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Synthesis and reactions of 3-alkylsulfanyl-1,3-dihydro-2,1-benzisothiazole 2,2-dioxides

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Abstract—Alkyl- and arylsulfanylation of 1,3-dihydro-2,1-benzisothiazole 2,2-dioxides (benzosultams) **1a–c** and pyridosultam **1d** with dialkyl and diaryl disulfides provides dithioacetals of 2-aminobenzaldehydes **6–13**. 1,3-Dimethylbenzosultam **19** with disulfides forms 3-alkyl(aryl)sulfanyl-1,3-dimethylbenzosultams **20–22** that undergo thermal extrusion of SO_2 followed by a [1,5] sigmatropic hydrogen shift in the intermediate aza-*ortho*-xylylene leading to 1-arylvinyl sulfides **24–26**. Tandem alkylation–sulfanylation of benzo- and pyridosultams **1a–d** with 4-bromobutyl thiocyanate gives tetrahydrothiopyrano-spiro-benzosultams **27–30** that, after extrusion of SO_2 and [1,5] hydrogen shift, form 2-aryl-5,6-dihydro-4*H*-thiopyrans **32–35**. Alkylation of pyridosultam **1d** with 3-chloropropyl thiocyanate leads directly to 2-pyrido-3,4-dihydrothiophene derivative **37**.

1. Introduction

Thermal extrusion of sulfur dioxide from 2,1-benzisothiazoline 2,2-dioxides (benzosultams)[1] provides 6-methylenecyclohexa-2,4-dien-1-imines (*ortho*-quinone methide imines, aza-*ortho*-xylylenes).[2] These reactive 1-azadienes undergo Diels–Alder reaction leading to 1,2,3,4-tetrahydroquinoline derivatives,[3] undergo [1,5] sigmatropic hydrogen shift leading to Schiff bases or 2-vinylanilines,[4] or add nucleophiles to form 2-aminobenzyl derivatives.[5,6] We were interested in how replacement of the hydrogen atoms in the exocyclic methylene group with heteroatoms would influence the reaction course of aza-*ortho*-xylylenes. In one of our previous papers, we described the extrusion of SO_2 from 3,3-dichlorobenzosultams and trapping of the generated 6-(dichloromethylene)cyclohexa-2,4-dien-1-alkylimines with amines.[7]

In this paper, we present results of our studies on the introduction of alkyl-(or aryl) thio substituents into the 3-position of benzosultams and the use of the obtained products as precursors of practically unknown aza-*ortho*-xylylenes bearing alkylsulfanyl substituents in the exocyclic methylene group.

Keywords: Benzosultams; Spiro compounds; Alkylsulfanylation; Extrusion; [1,5] Sigmatropic hydrogen shift; Aza-*ortho*-xylylenes; Dihydrothiopyrans; Phase-transfer catalysis; Sulfides; Disulfides.
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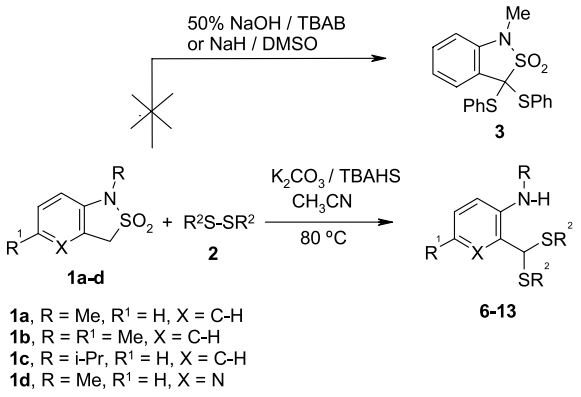
2. Results and discussion

Methods of introduction of thio substituents into position-α to electron-withdrawing groups deal with reactions of the corresponding carbanions with sulfanylating agents, such as *S*-alkyl methanethiosulfonates,[8–10] dialkyl disulfides,[11] or organic thiocyanates.[12] Numerous reactions of this type were performed under phase-transfer catalysis conditions employing both solid–liquid[10] and liquid–liquid[12] systems. Direct monosulfanylation of α-sulfonyl carbanions with dimethyl disulfide in the presence of sodium hydride in DMSO has also been described.[13]

Our attempts to employ these base-solvent systems to obtain 3-(phenylsulfanyl)benzosultam under analogous conditions failed. In the reaction of equimolar amounts of benzosultam **1a** and diphenyl disulfide in the presence of NaH in DMSO, the starting materials were completely consumed and a complex inseparable mixture of products, probably originating from mono- and di-sulfenylated benzosultams, was formed.

Attempts to obtain 3,3-di(phenylsulfanyl)benzosultam **3** from benzosultam **1a** and 2 mol of diphenyl disulfide under standard phase-transfer catalysis conditions [50% NaOH, tetrabutylammonium bromide (TBAB)] were also unsuccessful (Scheme 1). Similar results were obtained using other base-solvent systems such as NaH in DMSO or *t*-BuOK in DMF. In these instances GC–MS analysis of the reaction mixture has revealed presence of products whose molecular mass corresponded to an addition of diphenyl



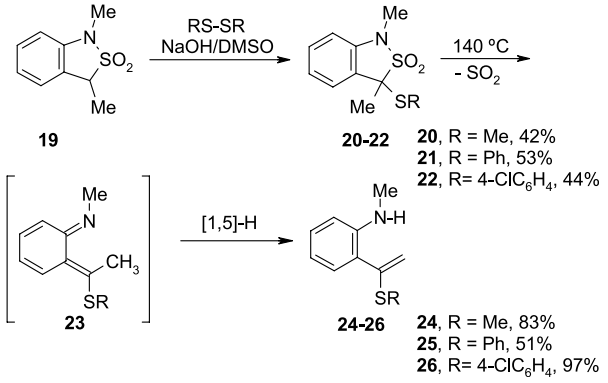
Product	R	R^1	X	R^2	Yield (%)
6	Me	H	C-H	Me	32
7	Me	H	C-H	Ph	37
8	Me_2CH	H	C-H	Ph	79
9	Me	Me	C-H	Ph	55
10	Me	Me	C-H	Me	50
11	Me_2CH	H	C-H	Me	54
12	Me	H	N	Me	54
13	Me	H	N	Ph	34

Scheme 1.

disulfide to the intermediate azaxylylene. Results of these attempts suggested low thermal stability of the expected mono- and/or bis-sulfenylated products. When this reaction was run in the presence of solid K_2CO_3 and tetrabutylammonium hydrogensulfate (TBAHS) as a phase-transfer catalyst in boiling acetonitrile (80 °C), TLC analysis has revealed the presence of one product. The reaction was complete in 24 h, and the dithioacetal of 2-aminobenzaldehyde **6** was isolated in 37% yield. Other benzosultams reacted similarly giving the dithioacetals **7**–**13** in moderate to good yields.

Plausible routes for the formation of these products are shown in the Scheme 2. The first one (**A**) involves extrusion of SO_2 from the initially formed 3-methylthio derivative **14** to form azaxylylene **15**, which intercepts the alkylthiolate anion generated from the disulfide. Another route (**B**) may follow heterolytic fission of the C–SO_2 bond leading to a zwitterionic species **16** isomeric to benzoxathiazine **17**. Both **16** and **17** can intercept a thiolate anion, with a consecutive elimination of SO_2 to form dithioacetal **6**. Both of these routes involve thermal instability of the intermediate monosulfanylated products. The reported thermal decomposition of relatively unstable α-alkylthiobenzyl sulfones occurred at temperature 130–170 °C.[13]

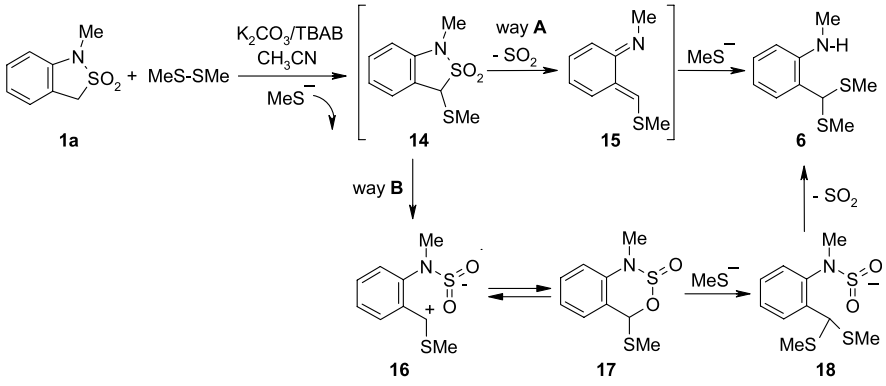
The alkyl- and arylsulfanylation of the tertiary carbanion of 1,3-dimethylbenzosultam **19** with dimethyl and diaryl disulfides in the presence of solid powdered NaOH in dimethylsulfoxide proceeded smoothly, and the expected 3-methylsulfanyl- and 3-arylsulfanylbenzosultams (**20**–**22**) were obtained (Scheme 3). Heating of 3-methyl-3-sulfanyl derivatives in boiling chlorobenzene (140 °C) results in extrusion of SO_2 and the intermediate aza-*ortho*-xylylenes **23** undergo [1,5]-sigmatropic hydrogen shift to give 1-arylvinyl sulfides **24**–**26** in good yields.



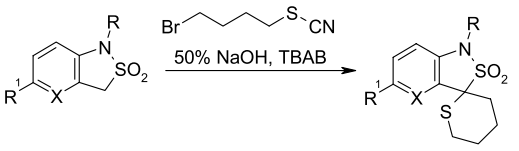
Scheme 3.

We next, investigated alkylation–sulfanylation of the sultams **1a**–**d** with 4-bromobutyl thiocyanate under phase-transfer catalysis conditions employing 50% aqueous NaOH and tetrabutylammonium bromide (TBAB). The expected spiro compounds **25**–**28** were obtained in good yields. Thermal extrusion of SO_2 from the spiro compounds proceeded smoothly and the intermediate azaxylylenes **31** underwent [1,5] sigmatropic hydrogen shift to form novel 6-aryl-3,4-dihydro-2*H*-thiopyrans **32**–**35** in good yields (Scheme 4).

Attempts to obtain analogous spiro compounds, spiro-2-thietanes and spiro-2-tetrahydrothiophenes, in reactions of benzosultams **1a**–**c** with 2-chloroethyl and 3-chloropropyl thiocyanates were unsuccesful. These reactions led to complex mixtures of products, from which isolation of expected spiro compounds proved impossible. Only in the



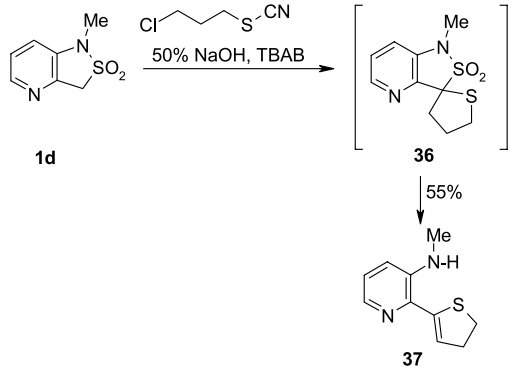
Scheme 2.



R	R^1	X	No.	Yield (%)	No.	Yield (%)
Me	H	C-H	**27**	63	**32**	95
Me	Me	C-H	**28**	53	**33**	91
Me_2CH	H	C-H	**29**	73	**34**	98
Me	H	N	**30**	34	**35**	73

Scheme 4.

case of alkylation of pyridosultam **1d** with 3-chloropropyl thiocyanate dihydrothiophene derivative **37** was obtained in moderate yield (Scheme 5). No intermediate spiro sultam **36** was isolated. This is probably due to an elimination of SO_2 facilitated by an antiperiplanar configuration of the C–H and C–SO_2 bonds in the intermediate spiro compound **36**. Similar elimination was observed earlier during alkylation of pyridosultam **1d** with 1,2-bis(bromomethyl)benzene.[14]



Scheme 5.

3. Conclusion

In conclusion, the reaction course of the 2,1-benzisothiazoline 2,2-dioxides (benzosultams) with sulfanylating agents depends on the structure of both starting materials. The alkylsulfanylation of benzosultams with dialkyl and diaryl disulfides in the presence of potassium carbonate in acetonitrile leads directly to 2-aminobenzaldehyde dithioacetal derivatives. 3-Alkylbenzosultams undergo 3-alkyl-(aryl)sulfanylation to form stable 3-alkyl-3-sulfanyl derivatives, that can transform into 1-arylvinyl sulfides via thermal extrusion of SO_2 followed by a [1,5] hydrogen shift in the intermediate aza-*ortho*-xylylene. Spirobenzosultams obtained in the reaction of benzosultams with 1,ω-haloalkyl thiocyanates transform into 2-aryldihydrothiopyrans and 2-aryldihydrothiophenes.

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H and ^{13}C NMR and spectra were obtained on a Varian Mercury 400 BB (400 and 100 MHz, respectively) instrument in $CDCl_3$ with TMS as internal standard. Coupling constants *J* are given in Hz. IR spectra were recorded with Perkin Elmer 2000 FTIR instrument. Mass spectra (electron impact, 70 eV) were obtained on AMD 604 (AMD Intectra GmbH, Germany) instrument. HRMS were measured in the presence of perfluorokerosene as the reference compound. Elemental analyses were obtained using a Elementar Vario EL III instrument. Column chromatography was performed using silica gel 240–400 mesh (Merck). Benzosultams **1a–c** and **19** were obtained from the corresponding *N*-alkyl-2-chloro-*N*-(alkanesulfonyl)anilines following the known procedures.[15,16] Pyridosultam **1d** was prepared according to the earlier described procedure.[14]

4.2. Reactions of benzosultams with disulfides. General procedure

Sultam **1a–d** (1 mmol), disulfide **2** (1.1 mmol), K_2CO_3 (0.5 g, 4 mmol) and tetrabutylammonium hydrogensulfate (34 mg, 0.1 mmol) were heated in acetonitrile (5 mL) at reflux under an argon atmosphere until the starting material disappeared (6–40 h, TLC control). The reaction mixture was then poured into water (50 mL), and product was extracted with dichloromethane (3×25 mL). The combined extracts were washed with water, dried with Na_2SO_4 and evaporated. Products were purified by column chromatography (silica gel–hexane/ethyl acetate 2:1 for **6–11** or hexane/ethyl acetate 1:2 for **12** and **13**). The following products were obtained:

4.2.1. {2-[Bis-(methylsulfanyl)methyl]phenyl}methylamine (6). Oil. ^{1}H NMR (400 MHz): δ=2.08 (s, 6H), 2.89 (s, 3H), 4.50 (br s, 1H), 4.89 (s, 1H), 6.71 (d, *J*=8.1 Hz, 1H), 6.73 (ddd, *J*=7.6, 7.4, 1.1 Hz, 1H), 7.23 (ddd, *J*=8.1, 7.4, 1.5 Hz, 1H), 7.30 (dd, *J*=7.6, 1.5 Hz, 1H). ^{13}C NMR (100 MHz): δ=14.99, 30.70, 53.65, 111.09, 116.65, 121.48, 128.70, 129.01, 146.76. IR (KBr, cm^{-1}) ν: 3395, 2980, 2915, 2813, 1724, 1657, 1602, 1581, 1512, 1462, 1425, 1315, 1273, 1171, 1063, 1044, 961, 748. MS (EI 70 eV, *m/z*, %): 213 (M^+, 9), 166 (70), 150 (7), 118 (100), 91 (34). HRMS for $C_{10}H_{15}NS_2$ calcd 213.0646, found 213.0656. Elemental analysis for $C_{10}H_{15}NS_2$ (213.36) calcd C 56.30, H 7.09, N 6.56, found C 56.34, H 6.95, N 6.50.

4.2.2. {2-[Bis-(phenylsulfanyl)methyl]phenyl}methylamine (7). Oil. ^{1}H NMR (400 MHz): δ=2.93 (s, 3H), 4.60 (br s, 1H), 5.54 (s, 1H), 6.58 (dt, *J*=7.4, 1.0 Hz, 1H), 6.71 (d, *J*=7.4 Hz, 1H), 7.16–7.24 (m, 8H), 7.31–7.35 (m, 4H). ^{13}C NMR (100 MHz): δ=30.93, 58.21, 111.27, 117.09, 122.14, 127.69, 128.80, 129.16, 129.33, 132.15, 134.51, 146.60. IR (KBr) ν: 3363, 3072, 3057, 2813, 1656, 1603, 1580, 1510, 1479, 1463, 1438, 1425, 1315, 1170, 1086, 1066, 1024, 742, 689. MS (EI 70 eV, *m/z*, %): 337 (M^+, 1), 228 (57), 150 (4), 118 (100), 91 (21). HRMS for $C_{20}H_{19}NS_2$ calcd 337.0959, found 337.0961. Elemental

analysis for $C_{20}H_{19}NS_2$ (337.49) calcd C 71.18, H 5.67, N 4.15, found C 71.27, H 5.61, N 4.21.

4.2.3. {2-[Bis-(phenylsulfanyl)methyl]phenyl}isopropylamine (8). Oil. ^{1}H NMR (400 MHz): δ=1.29 (d, J=6.2 Hz, 6H), 3.72 (sept, J=6.2 Hz, 1H), 4.35 (br s, 1H), 5.48 (s, 1H), 6.54 (dt, J=7.4, 1.1 Hz, 1H), 6.71 (d, J=8.0 Hz, 1H), 7.14 (ddd, J=8.3, 7.4, 1.5 Hz, 1H), 7.20–7.26 (m, 7H), 7.32–7.36 (m, 4H). ^{13}C NMR (100 MHz): δ=22.98, 44.14, 58.55, 112.25, 116.48, 122.00, 127.65, 128.80, 129.16, 129.37, 132.12, 134.80, 144.88. IR (KBr) ν: 3353, 3059, 2965, 2928, 1601, 1582, 1511, 1479, 1461, 1438, 1383, 1365, 1316, 1259, 1176, 1086, 1067, 1052, 1025, 742, 689. MS (EI 70 eV, *m/z*, %): 365 (M^+, 0.5), 256 (42), 162 (3), 146 (100), 131 (24), 110 (4). HRMS for $C_{22}H_{23}NS_2$ calcd 365.1272, found 365.1288. Elemental analysis for $C_{22}H_{23}NS_2$ (365.53) calcd C 72.28, H 6.34, N 3.83, found C 72.25, H 6.46, N 3.83.

4.2.4. {2-[Bis-(phenylsulfanyl)methyl]-4-methylphenyl}methylamine (9). Oil. ^{1}H NMR (400 MHz): δ=2.14 (s, 3H), 2.89 (s, 3H), 4.40 (br s, 1H), 5.53 (s, 1H), 6.62 (d, J=8.1 Hz, 1H), 7.00 (dd, J=8.1, 2.1 Hz, 1H), 7.03 (br s, 1H), 7.19–7.26 (m, 6H), 7.30–7.36 (m, 4H). ^{13}C NMR (100 MHz): δ=20.26, 31.13, 57.87, 111.49, 122.49, 127.58, 128.77, 129.36, 129.60, 129.74, 131.99, 134.70, 144.35. IR (KBr) ν: 3366, 3057, 2917, 2873, 2810, 1653, 1616, 1579, 1513, 1478, 1438, 1310, 1227, 1168, 1086, 1066, 1024, 943, 808, 739, 689. MS (EI 70 eV, *m/z*, %): 351 (M^+, 2), 242 (86), 164 (4), 132 (100), 117 (27), 105 (13). HRMS for $C_{21}H_{21}NS_2$ calcd 351.1115, found 351.1123.

4.2.5. {2-[Bis-(methylsulfanyl)methyl]-4-methylphenyl}methylamine (10). Oil. ^{1}H NMR (400 MHz): δ=2.09 (s, 6H), 2.26 (s, 3H), 2.87 (s, 3H), 4.87 (s, 1H), 6.63 (d, J=8.2 Hz, 1H), 7.04 (dd, J=8.2, 1.8 Hz, 1H), 7.12 (d, J=1.8 Hz, 1H). ^{13}C NMR (100 MHz): δ=15.02, 20.43, 30.97, 53.60, 111.39, 121.81, 125.92, 129.18, 129.41, 144.47. IR (KBr) ν: 3392, 3361, 2979, 2915, 2809, 1654, 1615, 1578, 1514, 1433, 1311, 1266, 1171, 960, 807. MS (EI 70 eV, *m/z*, %): 227 (12), 180 (65), 164 (7), 132 (100), 117 (33), 105 (16), 91 (4). HRMS for $C_{11}H_{17}NS_2$ calcd 227.0802, found 227.0795. Elemental analysis for $C_{11}H_{17}NS_2$ (227.37) calcd C 58.10, H 7.53, N 6.16, found C 58.11, H 7.43, N 6.22.

4.2.6. {2-[Bis-(methylsulfanyl)methyl]phenyl}isopropylamine (11). Oil. ^{1}H NMR (400 MHz): δ=1.26 (d, J=6.3 Hz, 6H), 2.07 (s, 6H), 3.69 (sept, J=6.3 Hz, 1H), 4.29 (br s, 1H), 4.86 (s, 1H), 6.66 (ddd, J=7.4, 7.4, 1.1 Hz, 1H), 6.72 (br d, J=8.1 Hz, 1H), 7.18 (ddd, J=8.1, 7.4, 1.5 Hz, 1H), 7.28 (dd, J=7.4, 1.5 Hz, 1H). ^{13}C NMR (100 MHz): δ=14.97, 28.86, 44.07, 53.84, 112.17, 116.08, 121.13, 128.86, 129.06, 145.06. IR (KBr) ν: 3378, 2967, 2916, 2869, 1601, 1582, 1513, 1458, 1435, 1383, 1365, 1319, 1261, 1209, 1176, 1156, 1053, 960, 871, 746. MS (EI 70 eV, *m/z*, %): 241 (M^+, 8), 211 (2) 194 (50), 169 (4), 146 (100), 136 (11), 131 (43), 117 (4), 105 (5). HRMS for $C_{12}H_{19}NS_2$ calcd 241.0959, found 241.0970. Elemental analysis for $C_{12}H_{19}NS_2$ (241.41) calcd C 59.70, H 7.94, N 5.80, found C 59.78, H 7.80, N 6.05.

4.2.7. {2-[Bis-(methylsulfanyl)methyl]pyridin-3-yl}methylamine (12). Colorless needles. Mp 72–73 °C (from cyclohexane). ^{1}H NMR (400 MHz): δ=2.10 (s, 6H), 2.89 (d, J=5.1 Hz, 3H), 4.56 (br s, 1H), 5.01 (s, 1H), 6.96 (dd, J=8.2, 1.3 Hz, 1H), 7.13 (dd, J=8.3, 4.7 Hz, 1H), 7.94 (dd, J=4.7, 1.3 Hz, 1H). ^{13}C NMR (100 MHz): δ=13.72, 30.15, 56.52, 117.25, 123.50, 136.66, 142.28. IR (KBr) ν: 3398, 2992, 2913, 2816, 1582, 1504, 1460, 1416, 1401, 1322, 1310, 1292, 1247, 1217, 1147, 1093, 964, 788, 762, 719, 652. MS (EI 70 eV, *m/z*, %): 214 (M^+, 9), 167 (100), 151 (98), 132 (10), 119 (63), 92 (32). HRMS for $C_9H_{14}N_2S_2$ calcd 214.0598, found 214.0607. Elemental analysis for $C_9H_{14}N_2S_2$ (214.34) calcd C 50.43, H 6.58, N 13.07, found C 50.24, H 6.56, N 12.97.

4.2.8. {2-[Bis-(phenylsulfanyl)-methyl]pyridin-3-yl}methylamine (13). Colorless plates. Mp 94–95 °C (from cyclohexane). ^{1}H NMR (400 MHz): δ=2.92 (s, 3H), 4.86 (br s, 1H), 5.87 (br s, 1H), 6.96 (d, J=7.8 Hz, 1H), 7.09 (dd, J=7.8, 4.3 Hz, 1H), 7.20–7.26 (m, 6H), 7.39–7.45 (m, 4H), 7.75 (d, J=4.3 Hz, 1H). ^{13}C NMR due to dynamic phenomena no legible spectrum recordable under standard conditions. IR (KBr) ν: 3362, 3339, 3054, 2817, 1583, 1437, 1425, 1321, 1292, 1250, 1162, 1086, 1023, 881, 794, 734, 688. MS (EI 70 eV, *m/z*, %): 338 (M^+, 0.5), 229 (100), 195 (96), 119 (55), 110 (13), 92 (25). HRMS for $C_{19}H_{18}N_2S_2$ calcd 338.0911, found 338.0909. Elemental analysis for $C_{19}H_{18}N_2S_2$ (338.35) calcd C 67.42, H 5.36, N 8.28, found C 67.20, H 5.41, N 8.25.

4.3. Reactions of 1,3-dimethylbenzosultam 19 with dialkyl(aryl) disulfides. General procedure

To a solution of 1,3-dimethylbenzosultam (400 mg, 2 mmol) and dialkyl(aryl) disulfide (2 mmol) in DMSO (5 mL), powdered sodium hydroxide (1.0 g, 25 mmol) was added in one portion. The reaction mixture was stirred under argon for 30 min at room temperature. The reaction mixture was then poured into water (50 mL) and extracted with ethyl acetate (3×25 mL). The combined extracts were washed with water and dried with Na_2SO_4. The products were purified by column chromatography on silica gel (hexane/ethyl acetate 4:1) and crystallized from ethanol. The following compounds were obtained:

4.3.1. 1,3-Dimethyl-3-methylsulfanyl-1,3-dihydro-2,1-benzisothiazole 2,2-dioxide (20). White solid. Mp 63–64 °C. ^{1}H NMR (400 MHz): δ=1.94 (s, 3H), 2.09 (s, 3H), 3.17 (s, 3H), 6.75 (d, J=8.0 Hz, 1H), 7.09 (dt, J=7.5, 1.0 Hz, 1H), 7.30–7.38 (m, 2H). ^{13}C NMR (100 MHz): δ=13.62, 22.53, 27.09, 69.05, 109.48, 122.46, 124.36, 125.17, 130.05, 140.20. IR (KBr) ν: 2929, 1602, 1482, 1467, 1445, 1318, 1306, 1191, 1153, 1121, 1082, 1064, 1037, 847, 753. MS (EI 70 eV, *m/z*, %): 243 (M^+, 8), 197 (1), 196 (1), 179 (10), 164 (100), 149 (6), 132 (11), 130 (11), 117 (13). HRMS for $C_{10}H_{13}NO_2S_2$ calcd 243.0388, found 243.0376. Elemental analysis for $C_{10}H_{13}NO_2S_2$ (243.34) calcd C 49.35, H 5.39, N 5.76, found C 49.58, H 5.27, N 5.75.

4.3.2. 1,3-Dimethyl-3-phenylsulfanyl-1,3-dihydro-2,1-benzisothiazole 2,2-dioxide (21). White solid. Mp 96–97 °C. ^{1}H NMR (400 MHz): δ=1.98 (s, 3H), 2.88 (s, 3H), 6.48 (d, J=8.0 Hz, 1H), 7.05 (dt, J=7.7, 1.1 Hz, 1H),

7.16–7.22 (m, 2H), 7.26 (dt, 7.7, 1.4 Hz, 1H), 7.29–7.34 (m, 2H), 7.37–7.39 (m, 2H). ^{13}C NMR (100 MHz): δ=20.23, 26.92, 71.60, 109.37, 122.19, 124.38, 125.87, 128.31, 128.52, 129.95, 130.02, 137.39, 139.86. IR (KBr) ν: 3072, 1602, 1470, 1437, 1317, 1281, 1185, 1156, 1122, 1084, 1025, 841, 825, 762, 743, 691. MS (EI 70 eV, *m/z*, %): 305 (M^+, 6), 241 (30), 208 (5), 197 (14), 196 (31), 164 (100), 152 (11), 148 (19), 136 (11), 132 (62), 130 (22), 118 (20), 117 (32). HRMS for $C_{15}H_{15}NO_2S_2$ calcd 305.0544, found 305.0545. Elemental analysis for $C_{15}H_{15}NO_2S_2$ (305.41) calcd C 58.99, H 4.95, N 4.59, found C 58.98, H 4.80, N 4.56.

4.3.3. 1,3-Dimethyl-3-(4-chlorophenylsulfanyl)-1,3-dihydro-2,1-benzisothiazole 2,2-dioxide (22). White solid. Mp 93–94 °C. ^{1}H NMR (400 MHz): δ=1.98 (s, 2H), 2.89 (s, 3H), 6.50 (br d, J=7.8 Hz, 1H), 7.07 (dt, J=7.8, 1.0 Hz, 1H), 7.13–7.19 (m, 2H), 7.25–7.35 (m, 4H). ^{13}C NMR (100 Hz): δ=19.99, 26.81, 71.52, 109.41, 122.30, 124.31, 125.50, 126.97, 128.47, 130.24, 136.60, 138.54, 139.85. IR (KBr) ν: 3076, 2981, 2931, 1603, 1570, 1476, 1469, 1321, 1298, 1273, 1183, 1157, 1123, 1079, 1030, 1016, 832, 810, 770. MS (EI 70 eV, m/z, %): 339 (M^+, 7), 275 (22), 196 (74), 164 (100), 148 (36), 132 (95), 130 (34), 117 (43), 109 (10). HRMS for $C_{15}H_{14}NO_2S_2Cl$ calcd 339.0155, found 339.0163. Elemental analysis for $C_{15}H_{14}NO_2S_2Cl$ (339.86) calcd C 53.01, H 4.15, N 4.12, found C 52.97, H 4.19, N 4.09.

4.4. Extrusion of SO_2 from 1,3-dimethyl-3-alkyl(aryl) sulfanylbenzosultam. General procedure

Benzosultam (**20**–**22**, 1 mmol) was heated in chlorobenzene (5 mL) at reflux. The progress of the reaction was monitored by TLC (hexane/ethyl acetate 4:1, 1.5–6 h). The reaction mixture was then subjected to column chromatography. The chlorobenzene was eluted with hexane/ethyl acetate (50:1) and then product with hexane/ethyl acetate 2:1. The following compounds were obtained:

4.4.1. Methyl-[2-(1-methylsulfanylvinyl)phenyl]amine (24). Oil. ^{1}H NMR (400 MHz): δ=2.23 (s, 3H), 2.85 (s, 3H), 5.17 (s, 1H), 5.24 (s, 1H), 6.62 (br d, J=8.2 Hz, 1H), 6.68 (dt, J=7.5, 1.0 Hz, 1H), 7.10 (dd, J=7.5, 1.5 Hz, 1H), 7.23 (ddd, J=8.2, 7.5, 1.5 Hz, 1H). ^{13}C NMR (100 MHz): δ=15.31, 30.62, 109.75, 109.85, 116.23, 124.72, 129.54, 129.65, 144.19, 146.17. IR (KBr) ν: 3420, 2982, 2917, 2814, 1605, 1589, 1578, 1511, 1460, 1425, 1315, 1290, 1259, 1212, 1169, 1077, 1038, 858, 747. MS (EI 70 eV, *m/z*, %): 179 (M^+, 33), 164 (100), 149 (10), 132 (27), 130 (26), 117 (39), 103 (7). HRMS for $C_{10}H_{13}NS$ calcd 179.0769, found 179.0772. Elemental analysis for $C_{10}H_{13}NS$ (179.28) calcd C 66.99, H 7.31, N 7.81, found C 66.96, H 7.35, N 7.61.

4.4.2. Methyl-{2-[1-(phenylsulfanyl)vinyl]phenyl}amine (25). Oil. ^{1}H NMR (200 MHz): δ=2.87 (s, 3H), 4.60 (br s, 1H), 5.16 (s, 1H), 5.29 (s, 1H), 6.50–6.70 (m, 2H), 7.12–7.55 (m, 7H). ^{13}C NMR (100 MHz): δ=23.69, 102.85, 106.82, 109.17, 121.47, 122.07, 122.56, 123.02, 124.96, 127.33, 132.24, 139.25. IR (KBr) ν: 3425, 3059, 2917, 2814, 1721, 1602, 1577, 1512, 1477, 1460, 1439, 1425, 1315, 1260, 1207, 1169, 1075, 1039, 1024, 872, 744, 691. MS (EI 70 eV, *m/z*, %): 241 (M^+, 27), 164 (72), 149 (3), 132 (100), 131 (16), 130 (30), 117 (68), 115 (16), 105 (13), 99 (52). HRMS for $C_{15}H_{15}NS$ calcd 241.0925, found 241.0918.

4.4.3. {2-[1-(4-Chlorophenylsulfanyl)vinyl]phenyl}-methylamine (26). Oil. ^{1}H NMR (400 MHz): δ=2.84 (s, 3H), 4.60 (s, 1H), 5.22 (s, 1H), 5.31 (s, 1H), 6.54–6.75 (m, 2H), 7.05–7.30 (m, 6H). ^{13}C NMR (100 MHz): δ=30.64, 109.88, 114.75, 116.20, 123.60, 129.19, 129.71, 130.06, 131.36, 134.58, 135.27, 143.71, 146.17. IR (KBr) ν: 3424, 2916, 2815, 1629, 1600, 1575, 1513, 1475, 1424, 1388, 1314, 1260, 1170, 1093, 1012, 821, 747. MS (EI 70 eV, *m/z*, %): 275 (M^+, 28), 242 (7), 164 (46), 132 (100), 131 (11), 130 (20), 117 (37). HRMS for $C_{15}H_{14}ClNS$ calcd 275.0536, found 275.0539.

4.5. Synthesis of spiro compounds 27–30. General procedure

Sultam **1a**–**d** (2 mmol), 4-bromobutyl thiocyanate (2.2 mmol), tetrabutylammonium bromide (32 mg, 0.1 mmol) in toluene (5 mL) were stirred vigorously with 50% aqueous NaOH (10 mL) at room temperature under argon. The progress of the reaction was monitored by TLC (30–90 min). Then the reaction mixture was poured into water (50 mL) and the product was extracted with dichloromethane (3×25 mL). The combined extracts were washed with water and dried over Na_2SO_4. After evaporation of solvent the product was purified by column chromatography (hexane/ethyl acetate 2:1) and crystallized from ethanol. The following compounds were obtained:

4.5.1. 1-Methyl-1,3-dihydro-2,1-benzisothiazole-3-spiro-2′-tetrahydrothiopyran 2,2-dioxide (27). White solid. Mp 122–123 °C. ^{1}H NMR (400 MHz): δ=1.82–2.10 (m, 3H), 2.14–2.22 (m, 1H), 2.37 (ddd, J=14.3, 13.2, 3.7 Hz, 1H), 2.55 (ddd, J=14.0, 3.2, 2.9 Hz, 1H), 2.70 (ddd, J=14.3, 3.1, 2.9 Hz, 1H), 3.19 (s, 3H), 3.57 (ddd, J=13.5, 12.7, 2.7 Hz, 1H), 6.74 (br d, J=8.0 Hz, 1H), 7.05 (ddd, J=7.8, 7.7, 1.1 Hz, 1H), 7.28 (dd, J=8.0, 1.4 Hz, 1H), 7.33 (ddd, J=8.0, 7.7, 1.4 Hz, 1H). ^{13}C NMR (100 MHz): δ=22.78, 25.29, 27.57, 28.12, 31.45, 67.68, 109.86, 122.44, 124.37, 125.92, 130.20, 140.06. IR (KBr) ν: 2943, 2922, 1603, 1483, 1470, 1311, 1190, 1152, 1134, 1066, 1029, 839, 752. MS (EI 70 eV, m/z, %): 269 (M^+, 0.5), 205 (53), 176 (49), 162 (12), 144 (38), 130 (100), 117 (17). HRMS for $C_{12}H_{15}NO_2S_2$ calcd 269.0544, found 269.0557.

4.5.2. 1,5-Dimethyl-1,3-dihydro-2,1-benzisothiazole-3-spiro-2′-tetrahydrothiopyran 2,2-dioxide (28). Pale yellow solid. Mp 110–111 °C. ^{1}H NMR (400 MHz): δ= 1.75–2.20 (m, 4H), 2. 34 (s, 3H), 2. 36 (ddd, J=16.9, 13.2, 3.5 Hz, 1H), 2.50–2.57 (m, 1H), 2.69 (dt, J=14.2, 3.2 Hz, 1H), 3.17 (s, 3H), 3.57 (ddd, J=13.4, 12.8, 2.9 Hz, 1H), 6.65 (d, J=8.1 Hz, 1H), 7.09 (dd, J=1.7, 0.7 Hz, 1H), 7.13 (ddd, J=8.1, 1.7, 0.7 Hz, 1H). ^{13}C NMR (100 MHz): δ= 20.97, 22.78, 25.35, 28.09, 28.11, 31.41, 67.75, 110.07, 124.86, 125.93, 130.66, 132.22, 137.87. IR (KBr) ν: 2944, 2919, 2862, 1614, 1492, 1464, 1445, 1428, 1312, 1186, 1162, 1132, 839, 819. MS (EI 70 eV, m/z, %): 283 (M^+, 4), 219 (62), 204 (12), 190 (66), 176 (15), 158 (34), 144 (100), 130 (12), 115 (11). HRMS for $C_{13}H_{17}NO_2S_2$ calcd 283.0701, found 283.0693. Elemental analysis for

$C_{13}H_{17}NO_2S_2$ (283.39) calcd C 55.09, H 6.04, N 4.94, found C 54.97, H 6.38, N 4.98.

4.5.3. 1-Isopropyl-1,3-dihydro-2,1-benzisothiazoline-3-spiro-2′-tetrahydrothiopyran 2,2-dioxide (29). White solid. Mp 108–109 °C. ^{1}H NMR (400 MHz): δ=1.53 (d, J=7.0 Hz, 3H), 1.59 (d, J=6.9 Hz, 3H), 1.75–2.20 (m, 4H), 2.36 (ddd, J=14.1, 13.2, 3,6 Hz, 1H), 2.50 (ddd, J=13.7, 3.3, 3.0 Hz, 1H), 2.68 (ddd, J=14.1, 3.5, 3.2 Hz, 1H), 3.53 (ddd, J=13.4, 12.8, 2.8 Hz, 1H), 4.36 (dq, J=7.0, 6.9 Hz, 1H), 6.89 (br d, J=8.1 Hz, 1H), 7.02 (ddd, J=7.7, 7.6, 1.0 Hz, 1H), 7.25–7.31 (m, 2H). ^{13}C NMR (100 MHz): δ= 19.51, 21.52, 22.85, 25.36, 28.17, 31.46, 47.78, 67.35, 112.01, 122.02, 124.76, 126.56, 129.77, 138.28. IR (KBr) ν: 2979, 2935, 1600, 1476, 1311, 1262, 1166, 1142, 1017, 887, 762, 749. MS (EI 70 eV, m/z, %): 297 (M^+, 5), 233 (79), 218 (71), 204 (22), 190 (100), 184 (11), 162 (66), 158 (38), 157 (25), 156 (26), 148 (22), 144 (37), 130 (31, 115 (17). HRMS for $C_{14}H_{19}NO_2S_2$ calcd 297.0857, found 297.0852. Elemental analysis for $C_{14}H_{19}NO_2S_2$ (297.43) calcd C 56.53, H 6.44, N 4.71, found C 56.23, H 6.40, N 4.56.

4.5.4. 1-Methyl-1,3-dihydroisothiazolo[4,3-b]pyridine-3-spiro-2′-tetrahydrothiopyran 2,2-dioxide (30). White solid. Mp 108–109 °C. ^{1}H NMR (200 MHz): δ=1.80–1.96 (m, 2H), 2.05–2.21 (m, 2H), 2.60–2.78 (m, 3H), 3.21 (s, 3H), 3.54 (ddd, J=15.4, 12.7, 2.8 Hz, 1H), 7.03 (dd, J= 8.1, 1.3 Hz, 1H), 7.27 (dd, J=8.1, 5.0 Hz, 1H), 8.26 (dd, J=5.0, 1.3 Hz, 1H). ^{13}C NMR (100 MHz): δ=22.36, 25.05, 27.20, 27.75, 29.30, 68.49, 116.73, 124.72, 136.56, 143.21, 144.81. IR (KBr) ν: 2933, 1585, 1575, 1472, 1437, 1312, 1244, 1230, 1200, 1175, 1159, 1131, 1032, 839, 798. MS (EI 70 eV, m/z, %): 270 (M^+, 6), 206 (89), 205 (18),191 (37), 177 (57), 173 (54), 163 (30), 159 (60), 146 (40), 145 (100), 131 (36), 119 (21). HRMS for $C_{11}H_{14}N_2O_2S_2$ calcd 270.0497, found 270.0485. Elemental analysis for $C_{11}H_{14}N_2O_2S_2$ (270.38) calcd C 48.86, H 5.22, N 10.36, found C 48.96, H 5.47, N 10.19.

4.6. Synthesis of 2-aryl-5,6-dihydro-4*H*-thiopyrans 32–35. General procedure

Spiro compound 27–30 (1 mmol) was heated at reflux in 1, 2-dichlorobenzene (3 mL) for 30–60 min (TLC control). The reaction mixture was then subjected to column chromatography. The dichlorobenzene was eluted with hexane/ethyl acetate (50:1) and then product with hexane/ethyl acetate 2:1. The following compounds were obtained:

4.6.1. [2-(5,6-Dihydro-4*H*-thiopyran-2-yl)phenyl]methylamine (32). Oil. ^{1}H NMR (400 MHz): δ=2.02–2.09 (m, 2H), 2.28–2.32 (m, 2H), 2.84 (s, 3H), 2.99–3.01 (m, 2H), 4.50 (br s, 1H), 5.74 (t, J=4.4 Hz, 1H), 6.60 (dd, J=8.1, 1.0 Hz, 1H), 6.66 (dt, J=7.4, 1.0 Hz, 1H), 7.08 (dd, J=7.4, 1.6 Hz, 1H), 7.20 (ddd, J=8.1, 7.5, 1.6 Hz, 1H). ^{13}C NMR (100 MHz): δ=21.71, 24.50, 27.71, 30.69, 109.82, 116.38, 121.41, 126.03, 129.14, 129.75, 130.40, 146.52. IR (KBr) ν: 3419, 2918, 2833, 2813, 1598, 1579, 1514, 1460, 1427, 1316, 1267, 1168, 1070, 973, 960, 871, 853, 747. MS (EI 70 eV, *m/z*, %): 205 (M^+, 62), 190 (7), 176 (50), 162 (13), 144 (41), 130 (100), 117 (18), 103 (5), 91 (7). HRMS for $C_{12}H_{15}NS$ calcd 205.0925, found 205.0929. Elemental analysis for $C_{12}H_{15}NS$ (205.31) calcd C 70.19, H 7.36, N 6.82, found C 70.28, H 7.30, N 6.68.

4.6.2. [2-(5,6-Dihydro-4*H*-thiopyran-2-yl)-4-methylphenyl]methylamine (33). White solid. Mp 63–65 °C. ^{1}H NMR (400 MHz): δ=2.02–2.09 (m, 2H), 2.23 (s, 3H), 2.29–2.34 (m, 2H), 2.83 (s, 1H), 2.97–3.02 (m, 2H), 4.30 (br s, 1H), 5.73 (t, J=4.4 Hz, 2H), 6.53 (d, J=8.2 Hz, 1H), 6.92 (d, J=2.2 Hz, 1H), 7.01 (dd, J=8.2, 2.2 Hz, 1H). ^{13}C NMR (100 MHz): δ=20.20, 21.76, 24.52, 27.76, 31.07, 110.19, 121.30, 125.62, 126.17, 129.61, 130.39, 130.48, 144.35. IR (KBr) ν: 3412, 2908, 1632, 1612, 1579, 1515, 1473, 1443, 1431, 1401, 1313, 1276, 1265, 1168, 1128, 1070, 973, 848, 800. MS (EI 70 eV, *m/z*, %): 219 (M^+, 81), 204 (11), 190 (49), 176 (13), 158 (42), 144 (100), 130 (12), 115 (12). HRMS for $C_{13}H_{17}NS$ calcd 219.1082, found 219.1091. Elemental analysis for $C_{13}H_{17}NS$ (219.33) calcd C 71.18, H 7.81, N 6.39, found C 71.04, H 7.92, N 6.36.

4.6.3. [2-(5,6-Dihydro-4*H*-thiopyran-2-yl)phenyl]isopropylamine (34). Oil. ^{1}H NMR (400 MHz): δ=1.23 (d, J=6.3 Hz, 6H), 2.02–2.09 (m, 2H), 2.32–2.37 (m, 2H), 2.99–3.00 (m, 2H), 3.64 (sept, J=6.3 Hz, 1H), 4.50 (br s, 1H), 5.74 (dd, J=4.4, 4.3 Hz, 1H), 6.60–6.74 (m, 2H), 7.05–7.20 (m, 2H). ^{13}C NMR (100 MHz): δ=21.44, 21.82, 22.79, 24.56, 27.72, 111.95, 116.43, 121.71, 128.32, 129.01, 130.13, 130.45, 144.44. IR (KBr) ν: 3398, 2963, 2932, 1598, 1579, 1508, 1462, 1453, 1382, 1364, 1317, 1266, 1176, 1124, 1048, 974, 875, 745. MS (EI 70 eV, m/z, %): 233 (M^+, 91), 218 (67), 200 (11), 190 (100), 184 (16), 170 (11), 162 (57), 158 (50), 157 (38), 156 (35), 144 (52), 130 (39), 115 (22), 87 (80). HRMS for $C_{14}H_{19}NS$ calcd 233.1238, found 233.1232. Elemental analysis for $C_{14}H_{19}NS$ (233.37) calcd C 72.05, H 8.21, N 6.00, found C 72.01, H 8.28, N 5.80.

4.6.4. [2-(5,6-Dihydro-4*H*-thiopyran-2-yl)pyridin-3-yl]methylamine (35). Yellow needles. Mp 134–135 °C. ^{1}H NMR (200 MHz): δ=2.06–2.14 (m, 2H), 2.34–2.40 (m, 2H), 2.84 (s, 3H), 3.02–3.07 (m, 2H), 4.63 (br s, 1H), 6.01 (t, J=4.4 Hz, 1H), 6.90 (dd, J=8.2, 1.3 Hz, 1H), 7.11 (dd, J=8.2, 4.7 Hz, 1H), 7.95 (dd, J=4.7, 1.3 Hz, 1H). ^{13}C NMR (50 MHz): δ=21.64, 24.32, 27.41, 30.21, 116.87, 122.96, 123.66, 130.21, 136.63, 142.79, 143.34. IR (KBr) ν: 3355, 2919, 2811, 1579, 1494, 1424, 1317, 1258, 1162, 969, 795, 755. MS (EI 70 eV, *m/z*, %): 206 (M^+, 77), 191 (23), 177 (39), 173 (46), 163 (28), 159 (57), 146 (9100), 131 (37), 119 (21). HRMS for $C_{11}H_{14}N_2S$ calcd 206.0878, found 207.0886. Elemental analysis for $C_{11}H_{14}N_2S$ (206.30) calcd C 64.04, H 6.84, N 13.58, found C 63.84, H 7.08, N 13.39.

4.6.5. [2-(4,5-Dihydrothiophen-2-yl)pyridin-3-yl]methylamine (37). Pyridosultam **1d** (200 mg, 1 mmol) 3-chloropropyl thiocyanate (145 mg, 1.1 mmol), tetrabutylammonium bromide (32 mg, 0.1 mmol) in toluene (5 mL) were stirred vigorously with 50% aqueous NaOH (10 mL) at room temperature under argon. After 1 h the reaction mixture was poured into water (50 mL) and the product was extracted with dichloromethane (3×25 mL). The combined extracts were washed with water and dried over Na_2SO_4. After evaporation of solvent the product was purified by column chromatography (hexane/ethyl acetate 2:1) and crystallized from ethanol. Yield 106 mg (55%). Orange

solid. Mp 119–120 °C. ^{1}H NMR (400 MHz): δ=2.86 (d, J=5.0 Hz, 3H), 3.01–3.07 (m, 2H), 3.31–3.36 (m, 2H), 4.56 (br s, 1H), 6.07 (t, J=3.0 Hz, 1H), 6.92 (dd, J=8.3, 1.3 Hz, 1H), 7.09 (dd, J=8.3, 4.7 Hz, 1H), 7.97 (dd, J=4.7, 1.3 Hz, 1H). ^{13}C NMR (100 MHz): δ=30.32, 31.94, 37.09, 116.72, 121.92, 123.45, 137.18, 138.82, 141.34, 143.07. IR (KBr) ν: 3319, 2924, 2886, 2860, 2811, 1580, 1496, 1451, 1422, 1406, 1316, 1263, 1225, 1161, 1124, 1017, 946, 793, 753. MS (EI 70 eV, *m*/*z*, %): 192 (100, M^{+}), 177 (16), 175 (8), 164 (57), 159 (18), 149 (28), 145 (54), 133 (53), 132 (78), 131 (44), 118 (15), 104 (7). Elemental analysis for $C_{10}H_{12}N_2S$ (192.28) calcd C 62.47, H 6.29, N 14.57, found C 62.26, H 6.03, N 14.44.

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