Tetrahedron Vol. 44, No. 1, pp. 209 to 213, 1988
Printed in Great Britain.

0040-4020/88 $3.00+.00

VICARIOUS NUCLEOPHILIC SUBSTITUTION OF HYDROGEN ORTHO TO THE NITRO GROUP BY TERTIARY CARBANIONS OF α-CHLOROALKYL PHENYL SULPHONES[1]

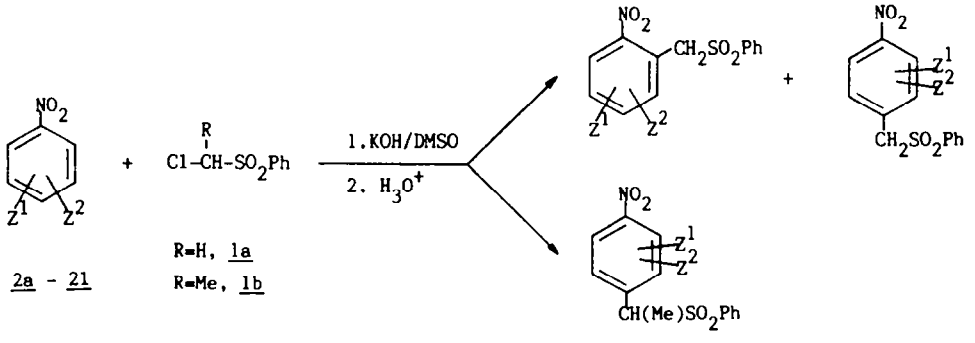
BOGUSŁAW MUDRYK and MIECZYSŁAW MĄKOSZA

Institute of Organic Chemistry, Polish Academy of Sciences
01-224 Warsaw, Poland

(*Received in UK 9 October* 1987)

Abstract - The tertiary carbanions of α-chloroalkyl phenyl sulphones readily enter the vicarious nucleophilic substitution of hydrogen ortho to the nitro group with a number of 4- and 3- substituted nitrobenzenes, when potassium tert-butoxide/DMF base-solvent system at -40°C ÷ -30°C is employed.

In our previous papers we have formulated the concept of the vicarious nucleophilic substitution of hydrogen (VNS) in nitroarenes with carbanions of general structure $(X)\overline{C}(R)(Y)$ where X is the leaving group, Z - the carbanion stabilizing group and R - hydrogen, alkyl or aryl, shown its general character and disclosed its specific features.[2-6] In these papers it was reported that the orientation of the VNS strongly depends on the structure of the carbanions, in particular the tertiary carbanions (R ≠ H) are generally not able to react with nitrobenzenes via the VNS at position ortho to the nitro group. Few exceptions refer to reactions involving the carbanions of α-chloroalkyl nitriles[7], dichloromethyl phenyl sulphoxide[8] and chloroform[9], the last case being originally interpreted by another mechanism. The orientation pattern of the secondary (R = H) and tertiary (R ≠ H) carbanions stabilized by the sulphonyl group differs substantially, particularly the reaction of chloromethyl phenyl sulphone 1a with nitroarenes carried out in KOH/DMSO base-solvent system resulted in the substitution of hydrogen in both ortho and para positions, whereas the tertiary carbanion of α-chloroethyl phenyl sulphone 1b effected exclusively the para substitution.[3] When the para position in a nitroarene was occupied by a substituent no ortho substitution product was obtained (Scheme I):



Scheme I

These results parallel those obtained in another base-solvent system namely potassium tert--butoxide/tetrahydrofuran. As it was shown these conditions strongly favour the ortho substitution with the secondary carbanions of chloromethyl phenyl sulphone[10] and some acetonitrile derivatives.[11]

Such a strong effect on the orientation was attributed to the interaction of the potassium cations (being under these conditions with the carbanions in the form of tight ion pairs) with the nitro group. This interaction results in attraction of the carbanion to the vicinity of this group and consequently in the exclusive formation of o-nitrobenzyl phenyl sulphone in the reaction of 1a with nitrobenzene.

Contrary to that the tertiary carbanion of α-chloroethyl phenyl sulphone 1b reacted with nitrobenzene under these conditions very poorly.[10] The significant difference in the orientation pattern of the vicarious nucleophilic substitution between secondary and tertiary carbanions of Ia and 1b has been rationalized in terms of the primary steric effect of substituent R in 1 which can operate on both the addition and particularly the elimination steps.[2,5] Now we would like to report that under specific conditions: potassium tert-butoxide in DMF at -40°C the VNS of hydrogen in the ortho positions of para-substituted nitrobenzenes and some other nitroarenes by the tertiary carbanion α-chloroethyl phenyl sulphone proceeds smoothly leading to high yields of ortho-substituted products as presented in table I.

Table I[a]

Nitroarene	Z^1,	Z^2,	Position of $CH(Me)SO_2Ph$	Products, Yield %
2a	H,	H	4	3, 65
			2	4, 3.8
2b	4-Cl,	H	2[b]	5, 82
2c	2-Cl,	4-Cl	6	6, 90
2d	3-Cl,	4-Cl	6	7, 81
2e	4-OMe,	H	2	8, 58
2f	$4-CF_3$,	H	2	9, 83
2g	$4-CO_2Bu-t$,	H	2[c]	10, 70
2h	4-F,	H	2	11, 50
			4[d]	3, 14
2i	$-C_4H_4-$[e]		2	12, 40
			4	13, 5
2k	3-Cl,	H	6	14, 16
			4	15, 64
2l	$3-CF_3$,	H	6	16, 58
			4	17, 5

a) Notations as on scheme I

b) In KOH/DMSO system 3 (16%) via replacement of the halogen and dechlorination and 4 (5%) were formed.

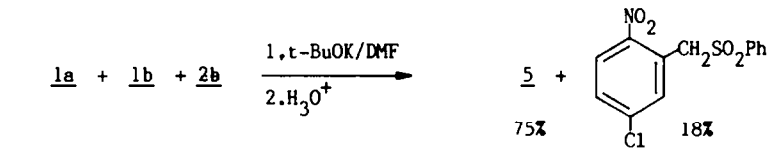
c) $p-CH_3C_6H_4SO_2CH(Me)Cl$ was used

d) In KOH/DMSO system only 3 (30%) was formed, see b).

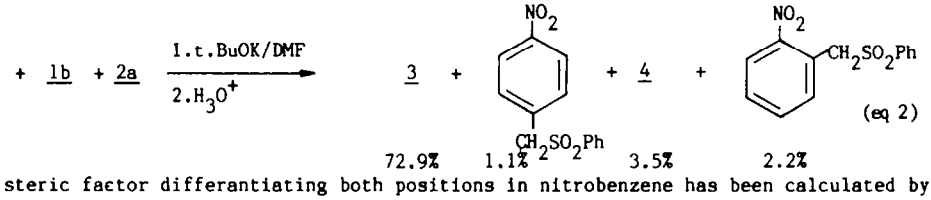
e) 1-Nitronaphthalene

Efficient VNS of hydrogen in ortho positions with the tertiary carbanions under conditions used in this paper in contrast to the failure of such process under other conditions can be accounted by a few factors. The most important of them seem to be high concentration of the strong, soluble base and low temperature. We have observed that the tertiary carbanion of 1b and also the o-nitrobenzylic carbanions of the corresponding products are unstable at room temperature. For example in the reaction of 1b with 1-nitro-4-trifluoromethylbenzene 2f after 5 min at -40°C the mixture contained 83% of 9 whereas when it was allowed to warm up to room temperature, the yield of 9 dropped to only 20% (estimated by GLC).

The steric hindrance of the methyl group in 1b strongly affects the orientation pattern in nitrobenzene (p/o = 17 compared to p/o = 0.5 for 1a) however this effect is not so dramatic as we have originally supposed. In fact the reaction of the tertiary carbanion of 1b ortho to the nitro group proceeds even faster than analogous reaction of the secondary carbanion of 1a as it was shown when both of these carbanions were competing in reaction with 1-chloro--4-nitrobenzene. It should be pointed out that no conventional substitution of halogen occured in these experiments (eq 1).



This result seems to reflect the superposition of two contradictory factors: on one side the greater bulkness of 1b hinders and on the other the higher nucleophilicity of 1b over 1a favours its reaction, nucleophilicity being, however dominating. Indeed, as it was shown in another competition experiment presenting the relative reactivities of 1a and 1b in the substitution of hydrogen at positions para and ortho in nitrobenzene (eq 2), the relative nucleophilicities of both carbanions (measured by the relative reactivities at position para (since no steric interactions with the nitro group operate here) differ significantly:



The overal steric factor differantiating both positions in nitrobenzene has been calculated by means of the integrated kinetic equations expressing the relative reactivities of 1a and 1b at positions ortho and para*:

$$\frac{k_p^{Me}}{k_p^{H}} = 120; \quad \frac{k_o^{Me}}{k_o^{H}} = 2.9; \quad \frac{k_p^{Me}}{k_p^{H}} : \frac{k_o^{Me}}{k_o^{H}} \cong 40$$

*The full derivation leading to the final equation expressing the relative reactivities of 1a and 1b in the para position is given below (an analogous derivation can be made for the ortho position):

(a) $$\frac{d\left[P_p^{H}\right]}{dt} = K_p^{H}\, k_{2p}^{H} \left[2a\right] \left[1a^-\right] \left[t\text{-}BuO^-\right]$$

(b) $$\frac{d\left[P_p^{Me}\right]}{dt} = K_p^{Me}\, k_{2p}^{Me} \left[2a\right] \left[1b^-\right] \left[t\text{-}BuO^-\right]$$

are the final kinetic equations expressing the rates of the formation of the products P_p^{H} and P_p^{Me} at the para position in 2a from 1a and 1b, respectively, in the two-step VNS (assuming a steady state concentration of the σ adduct) when the second base-induced elimination step is the rate-limiting one[12] (K_p^{H} and K_p^{Me} are the equilibrium constants of the σ adducts formation and k_{2p}^{H} and k_{2p}^{Me} are the rate constants of the base-induced elimination reactions at the para position for 1a and 1b, respectively):

Introducing: $K_p^{H}\, k_{2p}^{H} = k_p^{H}$ and $K_p^{Me}\, k_{2p}^{Me} = k_p^{Me}$ (the observed rate constants refering to the reactions at the para position for 1a and 1b, respectively) and

$$\left[1a^-\right] = \left[1a^-\right]_o - \left[P_p^{H}\right] - \left[P_o^{H}\right]$$
$$\left[1b^-\right] = \left[1b^-\right]_o - \left[P_p^{Me}\right] - \left[P_o^{Me}\right]$$

(P_o^{H} and P_o^{Me} - the "ortho" - products with 1a and 1b, respectively).

diving equations (b) by (a) and further transformations lead to the equation (c)

(c) $$\frac{d\left[P_p^{Me}\right]}{\left[1b^-\right]_o - \left[P_p^{Me}\right] - \left[P_o^{Me}\right]} = \frac{k_p^{Me}}{k_p^{H}} \cdot \frac{d\left[P_p^{H}\right]}{\left[1a^-\right]_o - \left[P_p^{H}\right] - \left[P_o^{H}\right]}$$

Integration of the last equation gives the final equation (d)

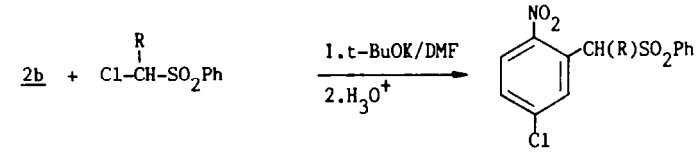
(d) $$\frac{k_p^{Me}}{k_p^{H}} = \frac{\left(\frac{\left[P_o^{H}\right]}{\left[P_p^{H}\right]} + 1\right) \ln\left[1 - \left(\frac{\left[P_o^{Me}\right]}{\left[P_p^{Me}\right]} + 1\right)\frac{\left[P_p^{Me}\right]}{\left[1b^-\right]_o}\right]}{\left(\frac{\left[P_o^{Me}\right]}{\left[P_p^{Me}\right]} + 1\right) \ln\left[1 - \left(\frac{\left[P_o^{H}\right]}{\left[P_p^{H}\right]} + 1\right)\frac{\left[P_p^{H}\right]}{\left[1a^-\right]_o}\right]}$$

In our conclusion the reaction of the tertiary α-chloroethyl phenyl sulphone carbanion with nitrobenzene proceeds about 40 times slower at position ortho to the nitro group than in position para, refering to the secondary chloromethyl phenyl sulphone carbanion. This value is in good agreement with that calculated from the p/o ratios for the single reaction of 1a and 1b with nitrobenzene (about 35) (Table I).

In the reaction of 1b with 1-fluoro-4-nitrobenzene the substitution of the ortho hydrogen still dominates over the conventional nucleophilic substitution of fluorine at the para position whereas in a control experiment using KOH/DMSO system the fluorine substitution product 3 is formed exclusively although in a moderate yield.

Finally the last three enteries show the ortho substitution abilities of 1b in nitroarenes other than 4-substituted nitrobenzenes. For 1-nitronaphthalene and 1b the reaction proceeds preferentially at position 2(1-nitronaphthalene and α-chloroethyl p-tolyl sulphone yield only 4-substituted product in low yield in KOH/DMSO system[13]). 1-Nitro-3-trifluoromethylbenzene reacts with 1b giving like 1a, mostly the 6-isomer (6-/4- = 12; for 1a : 6-/4- = 3.5 in KOH/DMSO system[10]). On the other hand, for 1-chloro-3-nitrobenzene and 1b isomer 4- is the major product (4-/6-ratio 4 : 1 closely corresponds to the 4-/6- value 3.5 obtained in reaction involving the secondary carbanion 1a[10]).

In some additional experiments we have found that the α-chloroalkyl phenyl sulphones $PhSO_2CH(R)Cl$ bearing alkyl groups R larger then Me readily enter the vicarious nucleophilic substitution of ortho hydrogen with 1-chloro-4-nitrobenzene (eq 3).



(eq 3)

R=Et, 18, 77%
iso-Bu, 19, 69%
Ph, no reaction

Until now, however, we failed to afford the reaction of more bulky and much less nucleophilic α-chlorobenzyl phenyl sulphone carbanion at position ortho to the nitro group.

The effect of steric hindrances in carbanion moiety on the rates of the addition and elimination steps in vicarious nucleophilic substitution of hydrogen is under current investigation and will be subject of forthcoming reports.

EXPERIMENTAL

^1H NMR spectra were recorded on a Varian M-360 (60MHz) spectrometer in $CDCl_3$ unless otherwise stated. The ratios of isomeric products were determined by gas chromatography performed on Chrom 5 apparatus equipped with 1.5 m stainless column packed with 3% OV-17 on Chromosorb W.Silica gel Merck 230-400 mesh was used for column chromatography. TLC analyses were made on Alufolien Merck $60F_{254}$. Ethanol or hexane - ethyl acetate were used as the solvents for recrystallization of the products. The melting points are uncorrected.

Materials. The aromatic nitrocompounds were commercial products, α-chloroethyl, α-chloropropyl and α-chloroisobutyl phenyl sulphones were obtained by alkylation of chloromethyl phenyl sulphone with the corresponding bromides in the catalytic two-phase system[10].

Reactions of nitroarenes with α-chloroalkyl phenyl sulphones - a typical procedure:

To a solution of potassium tert-butoxide (500 mg, 4.5 mmoles) in dry DMF (10 ml) a solution of a nitroarene (2 mmoles) and α-chloroalkyl phenyl sulphone (2 mmoles) in DMF (1 ml) was added in one portion at -40°C. The reaction mixture was magnetically stirred at -40 ± -30°C for 5-60 min, poured into diluted hydrochloric acid (300 ml), the products extracted with methylene chloride (2 x 20 ml), the extract washed twice with water to remove DMF and the solvent was evaporated. The products were purified by recrystallization or by column chromatography and identified by ^1H NMR spectra or, in some cases, by comparison with authentic samples prepared by methylation of the corresponding o-nitrobenzyl phenyl sulphones (1 equivalent) in the presence of t-BuOK (1 equivalent) in DMF or DMSO.

1-(4-nitrophenyl)ethyl phenyl sulphone 3, m.p. 98-99°C, ^1H NMR: 1.80(d, J=7.5, 3H); 4.45(q, J=7.5, 1H); 7.49(d, J=9, 2H); 7.72(s, 5H); 8.26(d, J=9, 2H).)Found: C, 57.60; H, 4.41; N, 4.67. Calc. for $C_{14}H_{13}NO_4S$::C, 57.72; H, 4.50; N, 4.81%):

1-(5-chloro-2-nitrophenyl)ethyl phenyl sulphone 5, m.p. 111-112°C, ^1H NMR: 1.77(d, J=7.5, 3H); 5.58(q, J=7.5, 1H); 7.4-8.15(m, 8H). (Found: C, 51.48; H, 3.70; N, 4.28. Calc.for $C_{14}H_{12}ClNO_4S$: C, 51.62; H, 3.71; N,4.30%).

1-(3,5-dichloro-2-nitrophenyl)ethyl phenyl sulphone 6, m.p. 111-113°C, ^{1}H NMR: 1.77(d, J=7, 3H); 4.31(q, J=7, 1H); 7.65(d, J=2, 1H); 7.7-8.0(m, 6H). (Found C, 46.50; H, 3.08; N, 3.82. Calc. for $C_{14}H_{11}Cl_2NO_4S$: C, 46.68; H, 3.08; N, 3.89%).

1-(4,5-dichloro-2-nitrophenyl)ethyl phenyl sulphone 7, m.p. 135-136°C, ^{1}H NMR: 1.75(d, J=7, 3H); 5.53(q, J=7, 1H); 7.8(m, 5H); 7.98(s, 1H); 8.12(s, 1H). (Found: C, 46.62; H, 3.05; N, 3.85. Calc. for $C_{14}H_{11}Cl_2NO_4S$: C, 46.68; H, 3.08; N, 3.89%).

1-(5-methoxy-2-nitrophenyl)ethyl phenyl sulphone 8, m.p. 119-121°C, ^{1}H NMR: 1.77(d, J=7.5, 3H); 3.93(s, 3H); 5.78(q, J=7.5, 1H); 7.00(dd, J=9 and 2.5, 1H); 7.35(d, J=2.5, 1H); 7.45-8.0(m, 5H); 8.02(d, J=9, 1H). (Found: C, 55.95; H, 4.69; N, 4.24. Calc. for $C_{15}H_{15}NO_5S$: C, 56.06; H, 4.71; N, 4.36%).

1-(5-trifluoromethyl-2-nitrophenyl)ethyl phenyl sulphone 9, m.p. 121-122°C, ^{1}H NMR: 1.83(d, J=7.5, 3H); 5.53(q, J=7.5, 1H); 7.4-8.3(m, 8H). (Found: C, 49.98; H, 3.43; N, 3.85. Calc. for $C_{15}H_{12}F_3NO_4S$: C, 50.14; H, 3.37; N, 3.90%).

1-(5-carbotert-butoxy-2-nitrophenyl)ethyl p-tolyl sulphone 10, m.p. 132-134°C, ^{1}H NMR: 1.65(s, 9H); 1.83(d, J=7, 3H); 2.48(s, 3H); 5.47(q, J=7, 1H); 7.3-8.5(m, 7H). (Found: C, 58.37; H, 5.43; N, 3.49 Calc. for $C_{19}H_{21}NO_6S$: C, 58.30; H, 5.41; N, 3.58%).

1-(5-fluoro-2-nitrophenyl)ethyl phenyl sulphone 11, m.p. 118-119°C, ^{1}H NMR: 1.79(d, J=7, 3H); 5.62(qd, J=7 and J_{HF}=1, 1H); 7.1-8.2(m, 8H). Found: C, 54.33; H, 3.94; N, 4.48. Calc. for $C_{14}H_{12}FNO_4S$: C, 54.36; H, 3.91; N, 4.53%).

1-(2-nitronaphtyl)ethyl phenyl sulphone 12, m.p. 126-127°C, ^{1}H NMR (CD_3COCD_3): 1.85(d, J=7, 3H); 4.67(q, J=7, 1H); 7.4-8.4(m, 11H). (Found: C, 63.53; H, 4.39; N, 3.91. Calc. for $C_{18}H_{15}NO_4S$: C, 63.33; H, 4.43; N, 4.10%).
1-(4-nitronaphtyl)ethyl phenyl sulphone 13, m.p. 176-178°C, ^{1}H NMR (CD_3COCD_3): 1.88(d, J=7, 3H); 5.73(q, J=7, 1H); 7-4-8.6(m, 11H): (Found: C, 63.60; H, 4.29; N, 3.88. Calc for $C_{18}H_{15}NO_4S$: C, 63.33; H, 4.43; N, 4.10%):

1-(4-chloro-2-nitrophenyl)ethyl phenyl sulphone 14, m.p. 102-104°C, ^{1}H NMR 1.77(d, J=7, 3H); 5.36(q, J=7, 1H); 7.25-7.95(m, 8H): (Found: C, 51.51; H, 3.62; N, 4.18. Calc.for $C_{14}H_{12}ClNO_4S$: C, 51.62; H, 3.71; N, 4.30%).

1-(2-chloro-4-nitrophenyl)ethyl phenyl sulphone 15, m.p. 128-129°C, ^{1}H NMR: 1.77(d, J=7, 3H); 4.99(q, J=7, 1H); 7.3-8.3(m, 8H); (Found: C, 51.59; H, 3.70; N, 4.24: Calc. for $C_{14}H_{12}ClNO_4S$: C, 51.62; H, 3.71; N, 4.30%).

1-(4-trifluoromethyl-2-nitrophenyl)ethyl phenyl sulphone 16, m.p. 96-97°C, ^{1}H NMR: 1.82(d, J=7, 3H) 5.56(q, J=7.5, 1H); 7.8(m, 5H); 8.11(s, 2H); 8.27(s, 1H). (Found: C, 50.20; H, 3.38; N, 3.73. Calc. for $C_{15}H_{12}F_3NO_4S$: C, 50.14; H, 3.37; N, 3.90%).

1-(5-chloro-2-nitrophenyl)propyl phenyl sulphone 18, m.p. 149.5-150.5°C, ^{1}H NMR: 0.92(t, J=7.5, 3H) 1.6-2.9(m, 2H); 5.23(dd, J=10.5 and 4.5, 1H); 7.25-7.85(m, 8H). (Found; C, 53.09; H, 4.05; N, 4.04; Calc. for $C_{15}H_{14}ClNO_4S$: C, 53.02; H, 4.15; N, 4.12%).

1-(5-chloro-2-nitrophenyl)-3-methylbutyl phenyl sulphone 19, m.p. 99-101°C, ^{1}H NMR: 0.84(d, J=6, 3H); 0.90(d, J=6, 3H); 1.1-2.5(m, 3H); 5.45(dd, J=8 and 6.5, 1H); 7.2-7.9(m, 8H). (Found: C, 55.60; H, 4.93; N, 3.74: Calc. for $C_{17}H_{18}ClNO_4S$: C, 55.51; H, 4.93; N, 3.81%).

1-(2-nitrophenyl)ethyl phenyl sulphone 4 and 1-(4-nitro-2-trifluoromethylphenyl)ethyl phenyl sulphone 17 not isolated in pure state were identified by ^{1}H NMR (quartets at 5.48 and 5.15, respectively) and by TLC and GLC comparison with the authentic samples.

Acknowledgment - This work was supported by the Polish Academy of Sciences Grant CPBP.01.13.

REFERENCES

1. Part 146 in the Series Reactions of Organic Anions: Part 145. M.Makosza and Z.Owczarczyk, Tetrahedron Letters 1987, 3021.
2. M.Makosza and J.Winiarski, Acc.Chem.Res. 20, 283 (1987).
3. M.Makosza, J.Golinski and J.Baran, J.Org.Chem. 49, 1488 (1984).
4. M.Makosza and J.Golinski, Synthesis 1023 (1983).
5. M.Makosza in Current Trends in Organic Synthesis (Edited by H.Nozaki) Pergamon Press, Oxford (1983) p.401
6. M.Makosza, B.Chylinska and B.Mudryk, Liebigs Ann.Chem. 8 (1984).
7. M.Makosza and J.Winiarski, J.Org.Chem. 49, 1494 (1984).
8. M.Makosza, J.Golinski and J.Pankowski, Synthesis 40 (1983).
9. E.T.McBee, E.P.Wesseler and T.Hodgins, J.Org.Chem. 36, 2907 (1971).
10. M.Makosza, T,Glinka and A.Kinowski, Tetrahedron 40, 1863 (1984).
11. M.Makosza, M.Wenäll, M.Golinski and A.Kinowski, Bull.Pol.Ac.Sci.Chem. 33, 427 (1985).
12. M.Makosza and T.Glinka, J.Org.Chem. 48, 3860 (1983).
13. M.Makosza, W.Danikiewicz and K.Wojciechowski, Liebigs Ann.Chem. (in press).