Regioselectivity in S_NH Reactions of Some 3-Nitro-1,8-naphthyridines with Chloromethyl Phenyl Sulfone

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A number of 2-X-3-nitro-1,8-naphthyridines (X = H,D,OH,Cl,NH_2, OEt) react with the anion of chloromethyl phenyl sulfone exclusively into 2-X-3-nitro-4-(phenylsulfonylmethyl)-1,8-naphthyridines in high yield. The reaction is found by quantum chemical calculations to be controlled by the interactions of the HOMO of the nucleophile with the LUMO of the substrate, and not by charge.

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There are numerous reports of nucleophilic substitution of hydrogen in nitroarenes and azaarenes (S_NH reactions [1a]). It has been reported that a *vicarious* S_NH substitution process takes place when these arenes react with the carbanion of chloromethyl phenyl sulfone [1b].

Our interest in the reactivity of naphthyridines toward nucleophilic agents [2] induced us to study the reaction of the carbanion of chloromethyl phenyl sulfone with some 2-X-3-nitronaphthyridines **3a-e**. There is only one report in the literature describing reactions of chloromethyl phenyl sulfone with unsubstituted 1,X-naphthyridines **1** (X = 5, 6, 7 and 8) [3]. In all cases the bisannelated products **2** were obtained.

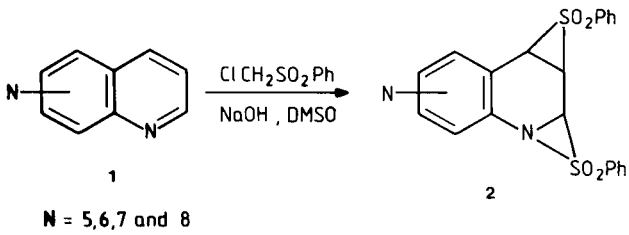


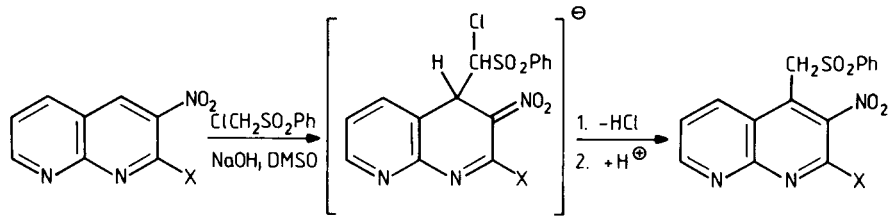
Figure 1

Results.

The reactions were carried out in the base/solvent system sodium hydroxide/dimethyl sulfoxide. The 1,8-naphthyridines **3a-e** were found to react easily with the carbanion of chloromethyl phenyl sulfone under mild conditions (see Experimental) to give exclusively the vicarious substitution products **5a-e** in high yield (80-90%).

This reaction can be described to consist of the following steps: i. a fast and reversible formation of the anionic σ-complex **4** between the reagents, ii. a base induced β-elimination of hydrogen chloride and iii. a subsequent protonation to form the final product **5**. No indication for the formation of an annelation product, like **2**, was found. Due to the presence of the strong electron accepting nitro group the negative charge in intermediate **4** is strongly delocalized which apparently leads to a favoured elimination of hydrogen chloride to form **5**.

The structure of compounds **5** was proved by ^{1}H-nmr spectroscopy. In the ^{1}H-nmr spectrum of **5a**, besides the presence of double doublets of the unsubstituted pyridine ring, the phenyl multiplet and a CH_2-singlet (δ 5.1-5.5), a singlet in the region at δ = 9.54 was observed. This observation showed that substitution has occurred either in the 2 or 4 position. To be



a. X = H, D
b. X = OH
c. X = Cl
d. X = NH_2
e. X = OEt

Figure 2

able to distinguish between substitution at the 2- or 4-position we synthesized 2-deuterio-3-nitro-1,8-naphthyridine (**3a**, X = D) and found that in the ^{1}H-nmr spectrum of the product obtained after reaction with chloromethyl phenyl sulfone the singlet at δ = 9.54 was absent. This indicates unequivocally that in **3a** the substitution has occurred in position 4. Since in the ^{1}H-nmr spectra of the compounds **5b-e** no singlet around δ = 9.5 is present, the conclusion is justified that substitution in **3b-e** has also occurred in position 4. It is of interest to mention that 4-amino-3-nitro-1,8-naphthyridine **6**, the isomer of **3d**, was completely unreactive towards the chloromethyl phenyl sulfone anion.

All results obtained show that in the 3-nitro-1,8-naphthyridines **3a-e** position 4 is strongly favoured towards attack of the carbanion of chloromethyl phenyl sulfone; when position 4 is occupied no reaction occurs. This substitution pattern has also been observed in the reaction of compounds **3** with liquid ammonia [2].

Quantum Chemical Calculations Concerning the Regioselectivity of the Reactions of 3-Nitro-1,8-naphthyridines with Chloromethyl Phenyl Sulfone.

To substantiate the highly regioselective course of the observed reactions we carried out MNDO quantum chemical calculations on the reactivity of 3-nitro-1,8-naphthyridines with the anion of chloromethyl phenyl sulfone [4].

According to the theory of Klopman and Hudson [5,6] the stabilization energy (ΔE) between substrate (A) and nucleophilic reagent (N) may depend on both the ionic (charge control) and covalent interaction (frontier control). This dependency is described by equation 1, consisting of two terms expressing the electrostatic (I) and covalent (II) interaction (c_r represent the coefficient of the HOMO orbitals, c_s those of the LUMO orbitals).

$$\Delta E_{AN} = \underbrace{\frac{Q_A Q_N}{R_{AN} \cdot \varepsilon}}_{\text{I}} + 2 \underbrace{\frac{(c_s \cdot c_r \beta_{rs})^2}{E^N_{HOMO} - E^A_{LUMO}}}_{\text{II}} \qquad (1)$$

The presence of a formal negative charge on the reagent (N) suggests the possibility that the reaction is charge controlled (term I in equation 1). Based on the calculation of formal electron charges on the carbon atoms C-2, C-3, C-4, C-5, C-6 and C-7 and the nitrogen atoms N-1 and N-8 (see Table 1) it was concluded that the reaction is not charge-controlled since in a charge-controlled reaction the nucleophilic substitution in **3a** should have the reactivity order: C-2 > C-4 > C-7 > C-5. Experimentally, this order is not observed; substitution exclusively takes place in position 4 and no reaction products are found resulting from substitution in the C-2, C-7 and/or C-5 position.

Therefore the effect of the second term II, *i.e.* the interactions of the HOMO of the nucleophile N with the LUMO of the substrate A was considered. In such case equation 1 can be simplified to equation 2.

$$\Delta E_{AE} = 2 \frac{(c_s \cdot c_r \beta_{rs})^2}{E^N_{HOMO} - E^A_{LUMO}} \qquad (2)$$

Since for a homogeneous reaction series the terms $c_r^2 \beta_{rs}^2$ may be assumed to be constant it is justified to assume that in the first approximation ΔE is proportional to c_s^2.

Table I

Compound	Formal Charge at the Atoms: N-1	C-2	C-3	C-4	C-5	C-6	C-7	N-8	Preferable Position for $^-CHClSO_2Ph$ Attack (under charge control)
3a	-0.1939	0.1404	-0.1657	0.1185	0.0385	-0.1318	0.1108	-0.1956	C-2 > C-4 > C-7 > C-5
3b	-0.2965	0.2973	-0.1695	0.1459	0.0526	-0.1493	0.1225	-0.2119	C-4 > C-7 > C-5
3c	-0.1737	0.1769	-0.1408	0.1238	0.0388	-0.1279	0.1137	-0.1922	C-4 > C-7 > C-5
3d	-0.3012	0.3012	-0.2210	0.1581	0.0522	-0.1627	0.1283	-0.2203	C-4 > C-7 > C-5

Table II

Compound	Values of c_s Coefficients of LUMO at Atoms N-1	C-2	C-3	C-4	C-5	C-6	C-7	N-8	E_{LUMO} [eV]
3a	-0.215	-0.084	0.414	-0.498	-0.315	-0.052	-0.370	0.172	-1.87
3b	0.243	-0.037	-0.398	-0.531	-0.336	0.088	-0.367	-0.160	-1.82
3c	-0.216	-0.079	0.424	-0.507	0.317	-0.047	-0.373	-0.166	-2.05
3d	0.243	-0.077	-0.369	-0.527	-0.324	0.105	-0.358	0.188	-1.64

Considering the values of c_s coefficients calculated for LUMO orbitals (Table II) the nucleophilic substitution ought to occur predominantly at C-4 (maximum of the coefficient c_s values). The probability of substitution at C-7 is remarkably lower and substitution at C-2 seems practically impossible.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Kofler Plate. The ^{1}H-nmr spectra were recorded with a Tesla BS-478 (80 MHz) or a Varian EM-390 (90 MH2) spectrometer using TMS as internal standard. Ir spectra were recorded in potassium bromide on a Zeiss UR-20 apparatus. Mass spectra were determined on LKB 9000S-GCMS or AEI MS 902 apparatus. Quantochemical calculations were carried out using a Cyber 72 computer (Cyfronet Kraków).

1. Preparation of Starting Material and Reference Compounds.

The following starting and reference compounds were prepared according to known procedures: 3-nitro-1,8-naphthyridine (**3a**, X = H) [7], 2-deuterio-3-nitro-1,8-naphthyridine (**3a**, X = D) [8], 3-nitro-1,2-dihydro-1,8-naphthyridin-2-one (**3b**) [7], 2-chloro-3-nitro-1,8-naphthyridine (**3c**) [7], 2-amino-3-nitro-1,8-naphthyridine (**3d**) [7,9], 2-ethoxy-3-nitro-1,8-naphthyridine (**3e**) [7] and 4-amino-3-nitro-1,8-naphthyridine (**6**) [10]. Chloromethyl phenyl sulfone was obtained from sodium benzenesulfinate and dichloroacetic acid [11].

2. Reactions of 3-Nitro-1,8-naphthyridines with Chloromethyl Phenyl Sulfone.

a. General Procedure.

To a stirred suspension of powdered sodium hydroxide (0.01 mole) in dimethyl sulfoxide (3 ml) a solution of the 3-nitronaphthyridine (0.001 mole) and chloromethyl phenyl sulfone (0.001 mole) in dimethyl sulfoxide (10 ml) was added dropwise at room temperature. The reaction mixture was stirred for 2 hours at room temperature. Then the mixture was poured into diluted aqueous ammonia (for **3a**, **3c-e**) or into acetic acid (for **3b**). The products were filtered off, washed with water and dried. The crude reaction products were recrystallized from a convenient solvent.

b. Products.

3-Nitro-4-(phenylsulfonylmethyl)-1,8-naphthyridine (**5a**, X = H).

This compound had mp 215-216° (from ethanol, light-cream plates), yield 82%; ^{1}H-nmr (deuteriochloroform): δ 9.54 (s, H-2), 9.33 (dd, H-7), 8.72 (dd, H-5), 7.87-7.40 (multiplet, phenyl and H-6), 5.50 (s, CH_2); ms: m/z 329 (M^+), 283 ($M^+ - NO_2$), 188 ($M^+ - SO_2Ph$).

Anal. Calcd. for $C_{15}H_{11}N_3O_4S$: C, 54.71; H, 3.34; N, 12.76. Found: C, 54.95; H, 3.38; N, 12.88.

2-Deuterio-3-nitro-4-(phenylsulfonylmethyl)-1,8-naphthyridine (**5a**, X = D).

The compound was obtained in an identical manner as compound **5a** (X = H) starting from 2-deuterio-3-nitro-1,8-naphthyridine. The ^{1}H-nmr analysis showed that the contents of deuterium in position 2 was nearly 100%.

3-Nitro-4-(phenylsulfonylmethyl)-1,2-dihydro-1,8-naphthyridin-2-one (**5b**).

This compound had mp 321-322° (from methanol, pale-yellow plates), yield 81%; ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 9.26 (dd, H-7), 9.00 (dd, H-5), 8.1-7.7 (multiplet, phenyl and H-6), 5.16 (s, CH_2); ms: m/z 345 (M^+), 204 ($M^+ - SO_2Ph$).

Anal. Calcd. for $C_{15}H_{11}N_3O_5S$: C, 52.17; H, 3.21; N, 12.17. Found: C, 52.42; H, 2.92; N, 12.08.

2-Chloro-3-nitro-4-(phenylsulfonylmethyl)-1,8-naphthyridine (**5c**).

This compound had mp 263-264° (from methanol, white needles), yield 90%; ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 9.76 (dd, H-7), 9.56 (dd, H-5), 8.45 (dd, H-6), 8.0-7.7 (multiplet, phenyl), 5.29 (s, CH_2); ms: m/z 365/363 (M^+), 224/222 ($M^+ - SO_2Ph$).

Anal. Calcd. for $C_{15}H_{10}ClN_3O_4S$: C, 49.52; H, 2.77; N, 11.55. Found: C, 49.72; H, 2.92; N, 11.28.

2-Amino-3-nitro-4-(phenylsulfonylmethyl)-1,8-naphthyridine (**5d**).

This compound had mp 271-272° (sublimed/from 2-propanol, orange plates, yield 87%; ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 9.25 (dd, H-7), 8.92 (dd, H-5), 8.0-7.6 (multiplet, phenyl and H-6), 5.44 (s, CH_2); ms: m/z 344 (M^+), 298 ($M^+ - NO_2$), 203 ($M^+ - SO_2Ph$).

Anal. Calcd. for $C_{15}H_{12}N_4O_4S$: C, 52.32; H, 3.51; N, 16.27. Found: C, 52.60; H, 3.52; N, 16.32.

2-Ethoxy-3-nitro-4-(phenylsulfonylmethyl)-1,8-naphthyridine (**5e**).

This compound had mp 215-216° (from methanol, white plates), yield 83%; ^{1}H-nmr (deuteriotrifluoroacetic acid): δ 9.56 (dd, H-7), 9.0 (dd, H-5), 8.2 (dd, H-6), 8.1-7.7 (multiplet, phenyl), 5.26 (s, CH_2), 4.38 (q, CH_2), 1.56 (tr, CH_3); ms: m/z 373 (M^+), 344 ($M^+ - C_2H_5$).

Anal. Calcd. for $C_{17}H_{15}N_3O_5S$: C, 54.68; H, 4.05; N, 11.25. Found; C, 54.45; H, 4.12; N, 11.42.

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