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THE SMILES REARRANGEMENT

MECHANISM OF UNUSUAL ACYL AND 2,4-DINITROPHENYL MIGRATIONS IN ARYL ACYLAMINO ETHERS

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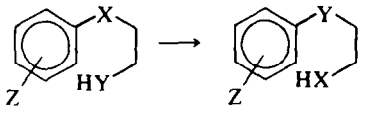
Abstract—The products of the reaction between various β-(N-acylamino)ethoxides and β-(amino)ethoxides with 2,4-dinitrofluorobenzene resulted from an intramolecular nucleophilic aromatic substitution (the Smiles reaction) combined with acyl group migration from nitrogen to oxygen. Stepwise and concerted mechanisms were considered, and evidence for the stepwise mechanism was provided by the synthesis of an intermediate.

The Smiles rearrangement[1] involves inversion of side chains attached to ring-activated aromatic systems.

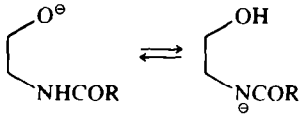


Examples of the Smiles rearrangement include intramolecular rearrangement of amino-ethers which are formed as primary substitution products.[2-5] In these cases the amino group becomes the attacking nucleophile and the alkoxide anion represents the leaving group.

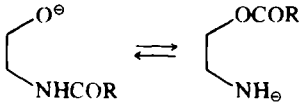
In the course of our studies of the Smiles rearrangement we observed that 2-(2',4'-dinitrophenylamino) ethanol **2** is obtained as the sole product of the reaction of 1-fluoro-2,4-dinitrobenzene (DNFB) with sodium 2-aminoethoxide. We assume that the ether **1** is formed as the intermediate and rearranges rapidly under the reaction conditions to yield **2**.

product lacking the properties of an ether. Instead, the IR, UV and NMR spectra indicated that the product obtained had structure **4**. This was confirmed by acylation of **2** which yielded a product identical with that obtained by direct reaction of DNFB with sodium 2-acylaminoethoxide.

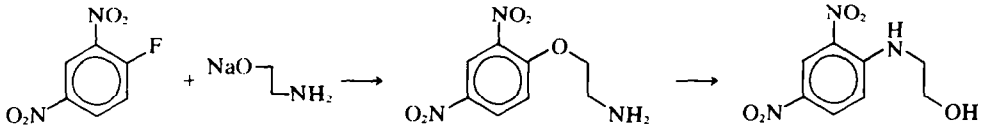
It appears that we are dealing here with a case of Smiles rearrangement combined with acyl group migration from nitrogen to oxygen. Another possibility, suggested by a Referee, is that the product may arise by rearrangement of alkoxide:



(i)



(ii)

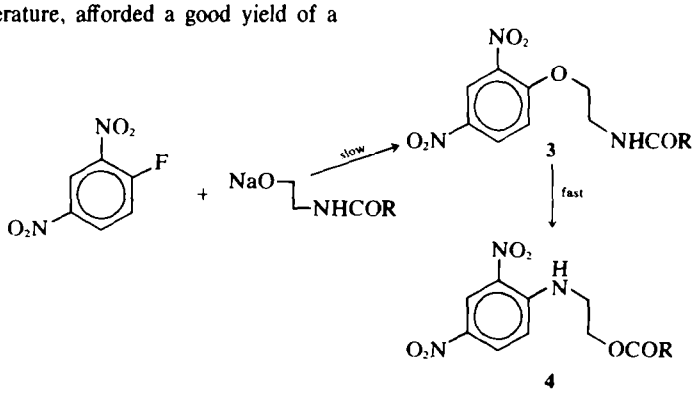


1 **2**

In an attempt to arrest the reaction at the stage of ether formation we treated DNFB with sodium 2-acylaminoethoxides, expecting the formation of ethers **3**.

Contrary to our expectations the reaction, carried out in THF at reflux temperature, afforded a good yield of a

If the equilibrium (i) or (ii) takes place the reaction with p-fluoronitrobenzene, which is slower than that with DNFB should not give the ether **5**, but only the derivative **6**.



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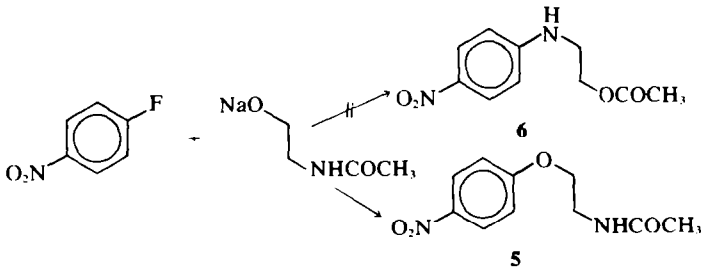
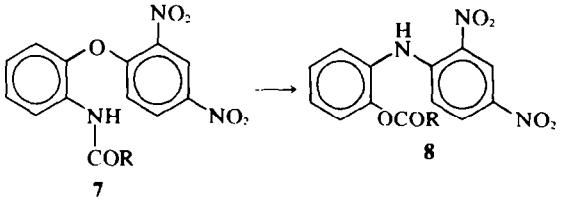


This was not the case. We obtained the ether **5** as the sole product of this reaction. For this reason we believe that we are dealing here with the case of the Smiles rearrangement combined with acyl group migration from N to O.

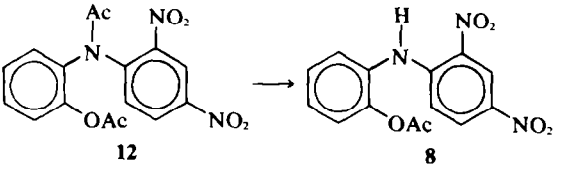
Contrary to **3**, the ether **5** does not rearrange unless the acyl group is removed by hydrolysis. After hydrolysis the rearrangement takes place with the formation of 2-(p-nitrophenylamino)ethanol.

A rearrangement similar to the formation of **4** from **3** has been observed earlier[2] in the case of the diaryl ethers **7**.

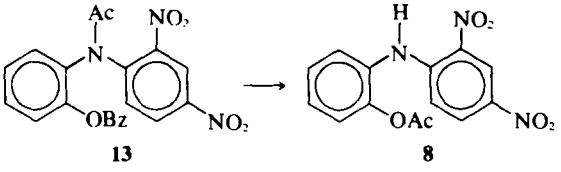


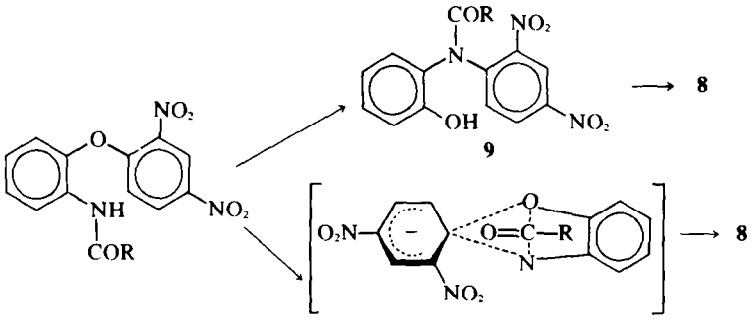
In both cases the migration of both groups being exchanged may be stepwise or concerted and two possible mechanisms have to be considered:

This approach failed, however, as partial hydrolysis of **12** yielded directly the rearranged product **8**.



This result raised the question whether **8** is formed by simple hydrolysis of **12** or by rearrangement of **9** which can be envisaged to be an intermediate also in this reaction. To answer this we prepared the N-acetyl-O-benzoyl derivative **13**. Alcoholysis of this derivative also yielded the rearrangement product **8**.





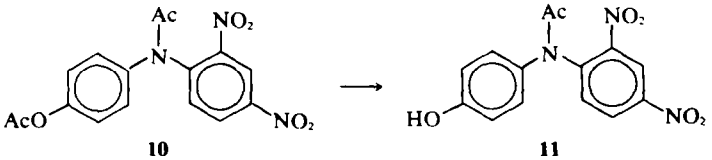
The second scheme is analogous to the recently described mechanism of dyotropic rearrangement[4] involving the concerted migration of two substituents.

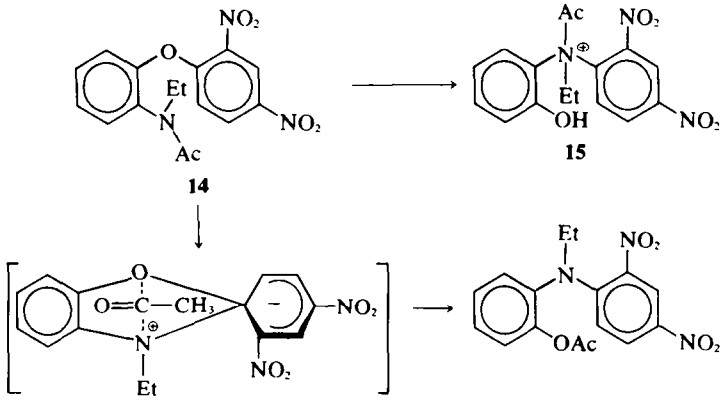
In order to determine which mechanism is operative in this case, we decided to prepare the possible intermediate **2** and to attempt its rearrangement to **8**, reasoning that failure of rearrangement would support the concerted mechanism.

Our approach to the synthesis of **9** was similar to the known preparation[7] of N-acetyldiphenylamine derivative **11** which was obtained by partial hydrolysis of **10**.

This indicates that the first step in this reaction consists in the alcoholysis of the ester group, followed by rapid rearrangement of **9** formed in the first step. Thus, our attempt to eliminate the possibility of reaction **9** → **8** failed and the established facts support the stepwise mechanism.

To obtain additional evidence we prepared the ether **14**, which should not rearrange by a stepwise mechanism because of the very high energy of intermediate **15** whereas its rearrangement by a concerted mechanism should be as easy as the rearrangement of **7**.





In fact, prolonged heating of **14** in polar solvents (DMSO, pyridine) was without effect. We therefore conclude that, contrary to our initial belief, the rearrangement proceeds by the stepwise mechanism.

EXPERIMENTAL

M.ps (uncorrected) were determined in capillary tubes. IR spectra were recorded with a Zeiss UR-10 spectrometer and UV spectra were measured with an Unicam SP-700 apparatus. ^{1}H NMR spectra were obtained with Tesla 80 spectrometer using 10–15% solutions in $CDCl_3$ or in $(CD_3)_2CO$ with HDMS as standard. Column chromatography was performed on silica gel (Merck). TLC plates were prepared with silica gel G (Merck). Nitro compounds were made visible on chromatograms by spraying with 1% fluorescein solution and viewing under a UV lamp.

2-(2',4'-Dinitrophenylamino)ethanol **2**

2-Aminoethanol (6.1 g, 0.1 mole) was dissolved in dry THF (50 ml) and NaH (2.0 g, 0.083 mole) was added and the mixture was heated to reflux temperature with constant stirring. After 1 h the resulting solution was treated with a solution of 1-fluoro-2,4-dinitrobenzene (14.9 g, 0.080 mole) in THF (50 ml). The reaction mixture became dark-red and the precipitated alkoxide dissolved. The mixture was then heated at reflux temperature for 90 min and poured into ice-water (1 l). The oil that separated was crystallized from ethanol to yield compound **2** (11.1 g, 60.1%) as golden plates, m.p. 90° (lit.[8] 89.5–90.5°).

The same compound was obtained by refluxing an ethanolic solution of 2-aminoethanol with stoichiometric amounts of 1-chloro-2,4-dinitrobenzene and anhydrous sodium acetate.

2-(2',4'-Dinitrophenylamino)ethyl acetate

A 69% yield of this compound was obtained using the procedure described above for the preparation of **2** with 2-acetyloaminoethanol[9] in place of 2-aminoethanol. The product was purified by crystallization from ethanol and then from benzene. M.p. 128–129°. IR(KBr) cm^{-1} ν(C=O) 1734, ν(N–H) 3330; NMR δ(ppm) 2.30 s (3 H, CH_3); 3.88 q (2 H, N–CH_2); 4.32 t (2 H, O–CH_2) J = 6 Hz; 7.17 d, 8.46 q, 9.30 d (3 × 1 H, aromatic AMX system) $J_{AX} \sim 0$, $J_{AM} = 10$, $J_{MX} = 2.5$ Hz; 8.92 s (1 H, N–H). UV(95% EtOH) cm^{-1} 48700 (E, 18040), 43400 (E, 9530), 38300 (E, 8980), 28600 (E, 5410). Found: C, 44.58; H, 4.20; N, 15.56. $C_{10}H_{11}N_3O_6$ requires: C, 44.62; H, 4.12; N, 15.61%. An identical product was obtained from **2** by simple acetylation with Ac_2O.

2-(2',4'-Dinitrophenylamino)ethyl benzoate

This compound was obtained using the procedure described for the preparation of **2**, with 2-benzoylaminoethanol[9] replacing 2-aminoethanol. The yield was 65.2%. The product was purified by column chromatography of the oil obtained when the reaction mixture was poured into water. The column was packed with silica gel and was developed with 1:1 mixture of benzene and ethyl acetate. After crystallization from benzene-cyclohexane mixture it had m.p. 113.5–114°. IR(KBr) cm^{-1} ν(C=O) 1685, ν(N–H) 3345; NMR δ(ppm) 4.10 q (2 H, N–CH_2); 5.00 t (2 H, O–CH_2) J = 6 Hz; 7.38 d, 8.55 q, 9.34 d (3 × 1 H, AMX aromatic system) $J_{AX} \sim 0$, $J_{AM} = 10$, $J_{MX} = 2.5$ Hz; 7.77 m (3 H, aromatic); 8.32 m (2 H, aromatic). UV(95% EtOH) cm^{-1} 49200 (E, 16250), 43300 (E, 22490), 38400 (E, 10755), 28600 (17216), 25000 (E, 6994). Found: C, 54.10; H, 4.05; N, 12.52. $C_{15}H_{13}N_3O_6$ requires: C, 54.38; H, 3.96; N, 12.68%. The same compound was obtained by benzoylation of **2** with benzoyl chloride.

2-Acetylaminoethyl p-nitrophenyl ether **5**

A 56%yield of **5** was obtained by the same procedure as described for **2** using 2-acetylaminoethanol[9] instead of 2-aminoethanol and replacing DNFB with p-nitrofluorobenzene. The product was purified by column chromatography of the solids obtained when the reaction mixture was poured into water. The column was eluted with benzene–ethyl acetate–methanol mixture, with gradually increasing methanol concentration until the proportion of 1:1:1 was obtained. The ether **3** was identified as the third fraction. It forms needles melting at 119–20° after crystallization from benzene. IR(KBr) cm^{-1} ν(C=O) 1650, ν(N–H) 3290; NMR δ(ppm) 2.47 s (3 H, CH_3); 4.02 q (2 H, N–CH_2); 4.52 t (2 H, O–CH_2), J = 5.6 Hz; 7.05 s (1 H, N–H); 7.30 d, 8.47 d (2 × 2 H, aromatic) J = 9.5 Hz; UV(95% EtOH) cm^{-1} 48800 (E, 23490), 44100 (E, 18997), 32600 (E, 28405). Found: C, 53.29; H, 5.48; N, 12.39. $C_{10}H_{12}N_2O_4$ requires: C, 53.57, H, 5.39; N, 12.49%. The ether **3** remains unchanged after 12 h heating in DMF at 120°.

N-Acetyl-2-acetoxy-2',4'-dinitrodiphenylamine **12**

2-Hydroxy-2',4'-dinitrodiphenylamine[2b] (10.0 g) was dissolved in acetic anhydride (80 ml) and 97% H_2SO_4 (3 ml) was added.

The mixture was kept at room temperature for 10 h and then poured into water and neutralised with solid $NaHCO_3$. The precipitated solid was filtered off and washed with water. Crystallization from ethanol-water mixture yielded 7.3 g (56.2%) of pale yellow powder. M.p. 128–129°. IR(KBr) cm^{-1} ν(C=O, amide) 1700, ν(C=O ester) 1770, NMR δ(ppm) 2.47 s (3 H, CH_3amide); 2.60 s (3 H, CH_3 ester); 7.72 m (5 H, aromatic); 8.60 q, 9.12 d (2 × 1 H, part of the aromatic AMX system) $J_{AX} \sim 0$, $J_{AM} = 9.5$, $J_{MX} = 3$ Hz. Found: C, 52.85; H, 3.68; N, 11.57. $C_{16}H_{13}N_3O_7$ requires: C, 53.49; H, 3.65; N, 11.70%.

Partial hydrolysis of **12**

9 (2.0 g) in water-ethanol containing Na_2CO_3 and $NaHCO_3$(pH 9) was heated at 60° for 1 h. The solution was then cooled and neutralized with dilute acetic acid. The precipitated orange solid was filtered off and washed with water. Crystallization from ethanol yielded 1.2 g of 2-acetoxy-2',4'-dinitrodiphenylamine **5** of m.p. 150–151°. IR(KBr) cm^{-1} ν(C=O) 1775, ν(N–H) 3325; NMR δ(ppm) 2.60 s (3 H, CH_3); 7.43 d, 8.54 q, 9.43 d (3 × 1 H, aromatic AMX system) $J_{AX} \sim 0$, $J_{AM} = 10$, $J_{MX} = 4$ Hz; 7.74 m (4 H, aromatic); 10.0 s (1 H, N–H). Found: C, 52.93; H, 3.53; N, 13.10. $C_{14}H_{11}N_3O_6$ requires: C, 53.0; H, 3.49; N, 13.24%. The same compound was obtained from 2-hydroxy-2',4'-dinitrodiphenylamine with Ac_2O in presence of sodium carbonate.

2-Benzoyloxy-2',4'-dinitrodiphenylamine

This compound was obtained by benzoylation of 2-hydroksy-2',4'-dinitrodiphenylamine[2b] with benzoyl chloride and pyridine. After crystallization from ethanol the product was obtained as yellow needles, m.p. 145–145.5°. IR(KBr) cm^{-1} ν(C=O) 1750 ν(N–H) 3338; NMR δ(ppm) 7.47 d, 8.48 q, 9.32 d (3 × 1 H aromatic AMX system) $J_{AX} \sim 0$, $J_{AM} = 9.5$, $J_{MX} = 2.8$ Hz; 7.77 m (7 H, aromatic); 8.35 m (2 H, aromatic); 10.01 s (1 H, N–H). Found: C, 60.12; H, 3.74; N, 11.15. $C_{19}H_{13}N_3O_6$ requires: C, 60.16; H, 3.45; N, 11.08%.

2-Benzoyloxy-2',4'-dinitrodiphenylamine (7.80 g) was acetylated by the same procedure as described for **12**.† The precipitate was chromatographed on silica gel and eluted with benzene–acetone–chloroform 2:2:1 mixture. The elution was controlled by TLC. Evaporation and crystallization from acetone-n-hexane mixture yielded 5.2 g of **13** of m.p. 158–159°. IR(KBr) cm^{-1} ν(C=O, amide) 1700, ν(C=O, ester) 1745. NMR δ(ppm) 2.50 s (3 H, CH_3); 7.70 m (8 H, aromatic); 8.32 m (2 H, aromatic); 8.60 q, 9.0 d (2 × 1 H, part of the aromatic AMX system) $J_{AX} \sim 0$, $J_{AM} = 9.5$, $J_{MX} = 3$ Hz. Found: C, 59.63; H, 3.68; N, 9.94. $C_{21}H_{15}N_3O_7$ requires: C, 59.86, H, 3.59; N, 9.97%.

Partial alcoholysis of **13**

To a solution of **13** (0.808 g) in dry DMSO (12 ml) there was added 5 ml of methanol with a trace of sodium methoxide. The solution was allowed to stand at room temperature for 1 day, poured into water and the mixture was extracted with $CHCl_3$. After drying with $MgSO_4$ the solvent was removed and the oily residue was chromatographed on silica gel and eluted with n-hexane–benzene–acetone 2:1:1 mixture. The first fraction was identified as methyl benzoate (by GLPC and IR). The ester **8** (0.4100 g, 66.4%) was identified as the second, orange fraction. IR and NMR spectra of obtained compound was identical with the spectra of authentic **8**. The mixture m.p. was not depressed.

2-(N-Acetyl-N-ethyl)amino-2',4'-dinitrodiphenyl ether **14**

o-Acetylaminophenol[11] (1.0 g) was dissolved in dry THF (10 ml) and dry DMSO (0.4 ml). Sodium hydride (0.175 g) was added to this solution and the mixture was stirred for 2 h. The solution of 1-chloro-2,4-dinitrobenzene (1.5 g) in THF (5 ml) was then added. The reaction mixture was heated at 45° for 2.5 h and poured on water and the mixture was extracted with chloroform (3 × 100 ml). The combined extracts were dried with anhydrous $MgSO_4$ and evaporated. The oily residue (2.2 g) was purified by chromatography on silica gel with benzene–ethyl acetate mixture initially 2:1 then with 1:1 ratio. There was obtained 1.6 g of a substance ($R_f = 0.36$, benzene–ethyl acetate 2:1 which, after crystallization from cyclohexane-acetone, m.p. 97–98°. IR(KBr) cm^{-1} ν(C=O) 1665, ν(C–O–C) 1275. NMR:‡ At room temperature **14** exists in two forms, as shown by NMR spectroscopy. The equilibrium mixture consists of 34% of B and 66% of A. *Form A*: 8.72 d, 8.26 q, 7.00 d (aromatic AMX system), $J_{AM} = 9.0$, $J_{MX} = 2.8$, $J_{AX} \sim 0$ Hz; 7.27 m (4 H, aromatic); 3.75 m (2 H, N–CH_2), J = 7 Hz, 1.85 s (3 H, CH_3CO); 1.04 t (3 H, CH_3–CH_2) J = 7 Hz. *Form B*: 8.60 d, 8.14 q (part of the aromatic AMX system) $J_{AM} = 9.2$, $J_{MX} = 2.6$, $J_{AX} \sim 0$ Hz; 7.30–7.10 m (5 H, aromatic); 3.33 m (2 H, N–CH_2), J = 7 Hz; 2.10 s (3 H, CH_3–CO); 1.18 t (3 H, CH_3–CH_2) J = 7 Hz. At 62.3° there was observed simplification of the spectrum. This fact corresponds to the free rotation of the single bonded groups. 8.67 d, 8.19 q, 7.02 d (3 × 1 H, aromatic AMX system), $J_{AM} = 8.1$, $J_{MX} = 2.0$, $J_{AX} \sim 0$ Hz; 7.26 m (4 H, aromatic); 3.63 broad s (2 H, N–CH_2); 1.86 s (3 H, CH_3CO); 1.08 t (3 H, CH_3CH_2) J = 6 Hz. Found: C, 55.66; H, 4.72; N, 12.58. $C_{16}H_{15}N_3O_6$ requires: C, 55.65; H, 4.38; N, 12.17%. The solutions of **14** in DMSO (5 ml) and in pyridine (5 ml) were heated at 67° in sealed tubes for 12 h, but no changes were detected by TLC.

†In this case the reaction time was 6 h.

‡These spectra were recorded on a JEOL JNM-PS-100 spectrometer. Correct integrations were obtained in all cases.

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