack) to give compounds **2**. The second chlorine atom in compound **2**, is easily replaced by the nitro group due to the activating effect of the newly substituted nitro group leading to compounds **3**. Such compounds, with two vicinal nitro groups are unstable[2] in the presence of the ambident nucleophile NO_2^- resulting in the formation of an unstable ester of nitrous acid **4**. The latter is converted into the final product **5** under the reaction conditions.

The byproducts of the reaction are chlorophenols **7**, which are formed as a result of the primary *O*-attack of the nitrite ion on the starting 1,2-dichlorobenzenes **1** via the formation of unstable nitrous acid esters **6** (Scheme 2).



Scheme 2

The highest yield of the 2-nitrophenols **5a–e** was obtained in dimethyl sulfoxide as solvent. When ethylene glycol or dimethylformamide were used, the conversion rate of the starting compounds did not change significantly, while the selectivity for 2-nitrophenols **5** decreased due to the formation of more chlorophenols **7**.

According to Schemes 1 and 2, the molar ratio of sodium nitrite to the 1,2-dichlorobenzenes **1a–e** for a full conversion of the latter into 2-nitrophenol **5a–e** should be 3 (for substrate **1c** it should be 6). However, the reaction should be carried out using a 4–5 fold excess of sodium nitrite (for **1c**, a 10–11 fold excess) to compensate for the side reactions caused by nitrite ions. With further increase of the nitrite/substrate ratio, the formation rate of the final products also increased, while the reaction selectivity for the 2-nitrophenols (75–85%) remained virtually unchanged. The results are summarized in Table 1. The structure of the new compounds was fully assigned on the basis of analytical and spectroscopic data.

The NMR spectrum of compounds **5a–e** confirms the location of the substituent X in the 4-position to the hydroxy group. The doublet ($J = \sim 2.5$, for **5b**, singlet) at the lowest field corresponds to the least shielded proton located between substituent X and a nitro group. If the substituent X occupies the 3-position to the hydroxy group, another doublet ($J = 8.56–9.30$), corresponding to the proton adjacent to the nitro group, would be located at the lowest field because of the negative inductive effect of the nitro and hydroxy groups. The 2-chlorophenols **7a–d** formed as byproducts were identified by GC/MS of the respective reaction mixtures (Table 2).

Table 1. 2-Nitrophenols **5** Prepared

Product	Reaction Time (h)	Yield[a] (%)	mp (°C) found (solvent)	mp (°C) reported	IR (KBr) ν (cm^{-1})	^1H NMR (DMSO/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
5a	2	65[b]	114–115 (MeOH)	113–114[7]	3440, 1570, 1305	8.70 (d, 1H, J = 2.85), 8.37 (dd, 1H, J = 9.3, 2.9), 7.29 (d, 1H, J = 9.3)	184 (M^+, 100), 154 (43), 107 (25)
5b	10	70	90–91 (toluene/PE)	91–92[8]	3420, 1670, 1530, 1340	8.22 (s, 1H), 7.94 (d, 1H, J = 8.56), 7.53–7.75 (m, 5H), 7.28 (d, 1H, J = 8.56)	243 (M^+, 82), 166 (77), 120 (26), 105 (100)
5c	13	66	232–233 (AcOH)	235[9]	3450, 1530, 1335, 1325, 1160	8.44 (d, 2H, J = 2.3), 8.07 (dd, 2H, J = 8.9, 2.5), 7.29 (d, 2H, J = 8.9)	340 (M^+, 100), 202 (11), 186 (66), 140 (16)
5d	4	70	132–133 (EtOH)	132–134[10]	3420, 1530, 1360, 1325, 1160	8.52 (d, 1H, J = 2.4), 8.15 (dd, 1H, J = 11.2, 2.4), 8.08 (dd, 2H, J = 9.6, 1.5), 7.81–7.70 (m, 3H), 7.39 (d, 1H, J = 8.8)	279 (M^+, 100), 186 (18), 140 (2)
5e	4	66	143–144 (toluene)	157–158[11]	3440, 1530, 1360, 1325, 1160	8.49 (d, 1H, J = 2.2), 8.12 (dd, 1H, J = 8.9, 2.2), 7.95 (d, 2H, J = 8.2), 7.50 (d, 2H, J = 8.1), 7.37 (d, 1H, J = 8.8)	294 (13), 293 (M^+, 91), 186 (36), 140 (22), 139 (100)

[a] Yield of isolated products **5** based on **1**, not optimized.

[b] A better yield of 76% was reported for this product in Ref. 8.

Table 2. MS Data of Compounds **5f, g** and **7a–d**

Product	MS (70 eV) m/z (%)
5f	207 (M^+, 207), 177 (21), 161 (14), 149 (22), 113 (19)
5g	181 (M^+, 23), 166 (100), 120 (37)
7a	173 (100), 175 (34) (M^+), 145 (13), 143 (38), 107 (12)
7b	232 (72), 234 (24) (M^+), 157 (32), 155 (100), 105 (58)
7c	336 (58), 338 (58), 340 (18), 342 (2.5) (M^+), 198 (4), 196 (21), 194 (32), 177 (34), 175 (100)[a]
7d	268 (100), 270 (41) (M^+), 177 (19), 175 (38), 125 (15)

[a] The same MS was obtained for an authentic specimen[12] of 4-hydroxy-3,3′,4′-trichlorophenyl phenyl sulfone.

When 1,2-dichloro-4-trifluoromethylbenzene (**1f**) and 3,4-dichloroacetophenone (**1g**) were used as starting materials, the corresponding 2-nitrophenols **5f,g** were identified in the reaction mixtures by GC/MS (Table 2), but were not isolated. The conversion of 1,2-dichlorobenzene **1f** was only 20%, obviously, due to the insufficient promoting influence of the trifluoromethyl group. In the case of substrate **1g**, the conversion was almost complete. However, along with the target product **5g**, 1-(3,4-dichlorophenyl)ethanol was formed as a result of reduction of the starting ketone **1g**. The yield of 2-nitrophenol **5g**, which was not isolated was 40% (according to GC).

Melting points were measured using a Büchi-520 apparatus and are uncorrected. IR spectra were recorded on a Nicolet 5 × IR spectrophotometer, ^1H NMR on a Bruker WP 200 (200 MHz) spectrometer and MS on a Hewlett-Packard 5890 spectrometer.

The 1,2-dichlorobenzenes **1a,f** were purchased from Aldrich Chemical Co. and Imperial Chemical Industries Ltd., respectively. Compounds **1b–e** and **1g** were prepared according to the literature.[13] Reagent quality DMSO and $NaNO_2$ were used without further purification.

4-Hydroxy-3-nitrophenyl Phenyl Sulfone (5d); Typical Procedure:
To a solution of 3,4-dichlorophenyl phenylsulfone (**1d**; 28.7 g, 0.1 mol) in DMSO (200 mL), was added $NaNO_2$ (27.6 g, 0.4 mol) and the mixture stirred at 170°C for 4 h. During the reaction, the evolution of yellow-brown vapors was observed. The mixture was then cooled, acidified with 5% aq HCl (300 mL) and extracted with EtOAc (3 × 70 mL). The organic phase was washed with water (200 mL) and the solvent was evaporated at reduced pressure. The solid residue was recrystallized from EtOH (50 mL) to afford **5d** as a yellow crystalline solid, which was isolated by suction; yield: 18.9 g (68%) (Table).

Compounds **5b, 5c, 5e** were synthesized at the same temperature as **5d**. Product **5a** was prepared at 120°C. The molar ratios of the $NaNO_2$ per starting 1,2-dichlorobenzene were 4.0, 4.8 and 10.4 for **5a, 5b,e** and **5c**, respectively. All the isolated 2-nitrophenols had a yellow colour.

The reaction of compounds **1f** and **1g** with $NaNO_2$ was carried out in a similar manner to **1d** and the products analyzed by GC/MS.

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