CONVERSION OF 1-(*o*-NITROARYL)ALKYL *p*-TOLYLSULFONES INTO ISOXAZOLES*

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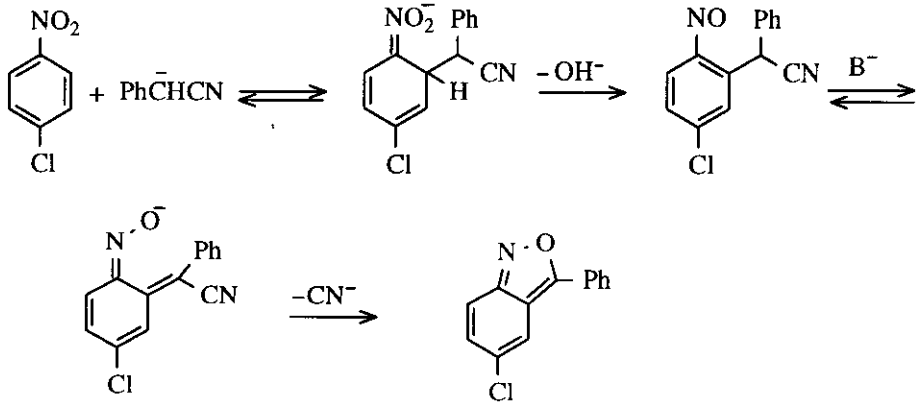
Abstract-*Partial reduction of o-nitrobenzyl p-tolylsulfones in alkaline medium results in the formation of the nitrosobenzylsulfone carbanions which cyclize to isoxazoles.*

Reactions of nucleophiles with nitroarenes can proceed in a variety of ways.[1] Among them there are some examples of reactions resulting in the formation of benzisoxazoles (anthraniles).[2] The process proceeds apparently *via* conversion of the σ^H adducts of the nucleophiles to nitroarenes into the nitroso compound which, upon deprotonation, enter intramolecular addition-elimination process.

Scheme 1



One can therefore suppose that nitrosoarenes containing CHRY substituents in the *ortho* position, where Y is a potential leaving group, should enter in alkaline media the transformations similar to that shown on Scheme 1 to give the corresponding benzisoxazoles.

For testing this hypothesis the most convenient model compounds appeared to be *o*-nitrobenzyl p-tolylsulfones (**1**) which are readily available *via* the vicarious nucleophilic substitution of hydrogen (VNS) in nitroarenes.[3]

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*Dedicated to Professor Rolf Huisgen on the occasion of his 75th birtday

These compounds upon reduction to the nitroso compounds and treatment with a base should give the carbanions able to cyclize to the isoxazoles.

The substantial difficulties in realization of this hypothesis are due to the fact that nitrosoarenes are usually reduced faster than the corresponding nitroarenes. In the cases of sulfones (**1**) it was supposed that the reduction carried out in a basic media, such that the nitroso- but not the nitroarylmethylsulfones (which are expected to be weaker CH acids) are deprotonated, should be arested on the nitroso compound stage hence allow the desired transformation to occur.

Scheme 2

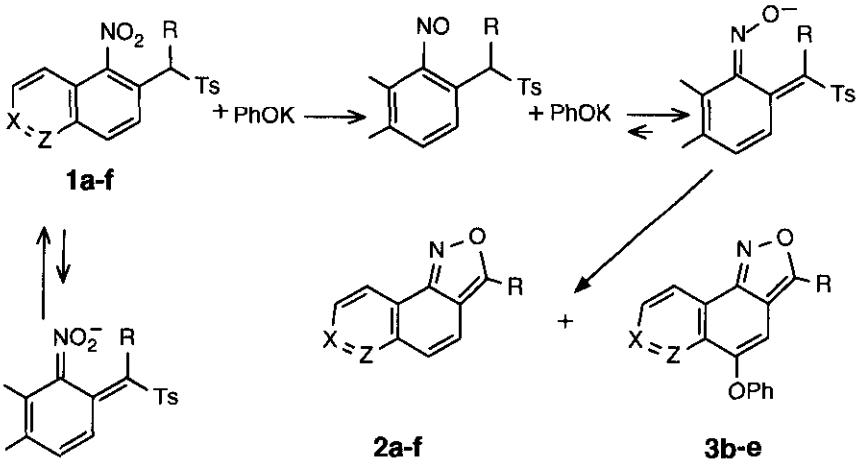

Table 1

Entry	Substrate	X	Z	R	time (h)	Products, Yield (%) **2**	**3**
1	**1a**	CH	CH	CH_3	10	73	-
2	**1b**	CH	CH	C_2H_5	40	28	27
3	**1c**	CH	CH	n-C_3H_7	50	26	29
4	**1d**	CH	N	CH_3	32	45	29
5	**1e**	CH	N	C_2H_5	40	30	37
6	**1f**	N	CH	CH_3	6	44	-

Indeed when 1-nitro-2-p-tolylsulfonylmethylnaphthalene (**1a**) was treated with potassium phenoxide in methanol such process took place to give isoxazole derivative (**2a**), the phenoxide being the reducing agent[4] and the base. The reaction appears to be of general character for bicyclic nitroarene derivatives (Table 1) but we were unable to extend it on less active nitrobenzenes. In some cases, besides of the expected anthraniles (**2**), corresponding 4-phenoxy derivatives (**3**) were also obtained. These products were apparently formed *via* the phenoxide anion addition to the nitroaromatic ring followed by elimination of hydroxide anion in the process analogous to that shown on Scheme 1. Thus the nitroso compound was generated which in turn undergoes deprotonation and subsequent cyclization according to the second part of Scheme 2. An alternative route including transformation of **2** to **3** *via* addition of phenoxide anion should be rejected on the ground of independent experiment in which **2d** treated with an excess of the phenolate failed to produce **3d**.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra were measured on Varian Gemini (200 MHz). Chemical shifts were expressed in ppm using TMS as reference. Coupling constants were expressed in hertz (Hz). The mass spectra were obtained on AMD-604 (AMD Intectra GmbH Germany). Column chromatography was performed on silica gel (70-230 mesh, Merck) using hexane-ethyl acetate (8:1 to 2:1) mixtures as eluents except entry in 2 and 3, Table 1 when hexane-benzene (10:1) mixture was used. Nitroarylmethyl *p*-tolylsulfones (starting materials for preparation of **1a-e**) were prepared according to the published procedure.[5,6]

(5-Nitro-6-isoquinolinyl)metyl *p*-tolylsulfone was prepared in the same manner, yield 93.5%: mp 180-183°C (DMF-H_2O-MeOH); ^{1}H-nmr: δ (DMSO-d_6): 2.44 (s,3H), 5.04 (s,2H), 7.42 (d,J=8.0,2H), 7.62-7.76 (m,4H), 8.42 (d,J=8.3,1H), 8.74 (d,J=6.1,1H), 9.51 (d,J=0.8,1H). Anal. Calcd for $C_{17}H_{14}N_2O_4S$: C, 59.64; H, 4.12; N, 8 18. Found: C, 59.61; H, 3.98; N, 8.12.

Alkylations of nitroarylmethyl *p*-tolylsulfones to **1a-f** were performed using MeI, EtBr or n-PrBr as the alkylating agents in DMF in the presence of K_2CO_3 as a base similiarly to procedure.[7]

1a: yield 80%; mp 159-161°C (DMF-H_2O-MeOH); ^{1}H-nmr: δ (DMSO-d_6): 1.73 (d,J=7.0,3H), 2.36 (s,3H), 4.60 (q,J=7.0,1H), 7.36 (d,J=8.4,2H), 7.53 (d,J=8.4,2H), 7.57-7.62 (m,1H), 7.69-7.78 (m,2H), 7.85 (d,J=8.8,1H), 8.11-8.19 (m,1H), 8.29 (d,J=8.8,1H). Anal. Calcd for $C_{19}H_{17}N_2O_4S$: C, 64.21; H, 4.82; N, 3.94. Found: C, 63.91; H, 4.66; N,3.71.

1b: yield 82%; mp 162-165°C (DMF-H_2O-MeOH); ^{1}H-nmr: δ (DMSO-d_6): 0.73 (t,J=7.2,3H), 2.12-2.30 (m,2H), 2.35 (s,3H), 4.30 (dd,J=8.1,4.7,1H), 7.34 (d,J=8.3,2H), 7.49 (d,J=8.3,2H), 7.51-7.59 (m,1H), 7.69-7.78 (m,2H), 7.82 (d,J=8.8,1H), 8.10-8.18 (m,1H), 8.29 (d,J=8.8,1H); ms (m/z): 369,323,295,214,197,186,165, 158; Anal. Calcd for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79. Found: C, 64.88; H,5.15; N, 3.64.

1c: yield 70%; mp 118-119°C (DMF-H_2O-MeOH); ^{1}H-nmr: δ (DMSO-d_6): 0.80 (t,J=7.1,3H), 0.80-1.30 (m,2H), 2.12-2.26 (m,2H), 2.36 (s,3H), 4.37 (dd,J=9.0,6.0,1H), 7.34 (d,J=8.1,2H), 7.47 (d,J=8.1,2H), 7.47-7.57 (m,1H), 7.68-7.79 (m,2H), 7.81 (d,J=8.8,1H), 8.12-8.17 (m,1H), 8.28 (d,J=8.8,1H); Anal. Calcd for $C_{21}H_{21}NO_4S$: C, 65.77; H, 5.52; N, 3.65. Found: C, 65.61; H,5.35; N, 3.55.

1d: yield 72.5%; mp 155-156°C (DMF-H_2O-MeOH); ^{1}H-nmr: δ (DMSO-d_6): 1.75 (d,J=7.0,3H), 2.37 (s,3H), 4.73 (q,J=7.0,1H), 7.34-7.41 (m,2H), 7.50-7.56 (m,2H), 7.75 (dd,J=8.7,4.2,1H), 8.09 (d,J=9.0,1H), 8.11 (ddd,J=8.7,1.5,0.9,1H), 8.37 (d,J=9.0,1H), 9.10 (dd,J=4.2,1.5,1H); Anal. Calcd for $C_{18}H_{16}N_2O_4S$: C, 60.66; H, 4.53; N, 7.86. Found: C, 60.71; H, 4.64; N, 7.71.

1e: yield 70%; mp 145-147°C (DMF-H_2O-MeOH); ^{1}H-nmr: δ (DMSO-d_6): 0.75 (t,J=7.6,3H), 2.30-2.80 (m,2H), 2.36 (s,3H), 4.46 (dd,J=10.1,5.1,1H), 7.35 (d,J=8.2,2H), 7.48 (d,J=8.2,2H), 7.54 (dd,J=8.7,4.2,1H), 8.07 (d,J=9 0,2H), 8.38 (d,J=9.0,1H), 9.10 (dd,J=4.2,1.5,1H); Anal. Calcd for $C_{19}H_{18}N_2O_4S$: C, 61.60; H, 4.90; N, 7.56. Found: C, 61.66; H, 4.86; N, 7.48.

1f: yield 40%; mp 134-135°C (DMF-H_2O-MeOH); ^{1}H-nmr: δ (DMSO-d_6): 1.74 (d,J=7.0,3H), 2.37 (s,3H), 4.78 (q,J=7.0,1H), 7.35-7.50 (m,3H), 7.53-7.56 (m,2H), 8.03 (d,J=8.8,1H), 8.53 (d,J=8.8,1H), 8.70 (d,J=6.0,1H), 9.55 (d,J=0.9,1H); Anal. Calcd for $C_{18}H_{16}N_2O_4S$: C, 60.66; H, 4.53; N, 7.86. Found: C, 60.55; H,4.58; N, 7.80.

Reaction of **1a-f** with potassium phenoxide. *General procedure:*

To a solution of potassium phenoxide (1.32 g, 10 mmol) in methanol (5 ml) powdered sulfone (1 mmol) was added and the mixture was refluxed with stirring for the time indicated in Table 1. The mixture was then poured onto 50 ml of satd. NH_4Cl solution, extracted with ethyl acetate (3x20 ml) and products were separated *via* column chromatography.

2a: mp 53-54°C (hexane); ^{1}H-nmr: δ ($CDCl_3$): 2.76 (s,3H), 7.17 (d,J=9.2,1H), 7.21 (d,J=9.2,1H), 7.54-7.63 (m,2H), 7.71 (dd,J=7.5,1.2,1H), 8.47 (ddd,J=7.7,0.8,0.8,1H); ms (m/z): 183, 170, 154, 140, 128, 114; Anal. Calcd for $C_{12}H_9O$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.60; H, 4.79; N, 7.61.

2b: oil; ^{1}H-nmr: δ ($CDCl_3$): 1.47 (t,J=7.6,3H), 3.15 (q,J=7.6,2H), 7.17 (d,J=9.2,1H), 7.25 (d,J=9.2, 1H), 7.51-7.65 (m,2H), 7.66-7.73 (m,1H), 8.46-8.50 (m,1H); ms (m/z): 197, 182, 168, 154, 140, 127, 113; HRMS: Calcd for $C_{13}H_{11}NO$: 197.0841. Found: 197.0839.

3b: oil; ^{1}H-nmr: δ ($CDCl_3$): 1.39 (t,J=7.6,3H), 3.03 (q, J=7.6,2H), 6.58 (s,1H), 7.08-7.20 (m,3H), 7.34-7.44 (m,2H), 7.58-7.70 (m,2H), 8.08-8.18 (m,1H), 8.48-8.58 (m,1H); ms (m/z): 289, 274, 261, 246, 233, 227, 212, 184, 167, 156; HRms: Calcd for $C_{19}H_{15}NO_2$: 289.1103. Found: 289.1101.

2c: oil; ^{1}H-nmr: δ ($CDCl_3$): 1.03 (t,J=7.2,3H), 1.88 (qt,J=7.2,7.2,2H), 3.11 (t,J=7.2,2H), 7.17(d,J=9.2,1H), 7.29(d,J=9.2,1H), 7.52-7.66 (m,2H), 7.68-7.74 (m,1H), 8.46-8.51 (m,1H); ms (m/z: 211, 196, 182, 168, 154, 141, 127; HRms: Calcd for $C_{14}H_{13}NO$: 211.0997. Found: 211.0997.

3c: oil; ^{1}H-nmr: δ ($CDCl_3$): 0.98 (t,J=7.4,3H), 1.73-1.86 (m,2H), 2.98 (t,J=7.6,2H), 6.58 (s,1H), 6.98-7.21 (m,3H), 1.73-1.86 (m,2H), 2.98 (t,J=7.6,2H), 6.58 (s,1H), 6.98-7.21 (m,3H), 7.34-7.44 (m,2H), 7.61-7.70 (m,2H), 7.99-8.06 (m,1H), 8.50-8.58 (m,1H); ms (m/z): 303, 288, 275, 262, 246, 233, 198; HRMS: Calcd for $C_{20}H_{17}NO_2S$: 303.1259. Found: 303.1227.

2d: mp 110-112°C; ^{1}H-nmr: δ ($CDCl_3$): 2.80 (s,3H), 7.40-7.53 (m,3H), 8.75 (ddd,J=7.9,1.8,0.6,1H), 8.92(dd,J=4.6,1.8,1H), ms (m/z): 184, 171, 155, 149, 141, 129; HRms: Calcd for $C_{11}H_8N_2O$: 184.0637. Found: 184.0649.

3d: mp 136-137°C; ^{1}H-nmr: δ ($CDCl_3$): 2.66 (s,3H), 6.67 (s,1H), 7.15-7.25 (m,3H), 7.37-7.47 (m,2H), 7.59 (dd,J=8.1,4.6,1H), 8.81 (dd,J=8.1,1.8,1H), 9.03 (dd,J=4.6,1.8,1H); ms (m/z): 276, 275, 259, 247, 219, 205, 199; Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.89; H, 4.38; N, 10.14. Found: C, 74.00; H, 4.27; N, 10.14.

2e: mp 56-57°C; ^{1}H-nmr: δ ($CDCl_3$): 1.50 (t,J=7.6,3H), 3.19 (q,J=7.6,2H), 7.42 (dd,J=9.4,0.6,1H), 7.49 (dd,J=8.0,4.6,1H), 7.52 (d,J=9.4,1H), 8.76 (ddd,J=8.0,1.8,0.6,1H), 8.92 (dd,J=4.6,1.8,1H); ms (m/z): 198, 183, 169, 155, 142; HRms: Calcd for $C_{12}H_{10}N_2O$: 198.0793. Found: 198.0779.

3e: mp 135-137°C; ^{1}H-nmr: δ ($CDCl_3$): 1.40 (t,J=7.6,3H), 3.04 (q,J=7.6,2H), 6.74 (s,1H), 7.13-7.25 (m,3H), 7.35-7.47 (m,2H), 7.59 (dd,J=8.0,4.5,1H), 8.82 (dd,J=8.0,1.7,1H), 9.03 (dd,J=4.5, 1.7,1H); ms (m/z): 290, 273, 261, 245, 235, 219, 213, 205. Anal Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.31; H, 4.70; N, 9.31.

2f: mp 105-108°C (AcOEt-hexane); ^{1}H-nmr: δ ($CDCl_3$): 2.82 (s,3H), 7.28 (d,J=9.2,1H), 7.37 (d,J=9.2,1H), 8.28 (d,J=4.9,1H), 8.78 (d,J=2.7,1H), 9.1 (s,1H); ms (m/z): 184, 171, 155, 142, 129; HRms: Calcd for $C_{18}H_{14}N_2O_2$: 184.0636. Found: 184.0635.

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