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TRANSFORMATIONS OF CARBANIONIC σ-ADDUCTS OF 6-AZAQUINOXALINE DERIVATIVES[1)]

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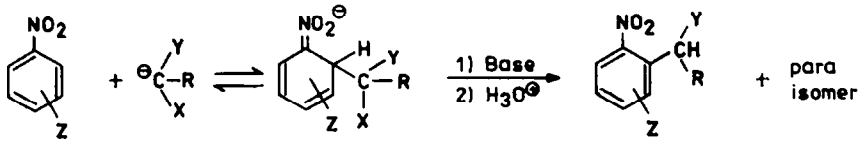
ABSTRACT - Carbanions of α-haloalkyl aryl sulphones react with 6-azaquinoxaline via two pathways: the vicarious nucleophilic substitution of hydrogen and the bis-annulation. Factors governing these two reactions were analyzed and possibility of controlling the reaction course on this basis was demonstrated.

The vicarious nucleophilic substitution of hydrogen (VNS) in nitroarenes is a general reaction between carbanions containing leaving groups X and a variety of nitroaromatic compounds. The reaction proceeds *via* addition of the carbanions to the nitrocompounds with the formation of the anionic σ-adducts. Base-induced β-elimination of HX followed by protonation during the work up procedure gives the substituted products[2)].

Scheme 1



X - leaving group, Y - carbanion stabilizing group, R - substituent

This reaction is a valuable general method for the introduction of a variety of substituents into electrophilic aromatic rings, amongst them nitroheterocyclic compounds like nitropyridines[3)], nitroquinolines[4)], nitrothiophenes[5)], etc., Also, some electrophilic heterocycles, which do not contain nitro group e.g. acridine, 1,2,4-triazine[6)], etc. enter this reaction. On the other hand, some highly electrophilic heteroarenes react with α-halocarbanions *via* an alternative pathway giving bis-annulated products. This pathway has been observed in the reaction of chloromethyl aryl sulphones with quinoxalines, naphthyridines[7)] and even with carbocyclic 1-cyanonaphthalene[8)].

The dramatic difference in the reaction mode between 1,2,4-triazines[6)] and nitronaphthalenes[9)] on the one hand and quinoxalines[7)] and cyanonaphthalene[8)] on the other we have accounted for by differences in the charge distribution in the intermediate anionic σ-adducts. High charge delocalization in the σ-adducts of the carbanions with 1,2,4-triazines and particularly nitroarenes favours base-induced β-elimination leading to the VNS products, whereas in the σ-adduct with quinoxaline the negative charge is mainly localized on the neighbouring nitrogen atom. The latter behaves therefore as a strong nucleophilic center which enters fast intramolecular substitution leading to the annulation product, whereas the β-elimination is suppressed. On the other hand

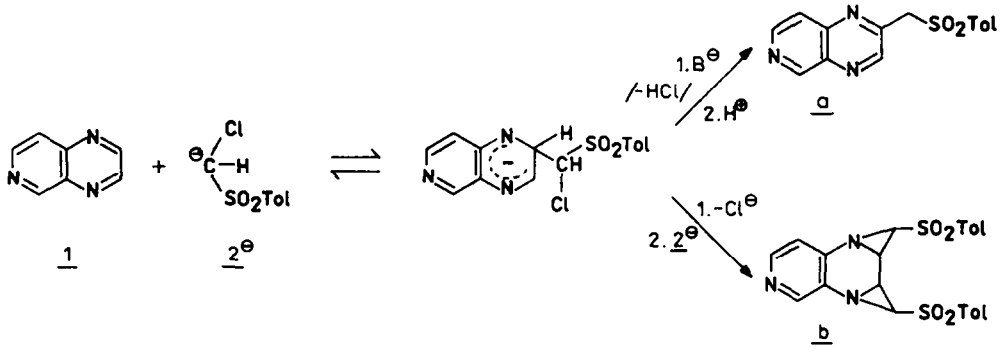
quinoxaline N-oxide reacts with chloromethyl aryl sulphones according to the VNS pathway[8], since the negative charge of its σ-adduct resides mostly on the oxygen atom. The differences in structure of the arenes, namely in the ability for delocalization of the negative charge were therefore the main reason for the observed dichotomy in the mode of conversion of the σ-adducts.

Taking into account substantial differences in the mechanisms of the alternative pathways for transformation of the σ-adducts we can set up an *a priori* hypothesis as to how the structure of the reactants and the conditions would affect competition between these two reactions.

The structure of the arenes governs the ability for delocalization of the negative charge in the σ-adducts, whereas the nature of the leaving group X and the substituent R in the carbanions affects substantially the relative tendency for β-elimination or intramolecular nucleophilic substitution in the σ-adducts. Many parameters of the conditions such as: temperature, solvent, kind and concentration of the base, total concentration, etc. can also affect this competition. One could expect, that high concentration of the reagents, excess of the base and low temperature would shift the reaction course toward the VNS, which proceeds *via* bimolecular base-induced β-elimination of HX from the σ-adduct.

Looking for a good model for an electrophilic arene, which would permit the study of the effects of various factors on the reaction mode we have selected pyrido[3,4-b]pyrazine (6-aza-quinoxaline) 1, which in preliminary experiments reacted with the anion of chloromethyl p-tolyl sulphone 2 *via* both - the VNS and the annulation pathways

Scheme 2



For further simplification all experiments were carried out in the same solvent, namely liquid ammonia (in order to observe the temperature effect the use of DMF was necessary) with potassium *tert*-butoxide or sodium hydroxide as bases for generation of the carbanion and the β-elimination of HX from the σ-adduct.

Keeping these starting compounds 1 and 2 constant, variations of the conditions resulted in substantial changes of the VNS (a) and the annulation (ANN, b) ratio (a/b).

Temperature. With both of these bases (NaOH, t-BuOK) ratio a/b was strongly affected by the temperature (Table 1).

This difference can be rationalized in terms of the entropy of the transition state. The intramolecular substitution process is associated with a relatively smaller change in entropy, as compared with the bimolecular elimination in which the entropy change should be negative and of substantial value. Consequently, the latter process should be strongly favoured at lower temperatures. One can also suppose, that for the entropic reason, too, at low temperature the σ-adducts exist in the form of tight ion pairs, therefore the intramolecular S_N2 process is decelerated and the β-elimination step becomes dominating. At room temperature this effect does not operate and intramolecular substitution proceeds faster than elimination.

Bases and concentrations. Differences between NaOH and t-BuOK are mostly due to the insolubility of the former in liquid ammonia and DMF, hence with NaOH base a fraction of the reaction proceeds on the solid surface. In order to compare the effect of the different strengths of soluble

bases - t-BuOK and the carbanion (which can also act as a base) were used (Table 2). The results show that the latter, being a weaker and more bulky base, is less efficient in the elimination leading to the VNS product (a).

The reaction leading from the common intermediate (σ-adduct)to the annulation product is monomolecular, whereas the VNS reaction is bimolecular, hence the a/b ratio should be sensitive toward the total concentration, as was indeed observed (Table 3).

Table 1. The temperature control of the reaction in scheme 2. 1 (1 mmol) and 2 (2.2 mmol) in DMF (2 mL) were added to the base in DMF (8 mL); time - 5 min.

Temp. [°C]	Yield [%] a	b	Ratio a/b	Total yield [%]
	NaOH/DMF system[a]			
20	0	84	0	84
0	8	51	0.16	59
-10	25	23	1.09	48
-30	44	0	only a	44
	t-BuOK/DMF system[b]			
19	<1	61	<0.002	~62[c]
19	39	32	1.22	71
-50	41	0	only a	41

[a] NaOH was used in about 20 fold excess to 2; [b] 2.3 mmol of t-BuOK; [c] the order of addition of reagents was changed - t-BuOK was slowly added dropwise to the DMF solution of 1 and 2.

Table 2. Base control of the reaction in scheme 2 (V_{NH_3} = 20 mL, temp. -29°C).

Base	Yield [%] a	b	Total yield [%]	Ratio a/b
t-BuO$^-$ [a]	60	14	74	4.29
t-BuO$^-$ [b]	30	36	66	0.83
Ts-$\overset{\overset{Cl}{|}}{CH}^-$ [c]	17	50	67	0.34
[d]	20	57	77	0.35

[a] 1 (1 mmol) and 2 (2.1 mmol) were added in 2 mL of THF to the base (6 mmol) during 3 min and the reaction was continued for further 7 min; [b] according to the procedure[a]; 2.2 mmol of t-BuOK; [c] 1 was added in 2 mL of THF to the carbanion solution earlier prepared using equimolar amounts of 2 and t-BuOK (time - 3 + 7 min); [d] as above, $NaNH_2$ was used instead of t-BuOK.

Table 3.: Effects of the concentration on the reaction in scheme 2[a].

V_{NH_3} [mL]	Temp. [°C]	Yield [%] a	b	Ratio a/b	Total yield [%]
	t-BuOK/$NH_{3liq.}$[b]				
10	-29	35	32	1.09	67
20	-29	30	36	0.83	66
80	-30	17	56	0.30	73
200	-30	11	53	0.21	64

[a] 1 (1 mmol) and 2 (2.1 mmol) in 2 mL of THF were added dropwise during 3 min to the base in liquid ammonia and the reaction was continued for 7 min; [b] 2.2 mmol of base was used.

Structure of the carbanion. Keeping constant the arylsulfonyl stabilizing group, the effects of some changes in the carbanion structures were studied, namely: nature of the leaving group X (Table 4) and the substituent R (Table 5) were varied.

For the different halosulphones studied (X = Br, Cl, F) the value of a/b ratio increases rapidly, which reflects the known phenomenon that in the row Br, Cl, F the ability of haloalkanes to undergo S_N2 type reactions decreases faster than the ability for β-elimination. For example, the relative rates of S_N2 substitution in methyl halides with the OH^- anion are $k_{Br} : k_{Cl} : k_F$ = = 393 : 27 : 1[10]; while the ratios for β-elimination of 2-arylethyl halides under similar conditions are 9 : 2 : 1[11] respectively.

In the VNS with acetonitrile derivatives α-aryloxy and α-arylthio substituents have been very efficient leaving groups. Thus, the reaction of the corresponding sulphone derivatives were attempted. In these cases only elimination was observed, but here the arylsulphinic acid moiety played the role of the leaving group, hence the corresponding ether (e) or thioether (c) were formed. In the latter case the reaction at lower temperature led to (d) as the major product.

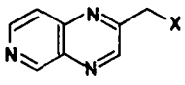
It was obviously formed *via* oxidation of the σ-adduct, however the nature of the oxidants is not clear. The redox process is rather complicated; we did not recover any of the starting pyrido [3,4-b]pyrazine and a substantial amount of very polar tars were formed (start spot on TLC). According to Stirling[12], the activities of ArS and $ArSO_2$ as leaving groups in base-induced β-elimination are similar. However, we have found elsewhere that in the VNS reaction of $PhSCH_2SO_2Ph$ with nitrobenzene the elimination of thiophenol prevailed[13].

No reaction was observed between pyrido [3,4-b]pyrazine and bis-arylsulphonylmethane (X= SO_2Ph), probably because of the low nucleophilicity of the respective carbanion.

Table 4. Reaction of 1 with sulphones XCH_2SO_2Tol bearing different leaving groups [conditions: V_{NH_3} = 20 mL, time - 15 min; 1 (1 mmol) and sulphone (2 mmol) were added in 2 mL of THF to t-BuOK (2.2 mmol) in liquid ammonia].

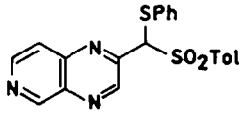
X	Conditions	Products and yields [%] ANN b	VNS a	OTHERS	Ratio ANN/VNS	Total yield [%]
-Br	-28°	65	≪1	-	>100	65
-Cl	-29°	43	32	-	1.34	75
-F	-28°	-	31	-	0	31
-SPh	-28°	-	-	c 19	0	19(25)[a]
-SPh	-60°, 2.5h	-	-	c 19 d 33	0	52
-OAr[b]	-28°	-	-	e 41	0	41
$-SO_2Ph$	-29°	-	-	-	-	-

a) the yield in brackets was calculated for consumed 1 (26% of 1 was recovered);
b) $2,4-C_6H_3Br_2-OCH_2SO_2Ph$ was used.



c: X = SPh

e: X = O-(2,4-$C_6H_3Br_2$)



d

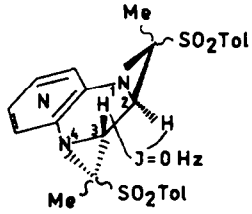


Fig. 1

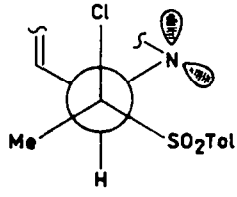


Fig. 2

Finally, the tertiary carbanion of α-chloroethyl p-tolyl sulphone (X = Cl, R = CH_3) was reacted with azaquinoxaline. In this case the reaction proceeded exclusively as the bis-annulation (Table 5). TLC (silica gel, $CHCl_3$: Me_2CO 10 : 1) showed the formation of three products, which were geometric isomers; two of them [R_F = 0.48(f, 38%) and R_F = 0.31(g, 41%)] dominated. On the basis of ^1H NMR spectra it was determined that the aziridine rings are located mutually trans (fig.1), due to the absence of coupling between H-2 and H-3 protons. According to the Karplus equation[14] it is possible only when the dihedral angles between C-H bonds equal c.a. 90° . A minor quantity of third product [R_F = 0.18(h)] was isolated by column chromatography and its molecular ion determined by HR-MS spectrum indicated that it was the third isomer. More detailed data (including X-ray structures) concerning all three isomers will be published elsewhere[15] .

It is well established[16] and supported by Molecular Orbital calculations[17], that the E2 elimination process is highly sensitive to the geometry of the transition state, which requires an antiperiplanar arrangement of H-C-C-X bonds (fig.2; in some cases of rigid system the β-elimination proceeds *via* less energetically convenient synclinal conformation of the transition state[18]). In the σ-adducts of tertiary carbanions with 6-azaquinoxaline these conformations are sterically

disfavoured as compared to corresponding σ-adducts of the secondary carbanions, hence annulation is preferred over the VNS. There is also substantial steric hindrance to the approach of the base to the H atom necessary for β-elimination from the σ-adducts.

Table 5. Reactions of secondary and tertiary sulphones ($ClCHRSO_2Tol$) with 1 [V_{NH_3} = 20 mL time - 15 min, temp, - -30°C; 1 (1 mmol) and sulphone (2.2 mmol) were added in 2 mL of THF to the base[a] in liquid ammonia].

Sulphone, R =	Products and yields VNS	[%]	ANN	[%]
H	a	32	b	43
CH_3	-		f - h	79

a) t-BuOK (2.3 mmol).

The results presented in this paper demonstrate that it is possible by a variety of ways to control the transformation of σ-adducts of carbanions with 6-azaquinoxaline. It can be a general method of control of these types of processes for other aromatic electrophilic compounds which show such dichotomy.

EXPERIMENTAL SECTION

^1H NMR spectra were recorded on Bruker CPX-300 (300 MHz) in $CDCl_3$ with TMS as internal standard. Coupling constants are expressed in hertz (Hz). MS spectra were measured on Finnigan 8200. Melting points were uncorrected. All new compounds a - g gave satisfactory microanalyses. All experiments were carried out according to one of the two general procedures (below). Some modifications are noted in the tables.

NaOH/DMF system. To a stirred suspension of powdered NaOH (800 mg, 20 mmol) in DMF (8 mL) a solution of 6-azaquinoxaline (131 mg, 1 mmol) and chloromethyl p-tolyl sulphone (430 mg, 2.1 mmol) in DMF (2 mL) was added dropwise at the room temperature during 3-4 min. The reaction was continued for 10 min, poured into water (150 mL) and extracted with chloroform (2x30 mL). The combined organic layers were washed with water (2x40 mL), dried over Na_2SO_4 and evaporated. After purification by column chromatography ($CHCl_3$: $(CH_3)_2CO$ - 10 : 1) bis-annulated product, b (374 mg, 80%) was obtained.

t-BuOK/NH_3 system. To a stirred solution of potassium *tert*-butoxide (250 mg, 2.23 mmol) in liquid ammonia (8 mL) cooled to -75°C a solution of 6-azaquinoxaline (131 mg, 1 mmol) and chloromethyl p-tolyl sulphone (240 mg, 1.17 mmol) in THF (1-1.5 mL) was added with a syringe during a period of 1 min. After additional 10 min ammonium chloride (0.5 g) was added in small portions and the ammonia was evaporated. To the residue chloroform (20 mL) and water (20 mL) were added, organic layer was separated and dried over Na_2SO_4. After evaporation of the solvent the crude product was purified *via* column chromatography ($CHCl_3$: $(CH_3)_2CO$ - 10 : 1), yielding pure product of vicarious nucleophilic substitution of hydrogen, a (206 mg, 69%).

Products: physical properties.

(a): m.p. 188-90°C /EtOH/; ^1H NMR: 9.58(s, 1H), 9.01(s, 1H), 8.83(d, J=5.8, 1H), 7.77(d, J=5.8, 1H), 7.59 & 7.28(2xAB, J=8.3, 4H), 4.78(s, 2H), 2.43(s,3H); MS, m/e (% rel.int.): 299($M^{+\cdot}$, 0.2), 235(100), 234(74), 220(17), 155(11), 144(13), 103(19), 91(80), 65(18).

(b): m.p. 219-21°C /EtOH/; ^1H NMR: 8.09(d, J=5.2, 1H), 7.90-7.75 & 7.50-7.40(2xm, 9H), 6.52(d, J=5.2, 1H), 3.72 & 3,46(2xd, J=2.6, 2H), 3.68 & 3.51(2xd, J=2.8, 2H), 2.51 & 2.49(2xs, 6H); MS, m/e (% rel.int.): 467($M^{+\cdot}$, 5), 312(51), 156(12), 139(100), 91(50), 65(16).

(c): m.p. 164-5°C /EtOH/; ^1H NMR: 9.57(s, 1H), 9.02(s, 1H), 8.88 & 7.89(2xd, J=5.9, 2H), 7.40-7.20(m, 5H), 4.45(s, 2H); MS, m/e (% rel.int.): 253($M^{+\cdot}$, 60), 221(34), 220(73), 144(40), 125(20), 103(48), 97(42), 83(42), 71(42), 69(56), 57(100), 55(62), 43(78).

(d): decomposition c.a.180°C; ^1H NMR: 9.58(s, 1H), 9.16(s, 1H), 8.84 & 7.78(2xd, J=5.8, 2H), 7.80-7.10(m, 9H), 5.61(s, 1H), 2.43(s, 3H); MS, m/e (% rel.int.): 407($M^{+\cdot}$, 2), 252(100), 219(69), 91(10).

(e): m.p. 154°C /EtOH/; ^1H NMR: 9.58(s, 1H), 9.38(s, 1H), 8.87 & 7.91(2xd, J=5.8, 2H), 7.80-6.85(m, 3H), 5.47(s, 2H); MS, m/e (% rel.int.): 397(3), 395(6), 393(3) - $M^{+\cdot}$, 316(97), 314(100), 251(10), 235(20), 223(11), 207(11), 144(69), 111(12), 103(62), 97(17), 83(17), 71(22), 69(22), 63(31), 57(31), 43(24).

(f): m.p. 266-70°C (dec.) /$(CH_3)_2CO$/; ^1H NMR: 8.13(d, J=5.2, 1H), 7.83(s, 1H), 7.93-7.85 & 7.48-7.40(m, 8H), 6.54(d, J=5.2, 1H), 3.63(s,1H), 3.58(s, 1H), 2.52 & 2.49(2xs, 6H), 1.34 & 1.33 (2xs, 6H); MS, m/e (% rel.int.): 495($M^{+\cdot}$, 26), 341(24), 340(78), 184(49), 170(16), 159(17), 155(14), 139(100), 91(67), 65(15).

(g): m.p. 208-10°C (dec.) /$(CH_3)_2CO$/; ^1H NMR: 7.99 & 7.46(2xd, J=8.1, 2H), 7.45-7.25(m,9H), 4.03(s, 1H), 2.80(s, 1H), 2.53 & 2.45(2xs, 6H), 1.70 & 1.31(2xs, 6H); MS, m/e (% rel.int.): 495($M^{+\cdot}$, 19), 341(20), 340(66), 184(42), 170(15), 159(25), 139(100), 91(63), 77(11), 65(17), 43(13).

(h): MS, m/e (% rel.int.): 495($M^{+\cdot}$, 4), 340(13), 235(59), 234(47), 184(10), 155(18), 139(70), 123(11), 103(18), 91(100), 71(16), 65(26), 57(22), 55(15), 43(17); HR: 495.1286 (calc. and found for $C_{25}H_{25}N_3O_4S_2$).

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