Vicarious Nucleophilic Substitution of Hydrogen in Nitroarenes with in situ Generated Carbanions of 1-Methyl-3-chloro-1,3-dihydro-2,1-benzisothiazole 2,2-Dioxides

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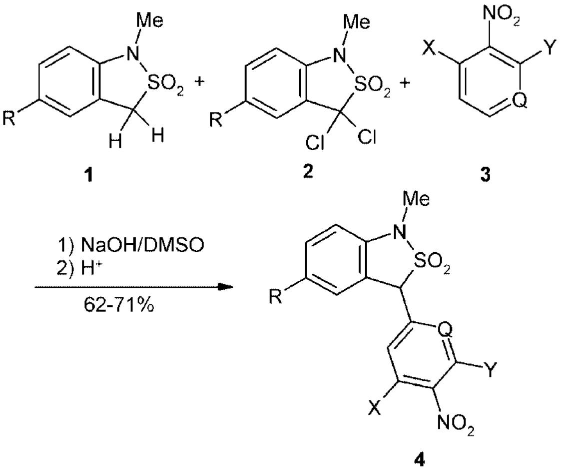
Abstract: Base-induced transformation of an equimolar mixture of 1-alkyl-1,3-dihydro-2,1-benzisothiazole 2,2-dioxides (benzosultams) and their 3,3-dichloro derivatives furnishes 1-alkyl-3-chloro-1,3-dihydro-2,1-benzisothiazole 2,2-dioxides which react with nitroarenes according to the vicarious nucleophilic substiution of hydrogen (VNS) mechanism giving 3-(nitroaryl)benzosultams.

Key words: benzosultams, halogenation, nitro compounds, carbanions, nucleophilic aromatic substitution

Thermal extrusion of sulfur dioxide from 1-alkyl-1,3-dihydro-2,1-benzisothiazole 2,2-dioxides (benzosultams)[1] leads to reactive cyclohexadiene methylene imines (aza-*ortho*-xylylenes)[2] being potential building blocks for the construction of heterocycles. In our studies directed towards the reactions of these reactive intermediates we were interested in reactions of derivatives substituted at the exocyclic C=C bond with an aryl substituent, which could be generated from 3-arylbenzosultams. Previously we synthesized 3-arylbenzosultams via an arylation of carbanions derived from benzosultams with 1-fluoro-4-nitrobenzene,[3] intramolecular S_NAr reaction in α-toluenesulfon-(3-nitro)anilides,[4] or intramolecular oxidative nucleophilic substitution of hydrogen.[3]

Now we present the synthesis of 3-arylbenzosultams by the vicarious nucleophilic substitution of hydrogen (VNS)[5] in nitroarenes by carbanions of 3-chlorobenzosultams. VNS is a general reaction between carbanions bearing leaving groups at the carbanionic center and nitroarenes which result in a replacement of hydrogen at *ortho* or *para* position to the nitro group.

One of the general methods to introduce halogens into α-position to the electron withdrawing group deals with chlorination of the corresponding carbanions with perhaloalkanes (tetrachloromethane or hexachloroethane).[6] In one of our previous papers[7] we have shown that benzosultams can be chlorinated with hexachloroethane in a catalytic two-phase system [50% aqueous NaOH, tetrabutylammonium bromide (TBAB)] to form corresponding 3,3-dichlorobenzosultams in good yields. Attempts to obtain mono halogeno derivatives from equimolar amounts of benzosultam and chlorinating agent (hexachloroethane or carbon tetrachloride) under these conditions were unsuccessful; the reactions led to an inseparable mixture of mono- and dichloro derivatives with unreacted benzosultam. A similar result was obtained when an equimolar mixture of sultam **1a** and its dichloro derivative **2a** was equilibrated under PTC conditions. The ^{1}H NMR spectrum of such a crude reaction mixture revealed the presence of about 70% of the desired monochloro derivative (based on the presence of three signals corresponding to N–Me groups and one signal at 5.6 ppm assigned to CHCl). Following this observation we decided to generate the monochlorosultam in situ and introduce it into vicarious nucleophilic substitution of hydrogen in nitroarenes.



Scheme 1

One example of such a reaction was presented earlier when a mixture of neopentyl phenylmethanesulfonate and its dichloro derivative reacted with nitrobenzene to form neopentyl (4-nitrophenyl)phenylmethanesulfonate.[8] Thus, when we treated a 1:1 molar mixture of sultams **1a** and **2a** with nitrobenzene in DMSO with powdered NaOH the reaction mixture turned deep-violet and after 30 minutes TLC analysis revealed complete disappearance of the starting materials. After quenching with diluted aqueous hydrochloric acid and standard work-up the expected 1-methyl-3-(4-nitrophenyl)-2,1-benzisothiazoline 2,2-dioxide (**4a**) was isolated in 62% yield (Scheme 1).

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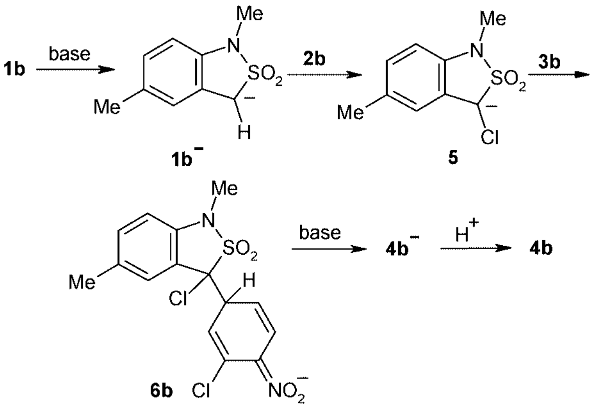
Table 1 Synthesis of 3-(Nitroaryl)benzosultams

Compounds **1–4**	R	Q	X	Y	Yield (%)
a	H	C-H	H	H	62
b	Me	C-H	H	H	63
c	Me	C-H	Cl	H	71
d	H	C-H	Cl	H	65
e	H	N	H	Cl	64
f	MeO	N	H	Cl	62
g	H	N	EtO	H	60

Other nitrobenzene and nitropyridine derivatives reacted similarly (Table 1). In all investigated instances, due to steric reasons, the replacement of hydrogen occurred at the *para* position to the nitro group, similarly as in the case of other tertiary α-chloro-α-sulfonyl carbanions.[9] A plausible reaction pathway is shown in the Scheme 2.



Scheme 2

Another possibility for the formation of nitroarylated products was an oxidative nucleophilic substitution of hydrogen by the carbanion of the starting sultam. However, when we reacted the 1,5-dimethylbenzosultam **1b** with 2-nitrochlorobenzene under employed conditions a complex mixture of products was formed from which the expected sultam **4b** was isolated in less than 10% yield. This confirms that the initial step of the investigated reaction was chlorination of the sultam by dichlorosultam.

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained with Varian Mercury 400 BB (400 MHz) and Varian Gemini (200 MHz) instruments in $CDCl_3$ with TMS as internal standard. IR spectra were recorded using a Perkin-Elmer 2000 FTIR instrument. Mass spectra (electron impact, 70 eV) were obtained on an AMD 604 (AMD Intectra GmbH, Germany) instrument. HRMS were measured in the presence of perfluorokerosene as the reference compound. Column chromatography was performed using silica gel 240–400 mesh (Merck).

Benzosultams were obtained from the corresponding *N*-alkyl-2-chloro-*N*-(methanesulfonyl)anilines following the procedure described by Bunnett.[10]

3,3-Dichlorobenzosultams were obtained by chlorination of benzosultams with hexachloroethane in a catalytic two-phase system.[7]

Arylation of Benzosultams; General Procedure

To a solution of benzosultam (**1**, 1 mmol), dichlorobenzosultam (**2**, 1 mmol) and nitroarene (**3**, 2.2 mmol) in DMSO (5 mL) solid powdered NaOH (1.5 g) was added in one portion. The reaction mixture was stirred at r.t. for 30 min and then poured into 5% diluted HCl with ice. The precipitate was separated, dissolved in CH_2Cl_2 (50 mL) and dried with Na_2SO_4. After evaporation of the solvent the product was chromatographed (cyclohexane–EtOAc, 4:1) and recrystallized from EtOH–EtOAc (10:1).

1-Methyl-3-(4-nitrophenyl)-1,3-dihydro-2,1-benzisothiazole 2,2-Dioxide (4a)

Mp 144–145 °C (decomp).

IR (KBr): 2917, 1606, 1520, 1481, 1466, 1349, 1320, 1298, 1180, 1150, 1116, 1057, 853, 759, 732 cm^{-1}.

^{1}H NMR (200 MHz): δ = 3.22 (s, 3 H), 5.54 (s, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 7.03–7.15 (m, 2 H), 7.30–7.40 (m, 3 H), 8.25–8.34 (m, 2 H).

^{13}C NMR (50 MHz): δ = 27.0, 65.8, 109.5, 122.6, 124.1, 125.7, 130.5, 131.3, 137.3.

MS (EI 70 eV): *m*/*z* (%) = 304 (21, M^+), 240 (22), 239 (47), 223 (33), 194 (27), 193 (100), 179 (9), 165 (10), 152 (12), 139 (3), 118 (13).

HRMS: *m*/*z* calcd for $C_{14}H_{12}N_2O_4S$: 304.0518; found: 304.0528.

1,5-Dimethyl-3-(4-nitrophenyl)-1,3-dihydro-2,1-benzisothiazole 2,2-Dioxide (4b)

Mp 156–158 °C (decomp).

IR (KBr): 2919, 1605, 1521, 1494, 1353, 1314, 1266, 1178, 1151, 1130, 1056, 865, 827, 818, 741 cm^{-1}.

^{1}H NMR (200 MHz): δ = 2.31 (s, 3 H), 3.18 (s, 3 H), 5.50 (s, 1 H), 6.77 (d, *J* = 8.2 Hz, 1 H), 6.86 (br s, 1 H), 7.25 (d, *J* = 8.2 Hz, 1 H), 7.46–7.57 (m, 2 H), 8.25–8.36 (m, 2 H).

MS (EI 70 eV): *m*/*z* (%) = 318 (21, M^+), 254 (30), 253 (49), 237 (36), 208 33), 207 (100), 193 (16), 180 (6), 178 (6), 165 (14), 152 (8), 148 (14), 132 (14).

HRMS: *m*/*z* calcd for $C_{15}H_{14}N_2O_4S$: 318.0674, found: 318.0691.

3-(3-Chloro-4-nitrophenyl)-1,5-dimethyl-1,3-dihydro-2,1-benzisothiazole 2,2-Dioxide (4c)

Mp 139–141 °C (decomp).

IR (KBr): 2937, 2913, 1597, 1583, 1529, 1494, 1357, 1318, 1270, 1176, 1148, 1131, 1052, 843, 828, 818 cm^{-1}.

^{1}H NMR (400 MHz): δ = 2.31 (s, 3 H), 3.17 (s, 3 H), 5.40 (s, 1 H), 6.76 (d, *J* = 8.0 Hz, 1 H), 6.86 (br s, 1 H), 7.24 (d, *J* = 8.0, 1 H), 7.38 (dd, *J* = 8.4, 1.8 Hz, 1 H), 7.49 (d, *J* = 1.8 Hz, 1 H), 7.92 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 20.9, 27.2, 65.3, 109.7, 121.2, 126.0, 126.2, 127.8, 129.4, 131.1, 133.4, 136.7, 139.2, 148.3.

MS (EI 70 eV): *m*/*z* (%) = 352, (11, M^+), 288 (26), 287 (34), 273 (10), 271 (13), 244 (21), 243 (41), 242 (60), 241 (100), 229 (12), 227 (15), 207 (29), 206 (44), 192 (22), 191 (24), 178 (13), 165 (21), 148 (22), 132 (23).

HRMS: *m*/*z* calcd for $C_{15}H_{13}N_2O_4SCl$: 352.0285, found: 352.0295.

Anal. Calcd for $C_{15}H_{13}N_2O_4SCl$: C, 51.07; H, 3.71; N, 7.94. Found: C, 51.70; H, 3.97; N, 8.04.

3-(3-Chloro-4-nitrophenyl)-1-methyl-1,3-dihydro-2,1-benzisothiazole 2,2-Dioxide (4d)

Mp 143–144 °C.

IR (KBr): 3101, 2936, 1606, 1595, 1584, 1537, 1479, 1464, 1414, 1366, 1326, 1309, 1276, 1171, 1144, 1112, 1055, 837, 826, 753 cm^{-1}.

^{1}H NMR (400 MHz): δ = 3.21 (s, 3 H), 5.46 (s, 1 H), 6.86 (d, *J* = 8.0 Hz, 1 H), 7.04–7.12 (m, 2 H), 7.38 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.46 (ddd, *J* = 8.0, 7.1, 1.8 Hz, 1 H), 7.50 (d, *J* = 2.0 Hz, 1 H), 7.92 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 27.0, 65.2, 109.7, 121.2, 122.7, 125.7, 126.1, 127.8, 129.4, 130.8, 133.4, 136.4, 141.4, 148.4.

MS (EI 70 eV): *m*/*z* (%) = 338 (14, M^+), 275 (24), 274 931), 273 (62), 257 (17), 239 919), 229 (41), 228 (60), 227 (100), 193 (25), 192 (39), 191 (15), 165 (13), 151 (12), 118 (24).

HRMS: *m*/*z* calcd for $C_{14}H_{11}N_2O_4ClS$: 338.0128, found: 338.0135.

Anal. Calcd for $C_{14}H_{11}N_2O_4ClS$: C, 49.64; H, 3.27; N, 8.27. Found: C, 49.71; H, 3.33; N, 8.23.

3-(6-Chloro-5-nitropyridin-2-yl)-1-methyl-1,3-dihydro-2,1-benzisothiazole 2,2-Dioxide (4e)

Mp 147–148 °C (decomp).

IR (KBr): 3085, 2936, 1576, 1528, 1487, 1469, 1430, 1379, 1340, 1307, 1271, 1203, 1169, 1124, 1050, 838, 747 cm^{-1}.

^{1}H NMR (400 MHz): δ = 3.22 (s, 3 H), 5.72 (s, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 7.00–7.08 (m, 2 H), 7.25 (d, *J* = 8.2 Hz, 1 H), 7.40 (dd, *J* = 8.2, 8.2 Hz, 1 H), 8.15 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 27.3, 67.2, 109.8, 120.6, 122.8, 123.4, 126.0, 131.0, 135.3, 141.4, 143.4, 144.6, 155.7.

MS (EI 70 eV): *m*/*z* (%) = 339 (40, M^+), 275 (27), 274 (61), 258 (11), 240 (16), 230 (18), 229 (53), 228 (100), 214 (8), 209 (9), 201 (14), 194 (36), 193 (68), 181 (11), 179 (15), 167 (26), 166 (21), 153 (22), 140 (13), 118 (61).

HRMS: *m*/*z* calcd for $C_{13}H_{10}N_3O_4SCl$: 339.0081, found: 339.0067.

Anal. Calcd for $C_{13}H_{10}N_3O_4SCl$: C, 45.96; H, 2.96; N, 12.37. Found: C, 45.62; H, 3.33; N, 12.43.

3-(6-Chloro-5-nitropyridin-2-yl)-5-methoxy-1-methyl-1,3-dihydro-2,1-benzisothiazole 2,2-Dioxide (4f)

Mp 126–128 °C.

IR (KBr): 3084, 2935, 1577, 1533, 1496, 1470, 1334, 1309, 1287, 1241, 1196, 1120, 1055, 1027, 836 cm^{-1}.

^{1}H NMR (400 MHz): δ = 3.18 (s, 3 H), 3.76 (s, 3 H), 5.67 (s, 1 H), 6.70 (d, *J* = 2.7 Hz, 1 H), 6.82 (d, *J* = 8.8 Hz, 1 H), 6.99 (dd, *J* = 8.8, 2.7 Hz, 1 H), 7.32 (d, *J* = 8.2 Hz, 1 H), 8.21 (d, *J* = 8.2 Hz, 1 H).

^{13}C NMR (100 MHz): δ = 28.1, 55.8, 67.5, 111.4, 112.2, 116.0, 122.0, 123.4, 135.27, 135.33, 135.36, 143.4, 155.66, 155.70.

MS (EI 70 eV): *m*/*z* (%) = 369 (4, M^+), 304 (8), 288 (4), 259 (6), 258 (12), 244 (4), 223 93), 216 (2), 181 (3), 170 (20), 64 (100).

HRMS: *m*/*z* calcd for $C_{14}H_{12}N_3O_5SCl$: 369.0186, found: 369.0187.

Anal. Calcd for $C_{14}H_{12}N_3O_5SCl$: C, 45.47; H, 3.27; N, 11.36. Found: C, 45.16; H, 3.79; N, 11.17.

3-(4-Ethoxy-5-nitropyridin-2-yl)-1-methyl-1,3-dihydro-2,1-benzisothiazole 2,2-Dioxide (4g)

Mp 161–163 °C (decomp).

IR (KBr): 3106, 2985, 1604, 1564, 1506, 1486, 1471, 1358, 1320, 1289, 1198, 1170, 1123, 1024, 988, 856, 835, 757 cm^{-1}.

^{1}H NMR (200 MHz): δ = 1.45 (t, *J* = 7.0 Hz, 3 H), 3.21 (s, 3 H), 4.16 (q, *J* = 7.0 Hz, 2 H), 5.70 (s, 1 H), 6.86 (d, *J* = 7.8 Hz, 1 H), 6.96 (s, 1 H), 7.00–7.18 (m, 2 H), 7.38–7.52 (m, 1 H), 9.00 (s, 1 H).

^{13}C NMR (50 MHz): δ = 14.0, 27.2, 66.1, 67.9, 109.7, 110.0, 121.0, 122.6, 125.8, 130.6, 136.6, 141.5, 147.0, 156.9, 158.9.

MS (EI 70 eV): *m*/*z* (%) = 349 (43, M^+), 285 (100), 284 (87), 270 (59), 257 (41), 256 (95), 242 (51), 240 (35), 239 (82), 229 (31), 212 (24), 211 (81), 210 (34), 209 (30), 196 (42), 183 (61), 182 (73), 168 (54), 154 (48), 140 (54), 128 (26), 118 (59).

HRMS: *m*/*z* calcd for $C_{15}H_{15}N_3O_5S$: 349.0732, found: 349.0726.

References

(1) For a review on benzosultams, see: Wojciechowski, K. *Heterocycles* **2002**, *57*, 1717.

(2) For a review on aza-*ortho*-xylylenes, see: Wojciechowski, K. *Eur. J. Org. Chem.* **2001**, 3587.

(3) Wojciechowski, K. *Synth. Commun.* **1997**, *26*, 135.

(4) Wojciechowski, K. *Pol. J. Chem.* **1992**, *66*, 1121.

(5) For recent reviews on vicarious nucleophilic substitution of hydrogen, see: (a) Mąkosza, M.; Wojciechowski, K. *Liebigs Ann./Recueil* **1997**, 1805. (b) Mąkosza, M.; Kwast, A. *J. Phys. Org. Chem.* **1998**, *11*, 341. (c) Mąkosza, M.; Wojciechowski, K. *Heterocycles* **2001**, *54*, 445.

(6) (a) Kattenberg, J.; de Waard, E. R.; Huisman, H. O. *Tetrahedron* **1973**, *29*, 4149. (b) For a review on chlorination of carbanions, see: Abele, E.; Lukevics, E. *Org. Prep. Proc. Int.* **1999**, *31*, 359.

(7) Wojciechowski, K.; Siedlecka, U.; Modrzejewska, H.; Kosiński, S. *Tetrahedron* **2002**, *58*, 7583.

(8) Mąkosza, M.; Goliński, J. *Synthesis* **1983**, 1023.

(9) Mąkosza, M.; Goliński, J.; Baran, J. *J. Org. Chem.* **1984**, *49*, 1488.

(10) Bunnett, J. F.; Kato, T.; Flynn, R. R.; Skorcz, J. A. *J. Org. Chem.* **1963**, *28*, 1.