Nucleophilic Substitution of Halogens with Amines in 2- and 4-Nitrophenols

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Abstract: Fluorine and chlorine in halonitrophenols are efficiently replaced with alkylamines in acetonitrile or in an excess of the amine at elevated temperature.

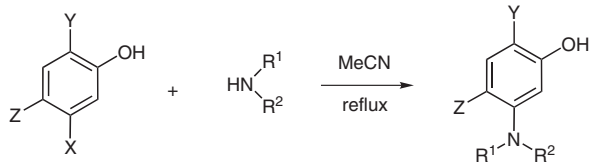
Key words: amines, nucleophilic aromatic substitutions, phenols, arenes

The nucleophilic substitution of halogens, mainly fluorine, located in positions *ortho* and *para* to the nitro group, is one of the most versatile methods for the synthesis of substituted nitrobenzenes.[1] The reaction is strongly affected by other groups bound to the aromatic ring, and can be inhibited when strong electron-donating substituents, especially negatively charged substituents conjugated with the nitro group, are present. This is the case with 2- and 4-nitrophenols when the reaction conditions or the nucleophile are sufficiently basic. Taking into account the acidity of 5-fluoro-2-nitrophenol (**1**) (pK_a 6.07 in EtOH–H_2O)[2] and the acidity of secondary amine conjugated acids (e.g, pK_a 8.78 in H_2O for morpholine),[3] replacing fluorine with such amines seems to be a bold idea since one would expect proton transfer as the sole reaction.

Since the nitration of 3-aminophenols seems to be effective only for the N-acylated derivatives,[4] the number of direct methods for the synthesis of aminonitrophenols is very limited; the substitution of fluorine with amines in O-silylated fluoronitrophenols[5] and with hydroxide ion in fluoronitroanilines have been reported.[6]

The aforementioned substitution of halogens in halonitrophenols with amines was, however, observed as an unexpected side process in the Mannich condensation of 5-fluoro-2-nitrophenol (**1**) or 3-fluoro-4-nitrophenol with piperidine in boiling ethanol, which gave the corresponding substitution products in rather moderate and low yields of 54% and 7% respectively;[7] there are only a few isolated reports of similar reactions.[8] In this paper we would like to present the results of a more regular examination of the scope of the reaction.

We decided to use aprotic solvents as the reaction medium, which should decrease the acidity of nitrophenols compared to the protonated alkylamines. According to literature data, changing the solvent from water to acetonitrile reduces the acidity of 2-nitrophenol from pK_a 7.2 to 22.4,[9] whereas that of protonated morpholine only from pK_a 8.36 to 16.61.[10]



1 X = F Y = NO_2 Z = H
2 X = Cl Y = H Z = NO_2
3 X = Cl Y = NO_2 Z = H

4a–f

5 Y = NO_2 Z = H
6 Y = H Z = NO_2

Equation 1

Thus, the reaction of **1** with various primary and secondary alkylamines (2.5-fold excess) was carried out in refluxing acetonitrile for one hour giving almost quantitative yields of substitution products **5** (Table 1). Less reactive aniline derivatives, however, reacted poorly under these conditions. Increasing the temperature to 125 °C and replacing acetonitrile with a large excess of the amine slightly improved the result (Table 1).

Nucleophilic substitution of chlorine is more difficult then that of fluorine even when located in the more activated *ortho* position to the nitro group. As a result, 3-chloro-4-nitrophenol (**2**) and 5-chloro-2-nitrophenol (**3**) required harsher conditions for the displacement of chlorine atom with alkylamines (Table 2). Reaction of **2** with five equivalents of morpholine (**4a**) in acetonitrile at 60 °C gave only a 36% yield of product **6a** after two days, while when **2** was refluxed in excess of **4a** used as a solvent (25 equiv, bp 129 °C) the reaction was complete within 30 minutes. Similarly the reaction of **2** with 1-methylpiperazine (bp 138 °C) (**4e**) was complete within one hour, while the reaction with benzylamine (**4c**) required heating for five hours at 120 °C. Reaction or **2** with lower-boiling butylamine (bp 78 °C) required reflux for 96 hours to go to completion.

The presented results show, that fluoronitrophenols can be excellent substrates for the direct preparation of the desired aminonitrophenols in reactions with alkyl amines. The corresponding chloronitrophenols are less reactive, although under appropriate conditions they give satisfactory yields of products. While high temperature and large excess of the amine significantly lower the reaction time, in the cases of costly amines, much slower reactions in boiling acetonitrile with only 2.5 equivalents of the amine may be more suitable.

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Table 1 Reaction of Amines with 5-Fluoro-2-nitrophenol (**1**)

Amine	NR^1R^2	Conditions	Time (h)	Product	Yield[a] (%)
4a	morpholin-4-yl	amine (2.5 equiv), MeCN, reflux	1	**5a**	97
4b	NHBu	amine (2.5 equiv), MeCN, reflux	1	**5b**	97
4c	NHBn	amine (2.5 equiv), MeCN, reflux	1	**5c**	98
4d	pyrrolidin-1-yl	amine (2.5 equiv), MeCN, reflux	1	**5d**	99
4e	4-methylpiperazin-1-yl	amine (2.5 equiv), MeCN, reflux	1	**5e**	87
4f	$4\text{-}ClC_6H_4NH$	amine (2.5 equiv), MeCN, reflux	24	**5f**	5
4f	$4\text{-}ClC_6H_4NH$	amine (12.5 equiv), 125 °C	72	**5f**	16

[a] Isolated yield.

Table 2 Reaction of 3-Chloro-4-nitrophenol (**2**) and 5-Chloro-2-nitrophenol (**3**) with Amines **4**

Substrate	Amine	NR^1R^2	Conditions	Temp (°C)	Time (h)	Product	Yield[a] (%)
3	**4a**	morpholin-4-yl	amine (2.5 equiv), MeCN	82	24	**5a**	83
3	**4a**	morpholin-4-yl	amine (12.5 equiv)	120	1.5	**5a**	85
3	**4d**	pyrrolidin-1-yl	amine (12.5 equiv)	87	48	**5d**	72
3	**4e**	4-methylpiperazin-1-yl	amine (2.5 equiv), MeCN	82	30	**5e**	67
2	**4a**	morpholin-4-yl	amine (2.5 equiv), MeCN	60	48	**6a**	36
2	**4a**	morpholin-4-yl	amine (12.5 equiv)	129	0.5	**6a**	95
2	**4b**	NHBu	amine (12.5 equiv)	78	96	**6b**	66
2	**4c**	NHBn	amine (12.5 equiv)	120	5	**6c**	75
2	**4e**	4-methylpiperazin-1-yl	amine (12.5 equiv)	138	1	**6e**	69

[a] Isolated yield.

Melting points are uncorrected. NMR spectra were recorded on a Varian Mercury 400 (400 MHz for ^1H and 100 MHz for ^{13}C) instrument in DMSO-d_6. MS spectra (EI, 70 eV) were obtained on an AMD-604 spectrometer. Silica gel Merck 60 (230–400 mesh) was used for column chromatography.

3-Chloro-4-nitrophenol (**2**) and 5-chloro-2-nitrophenol (**3**) were obtained according to literature procedures.[11] All other reagents are commercially available. The amines **4a**, **4b**, and **4d** were additionally dried by distillation and stored over KOH pellets.

Amino-Substituted Nitrophenols 5 and 6; General Procedure

The nitrophenol **1**–**3** (0.2 mmol) was mixed with the appropriate amine (0.5 mmol for reactions in MeCN, or 2.5 mmol for reactions carried out without solvent) and, when applicable, with anhyd MeCN (4 mL), then stirred at elevated temperature for the time specified in Tables 1 and 2. After cooling, the mixture was poured into dil HCl (1:10, 50 mL), then extracted with EtOAc (3 × 20 mL). The combined extracts were washed with brine, dried (Na_2SO_4), and evaporated. The crude product was purified by column chromatography (silica gel, hexane–EtOAc). Analytically pure samples were obtained by recrystallization (hexane–EtOAc).

In the case of reactions with 1-methylpiperazine (**4e**), as the products are reasonably basic, a better workup procedure was as follows: the mixture was evaporated in vacuo, then mixed with EtOAc (20 mL) and a small amount of H_2O was added, enough to obtain two separable layers. The inorganic layer was extracted with EtOAc, the combined organic extracts were washed with small volume of brine, dried (Na_2SO_4), and worked up further as usual.

5-(Morpholin-4-yl)-2-nitrophenol (5a)

Yellow crystals; mp 144–145 °C.

^1H NMR: δ = 10.70 (br s, 1 H), 7.85 (d, *J* = 9.0 Hz, 1 H), 6.50 (d, *J* = 2.6 Hz, 1 H), 6.45 (dd, *J* = 9.0, 2.6 Hz, 1 H), 3.00–2.96 (m, 4 H), 2.52–2.49 (m, 4 H).

^{13}C NMR: δ = 156.6, 156.4, 127.0, 124.7, 106.7, 99.3, 65.7, 46.3.

MS (EI): *m*/*z* (%) = 224 (96), 166 (100), 136 (22), 108 (11), 65 (13).

Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.35; H, 5.44; N, 12.53.

5-(Butylamino)-2-nitrophenol (5b)

Yellow crystals; mp 91–98 °C.

^1H NMR: δ = 11.28 (br s, 1 H), 7.79 (d, *J* = 9.4 Hz, 1 H), 7.55 (apparent t, 1 H), 6.32 (dd, *J* = 9.4, 2.6 Hz, 1 H), 6.05 (d, *J* = 2.6 Hz, 1 H), 3.11–3.17 (m, 2 H), 1.49–1.57 (m, 2 H), 1.32–1.42 (m, 2 H), 0.92 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR: δ = 157.9, 156.7, 127.1, 122.9, 108.1, 95.2, 42.1, 30.3, 19.6, 13.6.

MS (EI): *m*/*z* (%) = 211 (3), 210 (26), 168 (9), 167 (100), 122 (2), 121 (18), 120 (2).

Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32. Found: C, 57.15; H, 6.66; N, 13.22.

5-(Benzylamino)-2-nitrophenol (5c)
Yellow crystals; mp 122–124 °C.

^{1}H NMR: δ = 11.16 (br s, 1 H), 8.05 (apparent t, 1 H), 7.80 (d, *J* = 9.4 Hz, 1 H), 7.26–7.39 (m, 5 H), 6.38 (dd, *J* = 9.4, 2.4 Hz, 1 H), 6.08 (d, *J* = 2.4 Hz, 1 H), 4.42 (d, *J* = 6.0 Hz, 1 H).

^{13}C NMR: δ = 157.7, 156.5, 138.2, 128.5, 127.3, 127.2, 123.4, 108.1, 96.5, 45.9.

MS (EI): *m*/*z* (%) = 245 (8), 244 (55), 243 (6), 197 (2), 167 (3), 91 (100).

Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.87; H, 4.89; N, 11.41.

2-Nitro-5-(pyrrolidin-1-yl)phenol (5d)
Yellow crystals; mp 137–139 °C.

^{1}H NMR: δ = 11.19 (br s, 1 H), 7.87 (d, *J* = 9.7 Hz, 1 H), 6.33 (dd, *J* = 9.7, 2.6 Hz, 1 H), 6.04 (d, *J* = 2.6 Hz, 1 H), 3.38–3.42 (m, 4 H), 1.94–2.00 (m, 4 H).

^{13}C NMR: δ = 156.9, 153.7, 127.2, 123.1, 106.9, 97.1, 47.9, 24.8.

MS (EI): *m*/*z* (%) = 209 (12), 208 (100), 207 (92), 191 (2), 180 (5), 162 (8), 161 (17), 153 (6), 152 (11), 150 (5).

Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.70; H, 5.70; N, 13.39.

5-(4-Methylpiperazin-1-yl)-2-nitrophenol (5e)
Yellow crystals; mp 90–93 °C.

^{1}H NMR: δ = 10.9 (br s, 1 H), 7.87 (d, *J* = 9.7 Hz, 1 H), 6.66 (dd, *J* = 9.7, 2.7 Hz, 1 H), 6.42 (d, *J* = 2.7 Hz, 1 H), 3.44–3.48 (m, 4 H), 2.38–2.42 (m, 4 H), 2.21 (s, 3 H).

^{13}C NMR: δ = 156.8, 156.2, 127.0, 124.2, 107.0, 99.2, 54.1, 46.1, 45.5.

MS (EI): *m*/*z* (%) = 238 (14), 237 (100), 236 (11), 222 (7), 195 (7), 176 (5), 166 (19).

Anal. Calcd for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.51; H, 6.28; N, 17.59.

5-(4-Chlorophenylamino)-2-nitrophenol (5f)
Brown solid; mp 195–197 °C.

^{1}H NMR: δ = 11.04 (br s, 1 H), 9.35 (br s, 1 H), 7.91 (d, *J* = 9.2 Hz, 1 H), 7.40–7.44 (m, 2 H), 7.22–7.27 (m, 2 H), 6.52–6.57 (m, 2 H).

^{13}C NMR: δ = 156.8, 151.8, 138.8, 129.4, 127.7, 127.1, 126.3, 122.7, 108.0, 100.0.

MS (EI): *m*/*z* (%) = 264 (100), 218 (18), 206 (9), 154 (13).

Anal. Calcd for $C_{12}H_9ClN_2O_3$: C, 54.46; H, 3.43; N, 10.58. Found: C, 53.43; H, 3.54; N, 10.25.

3-(Morpholin-4-yl)-4-nitrophenol (6a)
Yellow crystals; mp 194–197 °C (dec).

^{1}H NMR: δ = 7.89 (d, *J* = 9.0 Hz, 1 H), 6.52 (d, *J* = 2.5 Hz, 1 H), 6.49 (dd, *J* = 9.0, 2.5 Hz, 1 H), 3.68–3.74 (m, 4 H), 2.92–2.98 (m, 4 H).

^{13}C NMR: δ = 163.2, 149.1, 133.7, 129.3, 109.0, 106.0, 66.1, 51.5.

MS (EI): *m*/*z* (%) = 225 (9), 224 (65), 223 (12), 208 (12), 207 (100), 206 (4), 191 (6), 190 (32), 189 (31), 178 (7), 177 (52), 163 (11), 162 (10), 161 (61), 149 (51).

Anal. Calcd for $C_{10}H_{12}N_2O_4$: C, 53.57; H, 5.39; N, 12.49. Found: C, 53.51; H, 5.41; N, 12.51.

3-(Butylamino)-4-nitrophenol (6b)
Yellow crystals; mp 100–101 °C.

^{1}H NMR: δ = 10.90 (br s, 1 H), 8.25 (t, *J* = 4.9 Hz, 1 H), 7.97 (d, *J* = 9.3 Hz, 1 H), 6.20 (d, *J* = 2.3 Hz, 1 H), 6.17 (dd, *J* = 9.3, 2.3 Hz, 1 H), 3.21–3.29 (m, 2 H), 1.56–1.66 (m, 2 H), 1.33–1.45 (m, 2 H), 0.90–0.96 (m, 3 H).

^{13}C NMR: δ = 165.0, 147.8, 129.0, 124.7, 106.3, 96.8, 41.9, 30.2, 19.7, 13.6.

MS (EI): *m*/*z* (%) = 210 (39), 167 (100), 149 (17), 134 (12), 122 (28), 109 (38), 94 (17).

Anal. Calcd for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32. Found: C, 57.02; H, 6.69; N, 13.34.

3-(Benzylamino)-4-nitrophenol (6c)
Yellow crystals; mp 193–196 °C (dec).

^{1}H NMR: δ = 10.75 (br s, 1 H), 8.77 (t, *J* = 6.0 Hz, 1 H), 7.97 (d, *J* = 9.5 Hz, 1 H), 7.32–7.39 (m, 4 H), 7.24–7.31 (m, 1 H), 6.16 (dd, *J* = 9.3, 2.4 Hz, 1 H), 6.10 (d, *J* = 2.4 Hz, 1 H), 4.54 (d, *J* = 6.0 Hz, 2 H).

^{13}C NMR: δ = 164.7, 147.6, 138.4, 129.0, 128.6, 127.1, 126.9, 125.0, 106.4, 97.7, 45.8.

MS (EI): *m*/*z* (%) = 244 (27), 226 (18), 210 (11), 197 (12), 196 (19), 105 (76), 91 (100).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{12}N_2O_3$: 244.0848; found: 244.0855.

3-(4-Methylpiperazin-1-yl)-4-nitrophenol (6e)
Yellow crystals; mp 199–200 °C.

^{1}H NMR: δ = 10.70 (br s, 1 H), 7.85 (d, *J* = 9.0 Hz, 1 H), 6.50 (d, *J* = 2.6 Hz, 1 H), 6.45 (dd, *J* = 9.0, 2.6 Hz, 1 H), 2.90–3.00 (m, 4 H), 2.49–2.52 (m, 4 H), 2.27 (s, 3 H).

^{13}C NMR: δ = 163.3, 149.1, 133.4, 129.3, 108.7, 106.0, 54.4, 50.9, 45.6.

MS (EI): *m*/*z* (%) = 237 (41), 207 (21), 202 (19), 190 (63), 147 (66), 135 (88), 43 (100).

Anal. Calcd for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71. Found: C, 55.63; H, 6.31; N, 17.63.

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