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Short Communication

Conversion of 1-(*o*-Nitroaryl)methyl *p*-Tolyl Sulfones into Anthranilic Ester Analogues

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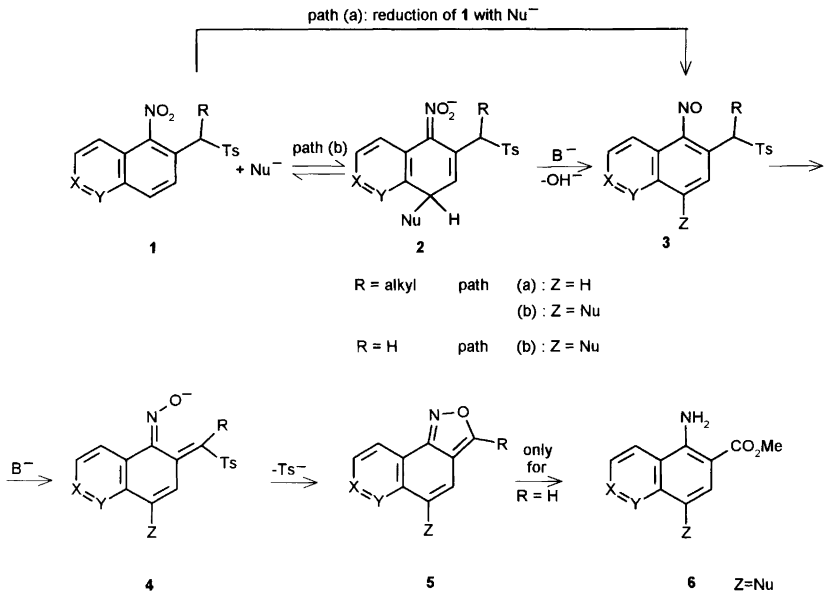
Many reactions of nitroarenes with nucleophiles proceed via transformations of the intermediate σ^H adducts into nitroso compounds.[1–6] However, only few of them give individual products in high yields. The main problem is connected with the high electrophility of the nitroso group, which is able to enter a variety of further reactions with nucleophiles and basic agents. Therefore, the only reactions of synthetic utility are those in which the nitroso intermediate is effectively trapped to form a stable product. Recently we have reported that 1-(*o*-nitroaryl)alkyl *p*-tolyl sulfones (**1**, R = alkyl) react with phenoxide anion in methanol to give products of the benzisoxazole type **5** which occasionally contain the phenoxide substituent (Scheme 1, Z = H or OPh).[7] We supposed that the mechanism of this transformation is that shown in Scheme 1.

Further investigations have now shown that similar nitroarenes without an alkyl substituent at the benzylic position (**1**, R = H) behave differently. When allowed to react with 2.5–10 equiv. of thiolate anions or stabilized carbanions in refluxing methanol compounds **1** were converted into amino esters **6** (Scheme 1, Z = Nu) in 21–90% yields (Table 1). We assume that this new reaction proceeds via benzisoxazole intermediates (**5**, R = H) according to pathway (b) in Scheme 1. Subsequent methanolysis of **5** yields **6**. It is known that benzisoxazoles substituted in the five-membered ring are stable to basic conditions, but that unsubstituted benzisoxazoles



Scheme 1

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Table 1. Reaction of 1-(*o*-nitroaryl)methyl *p*-tolyl sulfones **1** (R = H) with nucleophiles

X	Y	Nu^{-1}	Nu^-/**1** ratio	Product	Yield (%)[a]
CH	CH	MeS	10:1	**6a**	71
CH	CH	i-BuS	5:1	**6b**	21
CH	CH	t-BuS	10:1	**6c**	70
CH	CH	PhC(Me)CN	2.5:1	**6d**	29
CH	N	i-BuS	5:1	**6e**	41
CH	N	t-BuS	10:1	**6f**	90
CH	N	*p*-MeC_6H_4S	10:1	**6g**	64
CH	N	$BuC(CO_2Et)_2$	10:1	**6h**	32[b]
N	CH	t-BuS	10:1	**6i**	72

[a] Isolated products. [b] Reaction was carried out in EtOH to give the triethyl ester.

undergo basic solvolysis to give esters of anthranilic acids.[8] It should be noted that the presence of an α-alkyl substituent in the substrate molecule seems to make the nucleophilic addition **1**→**2** less favored, i.e. path (b) in Scheme 1. This behavior is probably due to a lower electrophilicity of the aromatic ring (less efficient conjugation of the NO_2 group with the ring because of steric hindrance).

A third type of product [**8**, Scheme 2] was obtained in the reaction of sulfone **1** (X = Y = CH, R = H) with the phenylacetonitrile anion in refluxing methanol. In this reaction, in addition to the expected **6j** and its hydrolysis product **7**, a substantial amount of oxime **8** (24%) was also isolated (mixture of four geometric isomers, ^1H NMR). On treatment of oxime **8** with NaOMe in methanol compounds **6j** and **7** were formed. This shows that **8** is a possible intermediate in the conversion of **1** into **6**. The conversion of **8** probably occurs by base-catalyzed double bond migration to form **4** (R = H, Z = PhCHCN), subsequent isoxazole formation and finally methanolysis.

Experimental

Melting points are uncorrected. ^1H NMR spectra were recorded on a Varian Gemini instrument (200 MHz). Chemical shifts are expressed in ppm using TMS as a reference. Mass spectra were obtained on AMD-604 (AMD Intectra GmbH, Germany). Silica gel (70–230 mesh, Merck) was used for column chromatography. For preparation of substrates see Ref 7.

Reaction between bicyclic (1-nitro-2-aryl)methyl p-*tolyl sulfones and nucleophiles. General procedure.* Sodium methoxide (2.5 to 10 mmol) in 10 ml of methanol was treated with an equimolar amount of the nucleophile precursor at room temperature. After stirring for 10 min powdered sulfone (1 mmol) was added in a single portion and the resulting suspension heated at reflux with stirring and exclusion of moisture for 20 min to 10 h (TLC control). After completion the reaction mixture was acidified with dil. aq. HCl, extracted with dichloromethane (3 × 50 ml), extracts dried, evaporated and the product purified by column chromatography.

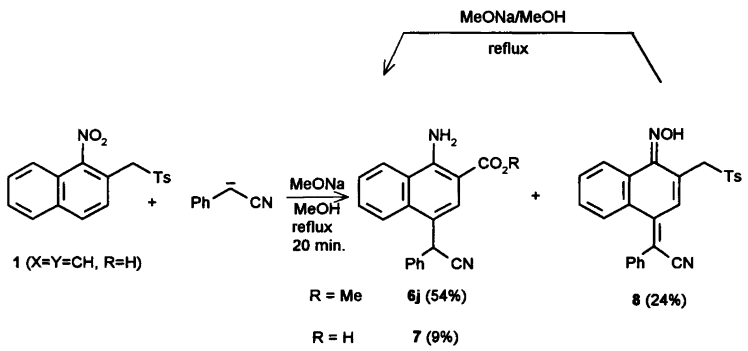
6a, m.p. 88–89 °C (ethyl acetate–hexane). ^1H NMR ($CDCl_3$): δ 2.42 (s, 3H), 3.92 (s, 3H), 7.50–7.53 (m, 1H), 7.64–7.67 (m, 1H), 7.91 (ddd, *J* = 8.4, 1.1, 0.5 Hz, 1H), 8.12 (s, 1H), 8.42 (ddd, *J* = 8.4, 0.7, 0.4 Hz, 1H). MS: *m/z* 247, 232, 215, 200, 187, 172, 128. Anal. $C_{13}H_{13}NO_2S$: C,H,N.

6b, m.p. 106–107 °C (ethyl acetate-hexane). ^1H NMR ($CDCl_3$): δ 1.01 (d, *J* = 6.6 Hz, 6H), 1.67–1.87 (m, 1H), 2.66 (d, *J* = 6.7 Hz, 2H), 3.93 (s, 3H), 6.90 (broad s, 2H), 7.47–7.56 (m, 1H), 7.62–7.70 (m, 1H), 7.91 (ddd, *J* = 8.4, 1.4, 0.7 Hz, 1H), 8.19 (s, 1H), 8.53 (ddd, *J* = 8.4, 1.3, 0.8 Hz, 1H). MS: *m/z* 289, 257, 232, 201, 186, 176, 146. Anal. $C_{16}H_{19}NO_2S$: C,H,N.

6c, m.p. 135–136 °C (ethanol–hexane). ^1H NMR ($CDCl_3$): δ 1.27 (s, 9H), 3.93 (s, 3H), 6.99 (broad s, 2H), 7.44–7.53 (m, 1H), 7.58–7.67 (m, 1H), 7.88 (ddd, *J* = 8.3, 1.4, 0.6 Hz, 1H), 8.24 (s, 1H), 8.71 (ddd, *J* = 8.3, 1.4, 0.6 Hz, 1H). MS: *m/z* 289, 233, 201, 173, 146, 128. Anal. $C_{16}H_{19}NO_2S$: C,H,N.

6d, m.p. 186–187 °C (ethanol–hexane). ^1H NMR ($CDCl_3$): δ 2.19 (s, 3H), 3.98 (s, 3H), 7.00 (broad s, 2H), 7.29–7.48 (m, 7H), 7.66–7.72 (m, 1H), 7.89–7.96 (m, 1H), 8.16 (s, 1H). MS: *m/z* 330, 315, 299, 283, 271, 255, 228. HRMS: *m/z* 330.1365 (M^+), calc. $C_{21}H_{18}N_2O_2$, 330.1368.

6e, m.p. 122–125 °C (ethanol-hexane). ^1H NMR ($CDCl_3$): δ 1.10 (d, *J* = 6.7 Hz, 6H), 1.83–2.06 (m, 1H), 2.89 (d, *J* = 6.7 Hz, 2H), 3.95 (s, 3H), 6.74 (broads s, 2H), 7.42 (dd, *J* = 8.5, 4.3 Hz, 1H), 8.25 (dd, *J* = 8.5,



Scheme 2

1.6 Hz, 1H), 9.03 (dd, J=4.3, 1.6, 1H). MS: m/z 290, 275, 257, 247, 234, 225, 215, 202, 174. Anal. $C_{15}H_{18}N_2O_2S$: C,H,N.

6f, m.p. 155–157 °C (ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$): δ 1.30 (s, 9H), 3.95 (s, 3H), 7.0 (broad s, 2H), 7.40 (dd, J=8.5, 4.2 Hz, 1H), 8.25 (dd, J=8.5, 1.7 Hz, 1H), 8.50 (s, 1H), 9.08 (dd, J=4.2, 1.7 Hz, 1H). MS: m/z 290, 234, 202, 174, 147, 136. Anal. $C_{15}H_{18}N_2O_2S$: C,H,N.

6g, m.p. 197–198 °C (ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 3.85 (s, 3H), 6.85 (broad s, 2H), 7.04–7.12 (m, 2H), 7.21–7.27 (m, 3H), 7.41 (dd, J=8.6, 4.2 Hz, 1H), 8.09 (s, 1H), 8.25 (ddd, J=8.6, 1.5, 0.7 Hz, 1H). MS: m/z 324, 292, 276, 264, 248, 237. Anal. $C_{18}H_{16}N_2O_2S$: C,H,N.

6h, m.p. 84–85 °C (hexane). ^{1}H NMR ($CDCl_3$): δ 0.81 (t, J=6.6 Hz, 3H), 1.10–1.30 (m, 4H), 1.16 (t, J= 7.0 Hz, 6H), 1.41 (t, J=7.1 Hz, 3H), 2.45–2.55 (m, 2H), 4.20 (q, J=7.0 Hz, 4H), 4.38 (q, J=7.1 Hz, 2H), 6.83 (broad s, 2H), 7.33 (dd, J=8.5, 4.2 Hz, 1H), 8.12 (dd, J=8.5, 1.7 Hz, 1H), 8.81 (dd, J=4.2, 1.7 Hz, 1H). MS: m/z 430, 401, 385, 374, 357, 341, 328, 311, 283. Anal. $C_{23}H_{30}N_2O_2$; C,H,N.

6i, m.p. 171–174 °C (ethyl acetate–hexane). ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 9H), 3.96 (s, 3H), 6.99 (broad s, 2H), 7.63 (dd, J=6.0, 0.9 Hz, 1H), 8.27 (s, 1H), 8.61 (d, J=6.0 Hz, 1H), 10.02 (d, J=0.9 Hz, 1H). MS: m/z 290, 234, 202, 174, 147. Anal. $C_{15}H_{18}N_2O_2S$: C,H,N.

6j, m.p. 173–176 °C (ethyl acetate–hexane). ^{1}H NMR (acetone-d_6): δ 3.91 (s, 3H), 6.09 (s, 1H), 7.32–7.64 (m, 7H), 7.76 (broad s, 2H), 7.87–7.93 (m, 1H), 8.13 (s, 1H), 8.37–8.42 (m, 1H). MS: m/z 316, 284, 257, 239, 230, 207. HRMS: m/z 316.12131 (M^+), calc. $C_{20}H_{16}N_2O_2$; 316.12118.

7, m.p. 242–250 °C (ethyl acetate–hexane). ^{1}H NMR (acetone-d_6): δ 6.09 (broad s, 1H), 7.33–7.65 (m, 7H), 7.83 (broad s, 2H), 7.89–7.93 (m, 1H), 8.17 (s, 1H), 8.36–8.41 (m, 1H). MS: m/z 302, 284, 255, 240, 230, 207. HRMS: m/z 302.10550 (M^+), calc. $C_{19}H_{14}N_2O_3$; 302.10553.

8, m.p. 175–178 °C (ethyl acetate–hexane). ^{1}H NMR (acetone-d_6): δ 2.40, 2.43 (two s, ratio 1:1, 3H), 4.54, 4.74, 5.00, 5.24 (four d, J=0.7 Hz, four isomers, ratio 4:4:1:1, 2H; $\mathbf{CH_2SO_2}$), 6.79–7.71 (m, 13H), 8.66–8.93 (m, 1H), 11.77, 11.82 (two s, ratio 1:1, 1H, NO**H**). MS: m/z 440, 429, 397, 370, 343, 295. Anal. $C_{26}H_{20}N_2O_3S$; C,H,N.

Conversion of oxime **8** *to amino ester* **6j**. Powdered oxime **8** (110 mg, 0.25 mmol) was added to a solution of sodium (23 mg, 1 mmol) in methanol (5 ml) and the resulting mixture stirred and refluxed for 30 min. After cooling the reaction mixture was poured onto dil. aq. HCl and the precipitated solid filtered off and dried to yield 80 mg (quantitative) of **6j** containing a small amount of acid **7**.

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