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Regular Trends in Nucleophilic Substitutions in 2-Alkylamino-4-chloronitrobenzenes

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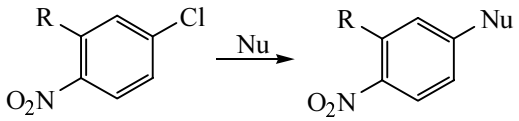
Abstract—The effect of substituents in position *2* on the reactivity of 2-alkylamino-4-chloronitrobenzenes in nucleophilic substitution by N-nucleophiles of various character was studied.

It is known that the replacement of an amino for nitro group in the *2* position of 1,2-dinitro-4-chlorobenzene **(I)** results in a sharp decrease in chlorine mobility in nucleophilic substitutions. However publications on studies of reactivity of the arising aromatic systems are virtually lacking. Only some descriptions of preparation procedures for specific compounds were reported [1, 2].

The scanty published data demonstrate that the nucleophilic substitution in aromatic systems with a halogen of reduced mobility is as a rule performed in solvents characterized by a high boiling point and a low dielectric constant, like DMSO, DMF, and HMPA. The presence of a catalyst is also necessary, and the most common catalyst is a copper(II) salt. Note that the yields of the target substitution products in these processes vary in a wide range (from 20 to 90%) and depend on the mobility of the halogen in the initial substrate, on the nucleophile character, and on reaction conditions.

We made an attempt to investigate the effect exerted by substituents in position *2* on the reactivity of (alkylamino)chloronitrobenzenes **Ia–Iu** in the nucleophilic substitution by various N-nucleophiles.

It turned out in the course of the study that the reaction of alkylaminochloronitrobenzenes **Ia–Iu** with N-nucleophiles in DMSO resulted in strong tarring. At the use as solvents of DMF and HMPA the target products of the chlorine substitution by the nucleophile were obtained alongside the products of an abnormal substitution of the chlorine by a dimethylamino group. We already mentioned formerly the similar behavior of DMF and HMPA in the nucleophilic substitution [3]. We concluded from observations during this research that the amount of abnormal substitution product strongly depended on the nucleophile character: The more sterically hindered and the less basic was the nucleophilic agent, the larger was the yield of abnormal substitution product. It should be noted that apart from the reduction of the target product yield due to formation of abnormal substitution products a partial tarring also occurred. Therefore the yields of the target products after purification by crystallization did not exceed 40%.



Ia–Iu **IIa–IIu–Va–Vu**

I–V, R = MeNH (**a**), EtNH (**b**), *i*-BuNH (**c**), *t*-$BuCH_2NH$ (**d**), $Ph(CH_2)_2NH$ (**e**), Me(Ph)CHNH (**f**), cyclopropylamino (**g**), BnNH(**h**), $HO(CH_2)_2NH$ (**i**), $HO(CH_2)_3NH$ (**j**), $HOCH_2(NH)CHCH_3$ (**k**), AllNH (l), (2-furylmethyl)amino (**m**), pyrrolidino (**n**), piperidino (**o**), morpholino (**p**), *N*-methylpiperazino (**q**), *N*-phenylpiperazino (**r**), *N*-benzylpiperazino (s), (3-pyridylmethyl)amino (t), azacycloheptane (**u**); Nu: pyrrolidino (**IIa–IIu**), piperidino (**IIIa, IIIe–IIIk, IIIm, IIIo, IIIu**), morpholino (**IVa, IVb, IVd–IVk, IVm–IVp, IVq, IVr, IVu**), *N*-methylpiperazino (**Va, Vb, Ve–Vk, Vm–Vp, Vu**).

To avoid the above mentioned complications we carried out the reactions between alkylaminochloronitrobenzenes **Ia–Iu** and N-nucleophiles in the medium of the nucleophile itself. The application of the latter as solvent significantly reduced the side products formation and increased the yield of the target compounds. However this procedure is limited to a large extent by the boiling point of the nucleophile and by its nature. It turned out

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that secondary aliphatic amines did not react with (alkylamino)chloronitrobenzenes **Ia–Iu,** and primary aliphatic amines reacted very slowly. Even at prolonged heating in amines (up to 20 h) the conversion did not exceed 50%. Besides we found that the reaction of compounds **Ia–u** with the primary aliphatic amines started at the reaction mixture temperature over 120°C, whereas the prolonged heating resulted in the tarring of the reaction mixture.

Good results were obtained in reactions of (alkylamino)chloronitrobenzenes **Ia–Iu** with secondary alicyclic amines. The process carried out in the amine afforded the target products in 60–90% yields. We established that the yields of target products depend on the character of the alicyclic amine and on the nature of the substituent in the position *2* of alkylaminochloronitrobenzenes **Ia–Iu**. The most readily the substitution occurred with pyrrolidine, the least easily with morpholine. It should be noted that pyrrolidine present as substituent in the position *2* of the substrate exerts the strongest deactivating effect on the chlorine atom. For instance, to attain the 100% conversion in the reaction of morpholinochloronitrobenzene (**Ip**) with pyrrolidine the reaction mixture should be boiled for 40 min, whereas the 100% conversion in the reaction of pyrrolidinochloronitrobenzene (**In**) was reached only after 4 h of boiling.

Thus we established that at performing the nucleophilic substitution in chloronitrobenzenes **Ia–Iu** the use of DMSO, DMF, and HMPA as solvents was unsuitable for it led to the formation of a lot of side products. Therefore the process should be carried out in the medium of the nucleophile proper. Among the N-nucleophiles tested the most reactive toward chloronitrobenzenes **Ia–Iu** were the secondary alicyclic amines, the secondary aliphatic amines did not enter into the reaction, and the primary aliphatic amines reacted very slowly even at prolonged boiling.

EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Bruker DPX-200, solvents DMSO-d_6 or deuterochloroform, as internal reference served the residual proton signals of the solvents.

Elemental composition of compounds was determined from their high resolution mass spectra measured on Varian MAT-311A instrument, gas xenon, accelerating voltage 2–6 kV, current 0.1–0.5 mA, resolution 30000.

The reaction progress was monitored by TLC on Silufol UV-254 plates using the following eluents: chloroform–hexane, 2:1 by volume; chloroform–methanol, 9:1 by volume; hexane–acetone–ethyl ether, 5:2:1 by volume; chloroform–methanol–ammonia 9:1:0.5 by volume.

***N*-Methyl-2-nitro-5-pyrrolidinoaniline (IIa).** A solution of 2.0 g (10.7 mmol) of chloroaniline (**Ia**) in 10 ml of pyrrolidine was boiled for 45 min. On completion of reaction the mixture was poured into water. The separated precipitate was filtered off, washed with water, and recrystallized from a mixture dichloromethane–methanol, 1:2 by volume, yield 2.3 g (92%), mp 205–207°C. ^{1}H NMR spectrum, δ, ppm.: 1.99 t (4H, $2CH_2$), 2.90 d (3H, CH_3), 3.38 t (4H, $2CH_2N$), 5.49 s (1H, CHNH), 6.03 d (1H, CHN), 7.87 d (1H, $CHNO_2$), 8.32 s (1H, NH). Found: M^+ 220. $C_{11}H_{15}N_3O_2$. Calculated: *M* 221.261.

Likewise were obtained compounds **IIb–IIu**.

2-(2-Nitro-5-pyrrolidin-1-ylanilino)-1-ethanol (IIi). Yield 2.4 g (90%), mp 219–221°C. ^{1}H NMR spectrum, δ, ppm: 2.02 t (4H, $2CH_2$), 3.32 d (2H, CH_2NH), 3.40 t (4H, $2CH_2N$), 3.68 m (2H, CH_2OH), 4.82sC (1H, OH), 5.58 s (1H, CHNH), 6.02 d (1H, CHN), 7.88 d (1H, $CHNO_2$), 8.49 s (1H, NH). Found: M^+ 251. $C_{12}H_{17}N_3O_3$. Calculated: *M* 251.268.

2-(2-Nitro-5-pyrrolidin-1-ylanilinomethyl)furan (IIm). Yield 2.5 g (80%), mp 173–175°C. ^{1}H NMR spectrum, δ, ppm: 1.99 t (4H, $2CH_2$), 3.55 t (4H, $2CH_2N$), 4.52 d (2H, CH_2NH), 5.69 s (1H, CHNH), 6.08 d (1H, CHN), 6.37 s (2H, 2CH), 7.54 s (1H, CHO), 7.89 d (1H, $CHNO_2$), 8.65 s (1H, NH). Found: M^+ 286. $C_{15}H_{17}N_3O_3$. Calculated: *M* 287.321.

4-(2-Nitro-5-pyrrolidinophenyl)piperidyl (IIo). Yield 2.5 g (85%), mp 165–167°C. ^{1}H NMR spectrum, δ, ppm: 2.05 t (4H, $2CH_2$), 3.02 t (4H, $2CH_2$), 3.37 t (4H, $2CH_2N$), 3.83 t (4H, $2CH_2O$), 5.90 d (1H, CHN), 6.11 d (1H, NCHN), 8.03 d (1H, $CHNO_2$). Found: M^+ 277. $C_{14}H_{19}N_3O_3$. Calculated: *M* 277.326.

1-(2-Nitro-5-pyrrolidinophenyl)-4-phenylpiperazine (IIr). Yield 3.0 g (80%), mp 165–167°C. ^{1}H NMR spectrum, δ, ppm: 1.99 t (4H, $2CH_2$), 3.15 s (4H, $2CH_2$), 3.27 t (4H, $2CH_2N$), 3.38 C (4H, $2CH_2$), 6.05 s (1H, NCHN), 6.23 d (1H, CHN), 6.79 t (1H, CH), 6.98 d (1H, CH), 7.23 t (1H, CH), 7.98 d (1H, $CHNO_2$). Found: M^+ 352. $C_{20}H_{24}N_4O_2$. Calculated: *M* 352.439.

1-(2-Nitro-5-pyrrolidinophenyl)azacycloheptane (IIu). Yield 2.7 g (85%), mp 170–172°C. ^{1}H NMR spectrum, δ, ppm: 1.94 t (4H, $2CH_2$), 3.26 t (4H, $2CH_2N$), 4.61 d (2H, CH_2NH), 5.52 s (1H, CHN), 6.02 d (1H,

CH), 7.34 t (1H, CH), 7.76 d (1H, CH), 7.89 d (1H, $CHNO_2$), 8.44 d (1H, CHN), 8.60 s (1H, NCH), 8.88 C (1H, NH). Found: M^+ 298. $C_{16}H_{18}N_4O_2$. Calculated: *M* 298.347.

***N*-Methyl-2-nitro-5-piperidinoaniline (IIIa).** A solution of 1.4 g (7.6 mmol) of chloroaniline (**Ia**) in 15 ml of piperidine was boiled for 1.5 h, and then the reaction mixture was poured into water. The separated precipitate was filtered off, washed with water, and recrystallized from ethanol, yield 1.5 g (82%), mp 103–105°C. ^{1}H NMR spectrum, δ, ppm: 1.63 s (6H, $3CH_2$), 2.95 d (3H, CH_3), 3.44 t (4H, $2CH_2N$), 5.88 s (1H, CHNH), 6.32 d (1H, CHN), 7.87 d (1H, $CHNO_2$), 8.28 s (1H, NH). Found: M^+ 235. $C_{12}H_{17}N_3O_2$. Calculated: *M* 235.288.

Likewise were obtained compounds **IIIe–IIIk, IIIm, IIIo, IIIu**.

***N*-(1-Phenylethyl)-2-nitro-5-piperidinoaniline (IIIe).** Yield 1.8 g (74%), mp 108–110°C. ^{1}H NMR spectrum, δ, ppm: 1.42 s (6H, $3CH_2$), 1.55 d (3H, CH_3), 3.24 d (4H, $2CH_2N$), 4.78 m (1H, $CHCH_3$), 5.73 s (1H, CHNH), 6.28 d (1H, CHN), 7.31 m (5H, C_6H_5), 7.86 d (1H, $CHNO_2$), 8.65 s (1H, NH). Found: M^+ 325. $C_{19}H_{23}N_3O_2$. Calculated: *M* 325.414.

2-(2-Nitro-5-piperidinoanilino)-1-ethanol (IIIi). Yield 1.4 g (68%), mp 116–118°C. ^{1}H NMR spectrum, δ, ppm: 1.64 s (6H, $3CH_2$), 3.35 d (2H, CH_2NH), 3.44 s (4H, $2CH_2N$), 3.67 d (2H, CH_2OH), 4.83 s (1H, OH), 5.94 s (1H, CHNH), 6.28 d (1H, CHN), 7.87 d (1H, $CHNO_2$), 8.48 s (1H, NH). Found: M^+ 265. $C_{13}H_{19}N_3O_3$. Calculated: *M* 265.315.

4-(2-Nitro-5-piperidinophenyl)piperidine (IIIo). Yield 1.7 g (75%), mp 80–82°C. ^{1}H NMR spectrum, δ, ppm: 1.67 s (6H, $3CH_2$), 3.03 s (4H, $2CH_2N$), 3.36 s (4H, $2CH_2$), 3.85 s (4H, $2CH_2O$), 6.26 s (1H, NCHN), 6.40 d (1H, CHN), 7.98 d (1H, $CHNO_2$). Found: M^+ 291. $C_{15}H_{21}N_3O_3$. Calculated: *M* 291.353.

***N*-Methyl-5-morpholino-2-nitroaniline (IVa).** A solution of 1.6 g (8.8 mmol) of chloroaniline (**Ia**) in 20 ml of morpholine was boiled for 7 h, then the reaction mixture was poured in water. The separated precipitate was filtered off, washed with water, and recrystallized from a mixture hexane–chloroform, 2:3 by volume, yield 1.5 g (74%), mp 187–188°C. ^{1}H, δ, ppm: 2.03 s (3H, CH_3), 3.38 s (4H, $2CH_2N$), 3.72 s (4H, $2CH_2O$), 5.93 s (1H, CHNH), 6.35 d (1H, CHN), 7.89 d (1H, $CHNO_2$), 8.31 s (1H, NH). Found: M^+ 237. $C_{11}H_{15}N_3O_3$. Calculated: *M* 237.260.

Likewise were obtained compounds **IVb, IVd–IVk, IVm–IVp, IVq, IVr, IVu**.

1-(5-Morpholino-2-nitroanilino)-2-propanol (IVk). Yield 1.7 g (70%), mp 156–158°C. ^{1}H NMR spectrum, δ, ppm: 1.32 d (3H, CH_3), 1.99 d (1H, OH), 3.31 m (6H, $2CH_2N$+CH_2NH), 3.84 t (4H, $2CH_2O$), 4.15 m (1H, CHOH), 5.95 s (1H, CHNH), 6.21 d (1H, CHN), 8.07 d (1H, $CHNO_2$), 8.58 s (1H, NH). Found: M^+ 281. $C_{13}H_{19}N_3O_4$. Calculated: *M* 281.314.

4-(2-Nitro-5-pyrrolidinophenyl)morpholine (IVn). Yield 1.4 g (58%), mp 115–117°C. ^{1}H NMR spectrum, δ, ppm: 1.98 t (4H, $2CH_2$), 3.22 m (8H, $4CH_2N$), 3.83 t (2H, $2CH_2O$), 6.09 s (1H, NCHN), 6.24 d (1H, CHN), 7.79 d (1H, $CHNO_2$). Found: M^+ 277. $C_{14}H_{19}N_3O_3$. Calculated: *M* 277.326.

4-[4-Nitro-3-(4-phenylpiperazino)phenyl]-morpholine (IVr). Yield 2.2 g (68%), mp 180–182°C. ^{1}H NMR spectrum, δ, ppm: 3.18 s (4H, $2CH_2N$), 3.36 m (8H, $4CH_2N$), 3.75 s (2H, $2CH_2O$), 6.47 s (1H, NCHN), 6.57 d (1H, CHN), 6.79 t (1H, CH), 6.96 d (1H, CH), 7.22 t (1H, CH), 7.92 d (1H, $CHNO_2$). Found: M^+ 368. $C_{20}H_{24}N_4O_3$. Calculated: *M* 368.439.

1-(5-Morpholino-2-nitrophenyl)azacycloheptane (IVu). Yield 1.8 g (65%), mp 203–205°C. ^{1}H NMR spectrum, δ, ppm: 3.28 t (4H, $2CH_2N$), 3.67 t (4H, $2CH_2O$), 4.64 d (2H, CH_2NH), 5.96 s (1H, CHNH), 6.33 d (1H, CHN), 7.32 t (1H, CH), 7.76 d (1H, CH), 7.92 d (1H, $CHNO_2$), 8.46 d (1H, CHN), 8.62 s (1H, NCH), 8.80 s (1H, NH). Found: M^+ 314. $C_{16}H_{18}N_4O_3$. Calculated: *M* 314.347.

N-Methyl-5-(4-methylpiperazino)-2-nitroaniline (Va). A solution of 1.7 g (9.2 mmol) of chloroaniline (**Ia**) in 15 ml of *N*-methylpiperazine was boiled for 4 h, then the reaction mixture was poured in water. The separated precipitate was filtered off, washed with water, and recrystallized from dichloromethane–hexane, 1:1 by volume, yield 1.8 g (80%), mp 81–83°C. ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, NCH_3), 2.41 t (4H, $2CH_2NCH_3$), 2.92 d (3H, CH_3), 3.40 t (4H, $2CH_2N$), 5.91 s (1H, CHNH), 6.35 d (1H, CHN), 7.87 d (1H, $CHNO_2$), 8.32 s (1H, NH). Found: M^+ 250. $C_{12}H_{18}N_4O_2$. Calculated: *M* 250.303.

Likewise were obtained compounds **Vb, Ve–Vk, Vm–Vp, Vu**.

***N*-(1-Phenylethyl)-5-(4-methylpiperazino)-2-nitroaniline (Vf).** Yield 2.1 g (68%), mp 154–156°C. ^{1}H NMR spectrum, δ, ppm: 1.57 d (3H, CH_3), 2.17 s (3H, NCH_3), 2.29 s (4H, $2CH_2N$), 3.23 m (4H, $2CH_2N$),

4.83 m (1H, $CHCH_3$), 5.81 C (1H, CHNH), 6.33 d (1H, CHN), 7.32 m (5H, C_6H_5), 7.88 d (1H, $CHNO_2$), 8.63 s (1H, NH). Found: M^+ 340. $C_{19}H_{24}N_4O_2$. Calculated: *M* 340.429.

***N*-Cyclopropyl-5-(4-methylpiperazino)-2-nitroaniline (Vg).** Yield 1.6 g (62%), mp 102–104°C. ^{1}H NMR spectrum, δ, ppm: 0.63 d (2H, CH_2), 0.84 d (2H, CH_2), 2.32 s (3H, NCH_3), 2.51 t (5H, $2CH_2N$+CHNH), 3.39 t (4H, $2CH_2N$), 6.20 d (1H, CHN), 6.34 s (1H, CHNH), 7.99 d (1H, $CHNO_2$), 8.34 s (1H, NH). Found: M^+ 276. $C_{14}H_{20}N_4O_2$. Calculated: *M* 276.341.

2-[5-(4-Methylpiperazino)-2-nitroanilinomethyl]furan (Vm). Yield 1.9 g (68%), mp 125–127°C. ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, NCH_3), 2.40 t (4H, $2CH_2N$), 3.40 t (4H, $2CH_2N$), 4.59 d (2H, CH_2NH), 6.11 s (1H, CHNH), 6.39 s (2H, CH+CHN), 7.56 s (1H, CHO), 7.89 d (1H, $CHNO_2$), 8.60 s (1H, NH). Found: M^+ 316. $C_{16}H_{20}N_4O_3$. Calculated: *M* 316.363.

1-Methyl-4-(4-nitro-3-pyrrolidinophenyl)piperazine (Vn). Yield 1.4 g (52%), mp 135–137°C. ^{1}H NMR spectrum, δ, ppm: 1.96 t (4H, $2CH_2$), 2.32 s (3H, NCH_3), 2.51 t (4H, $2CH_2N$), 3.21 t (4H, $2CH_2N$), 3.31 t (4H, $2CH_2N$), 6.09 s (1H, NCHN), 6.25 d (1H, CHN), 7.78 d (1H, $CHNO_2$). Found: M^+ 290. $C_{15}H_{22}N_4O_2$. Calculated: *M* 290.368.

1-[5-(4-Methylpiperazino)-2-nitrophenyl]azacycloheptane (Vu). Yield 2.2 g (75%), mp 140–142°C. ^{1}H NMR spectrum, δ, ppm: 2.19 s (3H, NCH_3), 2.34 s (4H, $2CH_2N$), 3.32 s (4H, $2CH_2N$), 4.62 d (2H, CH_2NH), 5.94 s (1H, CHNH), 6.36 d (1H, CHN), 7.34 t (1H, CH), 7.76 d (1H, CH), 7.90 d (1H, $CHNO_2$), 8.47 d (1H, CHN), 8.63 s (1H, NCH), 8.82 s (1H, NH). Found: M^+ 327. $C_{17}H_{21}N_5O_2$. Calculated: *M* 327.389.

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