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Specific Features of Nucleophilic Substitution in 1-Chloro-3,4-dinitrobenzene

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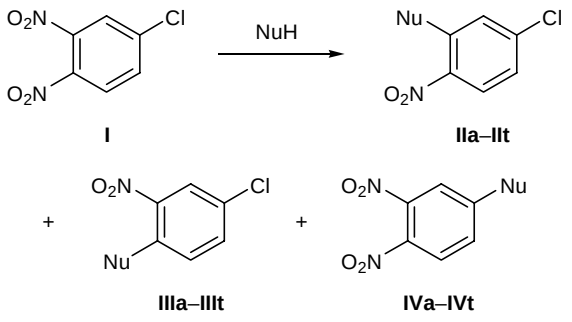
Abstract—Effects of the solvent, temperature, and nucleophile nature on the selectivity of nucleophilic substitution in 1-chloro-3,4-dinitrobenzene were studied, and optimal conditions were found for the synthesis and isolation of particular products.

Aromatic nucleophilic substitution reactions have been studied in sufficient detail [1]; nevertheless, these processes still attract strong interest from the viewpoints of both synthetic organic chemistry and kinetic studies. Up to now, a great number of studies have been reported on reactions of activated halobenzenes, e.g., 1-chloro-2,4-dinitrobenzene, with O-, S-, and N-nucleophiles. However, the properties of isomeric 1-chloro-3,4-dinitrobenzene remain almost unstudied. Relevant information dates back to 1930s. 1-Chloro-3,4-dinitrobenzene (**I**) is a polyfunctional substrate, and its chemical transformations are not limited to nucleophilic substitution of the nitro group in position *3*. Each intermediate product in this process is a reactive and interesting species which could give rise to compounds belonging to various classes, including phenol derivatives, fused systems, and heterocyclic compounds [2, 3].



II–**IV**, Nu = MeNH (**a**), EtNH (**b**), *t*-BuCH$_2$NH (**c**), Ph(CH$_2$)$_2$NH (**d**), Me(Ph)CHNH (**e**), cyclopropylamino (**f**), PhCH$_2$NH (**g**), HO(CH$_2$)$_2$NH (**h**), HO(CH$_2$)$_3$NH (**i**), HOCH$_2$CH(Me)NH (**j**), CH$_2$=CHCH$_2$NH (**k**), 2-furylmethylamino (**l**), 1-pyrrolidinyl (**m**), piperidino (**n**), morpholino (**o**), *N*-methyl-1-piperazinyl (**p**), *N*-phenyl-1-piperazinyl (**q**), *N*-benzyl-1-piperazinyl (**r**), 3-pyridylmethylamino (**s**), azepan-1-yl (**s**).

It is known [4, 5] that the solvent nature may affect not only the rate of a reaction but also its direction provided that several reaction centers are available. Moreover, the conditions for isolation of final products also depend on the solvent, although this aspect is seldom taken into account.

We examined solvents belonging to two main groups: aprotic (DMSO, acetone, and diethyl ether) and protic (methanol and ethanol). Reactions of chlorodinitrobenzene **I** with various aliphatic amines were carried out at room temperature, the molar ratio compound **I**–amine was 1:2, the reaction time in all cases was 6 h, and the conversion of **I** was no less than 95% (Table 1). According to the data in Table 1, in all cases the major product is that resulting from replacement of the nitro group in position *3*. It should be noted that the solvent nature considerably affects the ratio of the "anomalous" substitution products. However, from the viewpoint of isolation of the target product, the best solvent was methanol; in all experiments, the product spontaneously crystallized from the reaction mixture, and it generally required no additional purification (it contained more than 95% of the main substance).

The effect of temperature on the direction of nucleophilic substitution in chlorodinitrobenzene **I** was studied in methanol and ethanol at a **I**-to-amine molar ratio of 1:2 and a substrate concentration of 10 wt %; the reaction time was 10 h at 10°C, 6 h at 20°C, and 40 or 30 min in boiling methanol or ethanol, respectively (Table 2). It was found that rise in temperature reduces

Table 1. Ratios of products **II**, **III**, and **IV** (wt. %)[a] in nucleophilic substitution of the nitro groups and chlorine atom in 1-chloro-3,4-dinitrobenzene (**I**) in different solvents

Nucleophile	DMSO	Acetone	Diethyl ether	Methanol	Ethanol
Benzylamine	76:16:8	70:18:12	72:16:12	80:14:6	80:12:8
Ethylamine	74:16:10	70:25:5	67:20:13	75:17:8	73:17:10
2-Aminoethanol	75:15:12	69:18:13	65:20:15	76:15:9	75:15:10
Piperidine	80:15:5	77:18:5	78:15:7	82:15:3	80:13:7
Morpholine	74:12:14	70:17:13	69:16:15	75:12:13	72:12:16

[a] The overall amount of compounds **II**, **III**, and **IV** was taken as 100%.

Table 2. Ratios of products **II**, **III**, and **IV** (wt. %)[a] in nucleophilic substitution of the nitro groups and chlorine atom in 1-chloro-3,4-dinitrobenzene (**I**) in methanol and ethanol at different temperatures

Nucleophile	Methanol			Ethanol		
	10°C	20°C	64°C	10°C	20°C	78°C
Benzylamine	82:13:5	80:14:6	75:15:10	80:15:5	80:12:8	72:12:16
Morpholine	78:11:11	75:12:13	70:15:15	75:15:10	72:12:16	65:15:20

[a] See footnote [a] to Table 1.

the selectivity of nucleophilic substitution with respect to the 3-nitro group.

Primary aromatic and secondary alicyclic amines readily reacted with chlorodinitrobenzene **I**, and the major products were the corresponding 3-amino derivatives **II**. In reactions with secondary aliphatic amines, such as dimethylamine, diethylamine, and dibenzylamine, we succeeded in detecting only traces of substitution products even on heating in boiling dimethylformamide. Anilines also failed to react with compound **I**. Therefore, we examined how the degree of branching at the α-carbon atom in aliphatic amines affects the conversion of substrate **I**.

We found that the rate of the reaction of 1-chloro-3,4-dinitrobenzene (**I**) with 2-phenylethylamine is higher by a factor of ~2 than with (1-phenylethyl)-amine. An analogous relation was observed for 3-amino- and 2-amino-1-propanols. *tert*-Butylamine did not react with chlorodinitrobenzene **I**.

Thus the direction of the reaction of 1-chloro-3,4-dinitrobenzene (**I**) with primary aliphatic and alicyclic amines depends on all the above factors, solvent and amine nature and temperature. We succeeded in finding optimal conditions for nucleophilic substitution in compound **I** (solvent methanol, temperature 18–20°C, reaction time 6 h), which ensured preparation in good yields of a number of products resulting from replacement of the 3-nitro group in the substrate.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker DPX-200 spectrometer from solutions in DMSO-d_6; the chemical shifts were measured relative to the residual proton signals of the solvent. The elemental compositions were determined from the high-resolution mass spectra which were obtained on a Varian MAT-311A instrument (xenon, accelerating voltage 2–6 kV, current 0.1–0.5 mA, resolution 30000). The product ratios were determined by HPLC on a Varian 9065 Polychrom chromatograph equipped with a PUMP 9012 UV detector (λ 254 nm) and a 250× 4.6-mm column packed with Phenil reversed phase; eluent 50% MeCN–50% 0.05 M $NaClO_4$, flow rate 1 ml/min. The progress of reactions was monitored by TLC on Silufol UV-254 plates using chloroform–hexane (1:2), chloroform–methanol (9:1), or hexane–acetone–diethyl ether (5:2:1) as eluent.

***N*-Methyl-5-chloro-2-nitroaniline (IIa).** Methylamine, 6.2 g (20 mmol), was added with stirring to a solution of 20.2 g (10 mmol) of 1-chloro-3,4-dinitrobenzene (**I**) in 200 ml of methanol, and the mixture was vigorously stirred for 3 h at room temperature and cooled to 6–8°C. The precipitate was filtered off, washed with methanol, and dried in air. Yield 11.2 g (60%), mp 100–102°C. ^{1}H NMR spectrum, δ, ppm: 2.96 d (3H, CH_3), 6.64 d (1H, 4-H), 6.96 s (1H, 6-H), 8.05 d (1H, 3-H), 8.18 s (1H, NH). Found: M^+ 186.

$C_7H_7ClN_2O_2$. Calculated: *M* 186.599. Compounds **IIb**–**III** were synthesized in a similar way.

***N*-Ethyl-5-chloro-2-nitroaniline (IIb).** Yield 11.3 g (56%), mp 76–78°C. ^{1}H NMR spectrum, δ, ppm: 1.27 t (3H, CH_3), 3.36 m (2H, CH_2N), 6.60 d (1H, 4-H), 6.96 s (1H, 6-H), 8.03 d (1H, 3-H), 8.09 s (1H, NH). Found: M^+ 201. $C_8H_9ClN_2O_2$. Calculated: *M* 200.626.

***N*-(2,2-Dimethylpropyl)-5-chloro-2-nitroaniline (IIc).** Yield 15.8 g (65%), mp 96–98°C. ^{1}H NMR spectrum, δ, ppm: 1.27 s [9H, $(CH_3)_3$], 3.13 d (2H, CH_2N), 6.62 d (1H, 4-H), 7.08 s (1H, 6-H), 8.05 d (1H, 3-H), 8.21 s (1H, NH). Found: M^+ 243. $C_{11}H_{15}ClN_2O_2$. Calculated: *M* 242.707.

***N*-(2-Phenylethyl)-5-chloro-2-nitroaniline (IId).** Yield 12.5 g (45%), mp 60–62°C. ^{1}H NMR spectrum, δ, ppm: 3.02 t (2H, C**H**$_2$Ph), 3.54 t (2H, CH_2N), 6.59 d (1H, 4-H), 6.83 s (1H, 6-H), 7.29 m (5H, C_6H_5), 8.09 d (1H, 3-H), 8.40 s (1H, NH). Found: M^+ 276. $C_{14}H_{13}ClN_2O_2$. Calculated: *M* 276.725.

***N*-(1-Phenylethyl)-5-chloro-2-nitroaniline (IIe).** Yield 18.8 g (68%), mp 90–92°C. ^{1}H NMR spectrum, δ, ppm: 1.65 d (3H, CH_3), 4.64 m (1H, C**H**Ph), 6.56 d (1H, 4-H), 6.63 s (1H, 6-H), 7.33 m (5H, C_6H_5), 8.10 d (1H, 3-H), 8.45 s (1H, NH). Found: M^+ 276. $C_{14}H_{13}ClN_2O_2$. Calculated: *M* 276.725.

***N*-Cyclopropyl-5-chloro-2-nitroaniline (IIf).** Yield 12.7 g (60%), mp 78–80°C. ^{1}H NMR spectrum, δ, ppm: 0.66 m (2H, CH_2), 0.93 m (2H, CH_2), 2.55 m (1H, CH), 6.63 d (1H, 4-H), 7.27 s (1H, 6-H), 8.07 d (2H, 3-H, NH). Found: M^+ 213. $C_9H_9ClN_2O_2$. Calculated: *M* 212.637.

***N*-Benzyl-5-chloro-2-nitroaniline (IIg).** Yield 9.3 g (70%), mp 88–90°C. ^{1}H NMR spectrum, δ, ppm: 4.65 d (2H, C**H**$_2$Ph), 6.62 d (1H, 4-H), 6.81 s (1H, 6-H), 7.36 m (5H, C_6H_5), 8.14 d (1H, 3-H), 8.44 s (1H, NH). Found: M^+ 262. $C_{13}H_{11}ClN_2O_2$. Calculated: *M* 262.698.

2-(5-Chloro-2-nitrophenylamino)ethanol (IIh). Yield 14.1 g (65%), mp 108–110°C. ^{1}H NMR spectrum, δ, ppm: 1.81 s (1H, OH), 3.49 d (2H, CH_2N), 3.93 d (2H, C**H**$_2$OH), 6.62 d (1H, 4-H), 6.88 s (1H, 6-H), 8.11 d (1H, 3-H), 8.28 s (1H, NH). Found: M^+ 216. $C_8H_9ClN_2O_3$. Calculated: *M* 216.625.

3-(5-Chloro-2-nitrophenylamino)-1-propanol (IIi). Yield 12.9 g (56%), mp 75–77°C. ^{1}H NMR spectrum, δ, ppm: 1.87 s (1H, OH), 1.94 m (2H, CH_2), 3.43 m (2H, CH_2N), 3.84 m (2H, C**H**$_2$OH), 6.57 d (1H, 4-H), 6.85 s (1H, 6-H), 8.08 d (1H, 3-H), 8.26 s (1H, NH). Found: M^+ 230. $C_9H_{11}ClN_2O_3$. Calculated: *M* 230.653.

2-(5-Chloro-2-nitrophenylamino)-1-propanol (IIj). Yield 10.4 g (45%), mp 107–109°C. ^{1}H NMR spectrum, δ, ppm: 1.16 d (3H, CH_3), 3.26 m (2H, CH_2N), 3.90 s (1H, C**H**OH), 4.95 s (1H, OH), 6.62 d (1H, 4-H), 7.05 s (1H, 6-H), 8.05 d (1H, 3-H), 8.31 s (1H, NH). Found: M^+ 230. $C_9H_{11}ClN_2O_3$. Calculated: *M* 230.653.

***N*-Allyl-5-chloro-2-nitroaniline (IIk).** Yield 11.5 g (54%), mp 47–49°C; published data [2]: mp 52–53°C. ^{1}H NMR spectrum, δ, ppm: 4.04 t (2H, CH_2N), 5.25 t (2H, $=CH_2$), 5.91 m (1H, =CH), 6.66 d (1H, 4-H), 6.93 s (1H, 6-H), 8.06 d (1H, 3-H), 8.31 s (1H, NH). Found: M^+ 212. $C_9H_9ClN_2O_2$. Calculated: *M* 212.637.

***N*-(2-Furylmethyl)-5-chloro-2-nitroaniline (IIl).** Yield 13.9 g (55%), mp 63–65°C. ^{1}H NMR spectrum, δ, ppm: 4.49 d (2H, CH_2N), 6.31 d (2H, CH, furyl), 6.64 d (1H, 4-H), 6.92 s (1H, 6-H), 7.39 s (1H, CHO, furyl), 8.11 d (1H, 3-H), 8.33 s (1H, NH). Found: M^+ 253. $C_{11}H_9ClN_2O_3$. Calculated: *M* 252.659.

1-(5-Chloro-2-nitrophenyl)pyrrolidine (IIm). Pyrrolidine, 14.2 g (20 mmol), was added with stirring to a solution of 20.2 g (10 mmol) of 1-chloro-3,4-dinitrobenzene (**I**) in 200 ml of methanol, and the mixture was vigorously stirred for 5 h at room temperature and cooled to 6–8°C. The precipitate was filtered off and recrystallized from methanol. Yield 18.7 g (70%), mp 74–76°C. ^{1}H NMR spectrum, δ, ppm: 1.98 s (4H, CH_2), 3.19 s (4H, CH_2N), 6.65 d (1H, 4-H), 6.88 s (1H, 6-H), 7.68 d (1H, 3-H). Found: M^+ 267. $C_{10}H_{11}ClN_2O_3$. Calculated: *M* 266.664. Compounds **IIn**–**IIt** were synthesized in a similar way.

1-(5-Chloro-2-nitrophenyl)piperidine (IIn). Yield 15.6 g (65%), mp 64–66°C. ^{1}H NMR spectrum, δ, ppm: 1.68 m (6H, CH_2), 3.02 t (4H, CH_2N), 6.87 d (1H, 4-H), 7.04 s (1H, 6-H), 7.73 d (1H, 3-H). Found: M^+ 241. $C_{11}H_{13}ClN_2O_2$. Calculated: *M* 240.691.

4-(5-Chloro-2-nitrophenyl)morpholine (IIo). Yield 12.6 g (52%), mp 69–71°C. ^{1}H NMR spectrum, δ, ppm: 3.05 t (4H, CH_2N), 3.83 t (4H, $2CH_2O$), 6.99 d (1H, 4-H), 7.06 s (1H, 6-H), 7.77 d (1H, 3-H). Found: M^+ 242. $C_{10}H_{11}ClN_2O_3$. Calculated: *M* 242.664.

1-(5-Chloro-2-nitrophenyl)-4-methylpiperazine (IIp). Yield 11.8 g (46%), mp 73–75°C. ^{1}H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3N), 2.56 t (4H, C**H**$_2$NCH$_3$), 3.08 t (4H, CH_2N), 6.95 d (1H, 4-H), 7.05 s (1H, 6-H), 7.74 d (1H, 3-H). Found: M^+ 255. $C_{11}H_{14}ClN_3O_2$. Calculated: *M* 255.706.

1-(5-Chloro-2-nitrophenyl)-4-phenylpiperazine (IIq). Yield 15.9 g (50%), mp 125–127°C. ^{1}H NMR spectrum, δ, ppm: 3.26 t (8H, CH_2N), 6.79 t (1H, Ph), 6.94 t (1H, Ph), 7.20 d (1H, 4-H), 7.22 t (1H, Ph), 7.34 s (1H, 6-H), 7.85 d (1H, 3-H). Found: M^+ 318. $C_{16}H_{16}ClN_3O_2$. Calculated: *M* 317.778.

1-Benzyl-4-(5-chloro-2-nitrophenyl)piperazine hydrochloride (IIr). Yield 16.6 g (45%), mp 190–192°C. ^{1}H NMR spectrum, δ, ppm: 3.35 m (8H, CH_2N), 4.36 s (2H, C**H**$_2$Ph), 7.18 d (1H, 4-H), 7.35 s (1H, 6-H), 7.41 s (2H, Ph), 7.72 s (1H, Ph), 7.89 d (1H, 3-H). Found: M^+ 368. $C_{17}H_{18}ClN_2O_3$. Calculated: *M* 368.266.

***N*-(3-Pyridylmethyl)-5-chloro-2-nitroaniline (IIs).** Yield 11.1 g (42%), mp 90–92°C. ^{1}H NMR spectrum, δ, ppm: 4.68 d (2H, CH_2N), 6.64 d (1H, 4-H), 6.92 s (1H, 6-H), 7.30 t (1H, CH, pyridine), 7.74 d (1H, CH, pyridine), 8.07 d (1H, 3-H), 8.45 d (1H, CH, pyridine), 8.59 s (1H, CH, pyridine), 8.77 s (1H, NH). Found: M^+ 264. $C_{12}H_{10}ClN_3O_2$. Calculated: *M* 263.685.

1-(5-Chloro-2-nitrophenyl)azepane (IIt). Yield 10.2 g (40%), mp 63–65°C. ^{1}H NMR spectrum, δ, ppm: 1.59 s (4H, CH_2), 1.79 s (4H, CH_2), 3.24 t (4H, CH_2N), 6.73 d (1H, 4-H), 7.08 s (1H, 6-H), 7.64 d (1H, 3-H). Found: M^+ 255. $C_{12}H_{15}ClN_2O_2$. Calculated: *M* 254.718.

4-(4-Chloro-2-nitrophenyl)morpholine (IIIo). A solution of 1.92 g (1 mmol) of 1,4-dichloro-2-nitrobenzene in 20 ml of morpholine was heated for 2 h at the boiling point. The mixture was poured under stirring into 60 ml of cold water, and the precipitate was filtered off, and recrystallized from 70% methanol. Yield 1.2 g (50%), mp 45–47°C. ^{1}H NMR spectrum, δ, ppm: 3.00 s (4H, CH_2N), 3.81 s (4H, CH_2O), 7.10 d (1H, 6-H), 7.44 d (1H, 4-H), 7.79 s (1H, 3-H). Found: M^+ 242. $C_{10}H_{11}ClN_2O_3$. Calculated: *M* 242.664.

Compounds **IIIa**–**IIIm** and **IIIq**–**IIIt** were synthesized in a similar way. Products **IVa**–**IVt** were isolated from the reaction mixtures by column chromatography on silica gel (40–64 μm, Merck) using chloroform–hexane (1:2) as eluent. Their structure was proved by the ^{1}H and mass spectra.

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