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Reactions of Nitrosalicylic Aldehydes with Chloromethyl Tolyl Sulfone Anion. Synthesis of 2-Hydroxydihydrobenzofurans.

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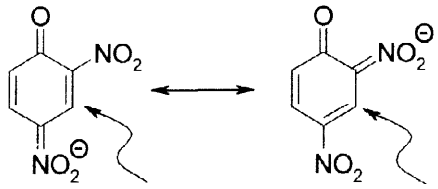
Abstract: Vicarious nucleophilic substitution of hydrogen (VNS) with chloromethyl tolyl sulfone carbanion does not occur in 3-, 4- and 5-nitrosalicylaldehydes. Instead, nucleophilic addition to the carbonyl group takes place leading to 2-hydroxydihydrobenzofurans. The same reaction course is observed for other salicyl aldehyde derivatives. © 1998 Elsevier Science Ltd. All rights reserved.

Substituents in nitroaromatic rings exert a strong effect on the rate and orientation of the vicarious nucleophilic substitution (VNS) of hydrogen.[1] A particularly interesting effect on the orientation was observed when electrondonating groups were conjugated with the nitro group in such nitroarenes as dinitrophenols,[2] dinitroanilines[3] and 2-alkoxy-5-nitropyridines.[4,5] Due to conjugation of the negative charge in 2,4-dinitrophenolate anion nucleophilic addition to the ring is not inhibited and directed in position 3, as can be rationalized by taking into account the resonance structures on scheme 1.[2]



Scheme 1

One can expect that a similar effect should operate in nitrophenolate anions containing other strongly electron-withdrawing substituents, such as carbonyl group. Moreover, conjugation of the negatively charged phenolate function with this group could decrease its electrophilic activity towards nucleophiles and thus decelerate competing nucleophilic addition to the carbonyl group.

To test this hypothesis we have studied reactions of 4-, 5- and 6-nitrosalicyl aldehydes **1a,b,c** with carbanions of chloromethyl tolyl sulfone **2**. When the reaction was carried out in the presence of *tert*-BuOK in DMF at -40 °C, standard work-up procedure gave substituted nitro-2,3-dihydrobenzofurans **3a,b,c**, which obviously were produced not *via* VNS of hydrogen in the aromatic ring, but *via* addition of the carbanion to the carbonyl group of the aldehyde (scheme 2).

The highest reactivity of the carbonyl group and the yield of **3** was found for **1b** where the nitro group is conjugated with the phenolate anion. The same reaction course was however also observed for **1a** and **1c**, where the negative charge is not conjugated with the nitro group, being in *meta* position, but only with the carbonyl

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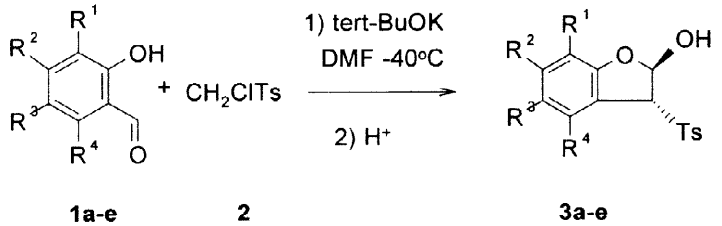
group, so the deactivating effect on the carbonyl group is maximized. Thus, it was not a surprise, that salicyl aldehyde **1d** and its 4-butyl-3,5-dichloro derivative **1e** also reacted analogously giving benzofurans **3d** and **3e** respectively (table 1).



1a-e **2** **3a-e**

Scheme 2

Table 1

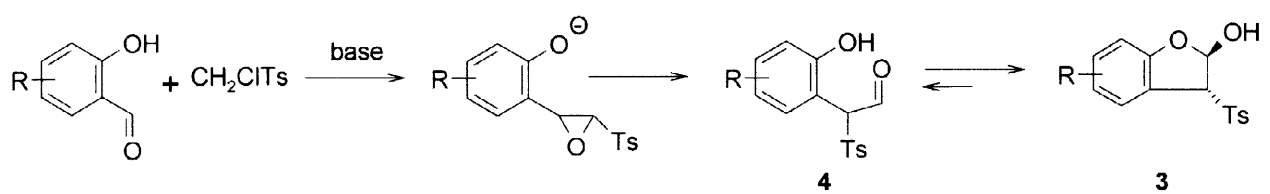
1	R^1	R^2	R^3	R^4	3	Yield (%)
a	H	NO_2	H	H	**a**	50
b	H	H	NO_2	H	**b**	84
c	H	H	H	NO_2	**c**	66
d	H	H	H	H	**d**	50
e	Cl	*n*-Bu	Cl	H	**e**	70

The structures of products **3a-d** were established on the basis of ^1H, ^{13}C NMR, and MS spectra as well as their chemical properties. The products are found to possess two "acidic" protons which even under practically neutral conditions (D_2O/acetone) are exchanged for deuterium. The exchange of the hydroxylic proton occurred immediately, whereas exchange of the second proton needed a few days at room temperature for completion.

This observation can be explained by an equilibrium between hemiacetal **3** and aldehyde **4**. The latter, being a very strong, readily enolisable *CH*-acid seems to be susceptible to the H/D exchange under these conditions. Extensive spectral examinations including DEPT, INEPT and $^{13}C/^1H$ correlations allow assignation of chemical shifts values to particular carbon and hydrogen atoms. Additionally, for one example (**3b**) the X-ray method was applied and the obtained results fully confirmed the supposed structure, proving the *trans* configuration of the dihydrofurane ring substituents.

The mechanism of this reaction was not examined, but the possible pathway, given in scheme 3 seems to be reasonable. α,β-Epoxysulfones are known to undergo spontaneous rearrangement to carbonyl compounds with the sulfone group migration, often followed by decarbonylation.[6,7,8] Since the phenolate function is present in position *ortho* to the newly formed aldehyde group rapid formation of the hemiacetal ring prevents the decarbonylation.

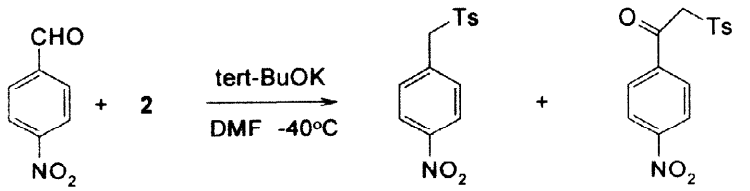
The role of the phenolate group may also be important on the epoxide rearrangement step, facilitating formation



4 **3**

Scheme 3

of the benzylic carbocations in the course of the ring opening process.[9] The fact, that contrary to **1c**, 4-nitrobenzaldehyde (**5**) reacts with **2** giving two products **6** and **7** in ratio 1:1.5 under the same reaction conditions supports this supposition (scheme 4).



5 6 7

Scheme 4

Only product **6** is apparently formed *via* analogous epoxide rearrangement and subsequent deformylation process. Formation of **7**, reported earlier without any explanation[8] can be considered as a result of the alternative base-promoted rearrangement of the intermediate oxirane which proceeds *via* abstraction of the most acidic nitrobenzylic proton. Numerous examples of such rearrangement are known, e.g. for diaryloxiranes.[10]

Thus our supposition, that conjugation of the formyl group with highly electrodonating phenolate anion should decrease its electrophilic reactivity sufficiently to enable the carbanion addition to the nitroaromatic ring was not confirmed. Nevertheless, the described reaction may be of some interest as a simple and interesting route to substituted derivatives of 2,3-dihydrobenzofuran-2-ol.

EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Gemini (200 MHz) and Brucker AM 500 (500 MHz) instruments. Chemical shifts are expressed in ppm referred to TMS, coupling constants in hertz. INEPT spectra were recorded on a Bruker AM 500 apparatus using a program SPT INEPT, Bruker, 8Hz. Mass spectra were obtained on a AMD-604 spectrometer. Silica gel Merck 60 70-230 mesh was used for column chromatography.

6-Nitro- and 4-nitrosalicylaldehydes were prepared as described earlier.[11] Remaining materials were commercial or were obtained from other sources[¶]. DMF was dried over CaH and distilled, commercial *tert*-BuOK was used after sublimation.

Reactions of nitrosalicylaldehydes with sulfone 2:

The reaction procedure varied from aldehyde to aldehyde as they differ in their reactivity, and stability of the sulfone carbanion under the applied conditions is limited. The common work-up procedure was as follows: the reaction mixture was poured into acidified water and extracted with ethyl acetate. The combined extracts were washed with water, dried with $MgSO_4$ and the solvent was evaporated. The products were separated using column chromatography.

6-Nitro-3-(toluene-4-sulfonyl)-2,3-dihydrobenzofuran-2-ol (3a): To a stirred solution of *tert*-BuOK (0.6 mmol, 70 mg) in DMF (1 ml) at -40^{0}C a mixture of the aldehyde (0.15 mmol, 25 mg) and sulfone **2** (0.3 mmol, 60 mg)

[¶] We are grateful to Dr M. Golinski for a sample of 4-butyl-3,5-dichlorosalicylaldehyde.

in DMF (1 ml) was added and the reaction was carried on for 20 min. Hexane/AcOEt mixture was used as eluent for column chromatography. **3a**: mp 194-8°C (Hexane/AcOEt);^{1}H NMR (500 MHz,-50°C,acetone d_6): 2.42 (s, 3H), 5.41 (s, 1H), 6.32 (d, J=6.0, 1H), 7.23 (d, J=8.1,1H), 7.44-7.46 (½AA'XX', 2H), 7.58-7.60 (½AA'XX', 2H), 7.66 (dd, J=8.1, 8.2, 1H), 7.77 (d, J=8.2, 1H), 8.06 (d, J=6.0, 1H). The low-temperature conditions allowed observation of a sharp OH signal and its vicinal coupling constant. MS: 335 (M^+, 2), 317 (2), 296 (0.5), 297 (0.5), 267 (0.3), 250 (0.4), 236 (0.5), 210 (2), 180 (100), 163 (70), 156 (38), 152 (9), 139 (22), 134 (23), 133 (17), 121 (6), 107 (15), 92 (44), 91 (48), 77 (22), 65 (28), 51 (13). HRMS: 335.045981, calc. for $C_{15}H_{13}NO_6S$: 335.046354.

*5-Nitro-3-(toluene-4-sulfonyl)-2,3-dihydrobenzofuran-2-ol (**3b**)*: To a stirred solution of *tert*-BuOK (5 mmol, 570 mg) in DMF (2.5 ml) at -40°C a mixture of the aldehyde (0.15 mmol, 25 mg) and sulfone **2** (0.3 mmol, 60 mg) in DMF (2 ml) was added. After 20 min an additional amount of **2** (0.1 mmol, 20 mg) was added and the reaction was continued for 30 min. Chloroform was used as eluent for column chromatography. **3b**: mp 174.5-175°C (chloroform); ^{1}H NMR (200 MHz, acetone d_6): 2.43 (s, 3H), 5.05 (dd, J=2.2, 1.0, 1H), 6.42 (dd, J=6.0, 1.8, 1H), 6.97 (d, J=8.9, 1H), 7.40 (d, J=6.0, 1H), 7.41-7.45 (½AA'XX', 2H), 7.68-7.73 (½AA'XX', 2H), 8.1 (dd, J=2.5, 0.9, 1H), 8.26 (dd, J=8.9, 2.5, 1H). MS: 335 (M^+, 4), 317 (7), 300 (1), 225 (1), 194 (2), 180 (100), 163 (8), 156 (13), 152 (15), 139 (14), 134 (44), 121 (2), 106 (9), 91 (34), 78 (12), 65 (15), 51 (7). HRMS: 335.048298, calc. for $C_{15}H_{13}NO_6S$: 335.046354. X-Ray crystallographic data are deposited at the Cambridge Crystallographic Data Centre.

*4-Nitro-3-(toluene-4-sulfonyl)-2,3-dihydrobenzofuran-2-ol (**3c**)*: To a stirred solution of *tert*-BuOK (0.24 mmol, 27 mg) in DMF (1 ml) at -40°C a mixture of the aldehyde (0.06 mmol, 10 mg) and sulfone **2** (0.12 mmol, 24 mg) in DMF (1 ml) was added dropwise and the reaction was continued for 60 min. Hexane/AcOEt mixture was used as eluent for column chromatography. **3c**: oil. ^{1}H NMR (500 MHz, $CDCl_3$): 2.45 (s, 3H), 4.76 (s, 1H), 6.34 (d, J=1.4, 1H), 7.29-7.31 (½AA'XX', 2H), 7.48 (d, J=8.3, 1H), 7.54-7.56 (½AA'XX', 2H), 7.57 (d, J=2.0, 1H), 7.89 (dd, J=8.3, 2.0, 1H). MS: 335 (M^+, 8), 317 (85), 307 (6), 301 (1), 287 (3), 271 (2), 253 (2), 223 (2), 210 (12), 180 (65), 163 (12), 156 (35), 152 (42), 139 (75), 134 (25), 122 (10), 107 (45), 91 (100), 77 (40), 65 (55), 51 (20). HRMS: 335.045981, calc. for $C_{15}H_{13}NO_6S$: 335.046354.

*3-(Toluene-4-sulfonyl)-2,3-dihydrobenzofuran-2-ol (**3d**)*: To a stirred solution of *tert*-BuOK (15 mmol, 1680 mg) in DMF (10 ml) at -40°C a solution of the aldehyde (3 mmol, 367 mg) in DMF, then a solution of sulfone **2** (4 mmol, 819 mg) in DMF (2 ml) was added dropwise for 30 min and the reaction was continued for an additional 15 min. A Hexane/AcOEt mixture was used as eluent for column chromatography. **3d**: oil. ^{1}H NMR (200 MHz, $CDCl_3$): 2.40 (s, 3H), 3.80 (s, 1H), 4.70 (s, 1H), 6.20 (d, J=1.1, 1H), 6.72 (dd, J=8.2, 0.5, 1H), 6.97 (ddd, J=7.5, 7.5, 1.0, 1H), 7.20-7.35 (m, 4H), 7.45-7.50 (½AA'XX', 2H). MS: 290 (M^+, 4), 163 (8), 135 (100), 117 (7), 107 (37), 91 (12), 79 (14), 65 (5). HRMS: 290.061256, calc. for $C_{15}H_{14}O_4S$: 290.061277.

*6-Butyl-5,7-dichloro-3-(toluene-4-sulfonyl)-2,3-dihydrobenzofuran-2-ol (**3e**)*: To a stirred solution of *tert*-BuOK (4 mmol, 448 mg) in DMF (3 ml) at -40°C a mixture of the aldehyde (1 mmol, 247 mg) and sulfone **2** (1 mmol, 205 mg) in DMF (2 ml) was added. After 20 min an additional amount of **2** (0.25 mmol, 51 mg) was added

and the reaction was continued for 30 min. Hexane/AcOEt mixture was used as eluent for column chromatography. **3e**: mp 145-6°C (hexane/AcOEt). ^{1}H NMR (500 MHz, $CDCl_3$): 0.95 (t, J=7.2, 3H), 1.37-1.52 (m, 4H), 2.40 (s, 3H), 2.84 (t, J=7.8, 2H), 4.73 (s, 1H), 5.1 (bs, 1H), 6.30 (s, 1H), 7.15 (d, J=0.7, 1H), 7.24-7.26 (½AA'XX', 2H), 7.52-7.54 (½AA'XX', 2H). MS: 414 (M^+, 4), 396 (1), 353 (4), 297 (3), 259 (100), 245 (12), 231 (19), 223 (11), 215 (16), 203 (11), 188 (15), 181 (9), 175 (9), 156 (12), 139 (11), 127 (10), 91 (25), 65 (13), 57 (21). HRMS: 414.047103, calc. for $C_{19}H_{20}O_4S$: 414.045993.

Reaction of 4-nitrobenzaldehyde with sulfone 2:

To a stirred solution of *tert*-BuOK (5 mmol, 560 mg) in DMF (5 ml) at -40°C a mixture of the aldehyde (1 mmol, 151 mg) and sulfone **2** (1 mmol, 205 mg) in DMF (1 ml) was added dropwise and the reaction was continued for 10 min. Benzene/$CHCl_3$/CH_2Cl_2 mixture was used as eluent for column chromatography.

4-Nitrobenzyl tolyl sulfone (6): mp 193-5°C ($CHCl_3$/acetone) (lit[12] mp 189-190°C, acetone). ^{1}H NMR (200 MHz, $CDCl_3$): 2.44 (s, 3H), 4.39 (s, 2H), 7.26-7.32 (½AA'XX', 4H), 7.52-7.56 (½AA'XX', 2H), 8.12-8.16 (½AA'XX', 2H). ^{13}C NMR (50MHz, $CDCl_3$): 21.2, 61.6, 123.2, 128.1, 129.5, 131.5, 134.4, 135.4, 145.0, 147.7. MS: 291 (M^-, 32), 227 (4), 200 (7), 165 (6), 155 (100), 139 (4), 136 (57), 120 (4), 106 (39), 91 (74), 78 (21), 65 (17), 51 (4). HRMS: 291.057058, calc. for $C_{14}H_{13}NO_4S$: 291.056526.

4-Nitrobenzoilmethyl tosyl sulfone (7): mp 151-2°C (hexane/AcOEt) (lit[13] mp 145°C). ^{1}H NMR (200 MHz, $CDCl_3$): 2.47 (s, 3H), 4.75 (s, 2H), 7.35-7.39 (½AA'XX', 2H), 7.73-7.77 (½AA'XX', 2H), 8.13-8.18 (½AA'XX', 2H), 8.30-8.36 (½AA'XX', 2H). ^{13}C NMR (50 MHz, $CDCl_3$): 21.72, 64.08, 123.94, 128.48, 130.01, 130.47, 135.31, 139.92, 145.86, 150.81, 186.98. MS: 319 (M^+, 4), 255 (100), 240 (10), 155 (44), 150 (65), 139 (4), 120 (7), 108 (11), 104 (9), 91 (67), 76 (5), 65 (12). HRMS: 319.051647, calc. for $C_{15}H_{13}NO_5S$: 319.051444.

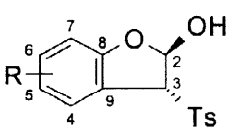


Table 2.
^{13}C NMR Chemical shifts for the bicyclic system of **3a-e**:

3	Solvent	C2	C3	C4	C5	C6	C7	C8	C9
a	acetone	102.7	74.3	148.3	117.7*	133.4	117.1*	162.2	114.2
b	acetone	103.8	73.2	123.7	142.9	128.6	111.1	165.3	121.2
c	acetone	102.7	79	126.9*	130.7*	150.7	128.2*	160.8	126.9
d	$CHCl_3$	100.3	74.2	126.7	121.8	131.3	110.6	159.2	117.8
e	$CHCl_3$	101.2	74.1	125.1	127	141.5	116.6	154.6	117.2

* the assignement can be interchanged.

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