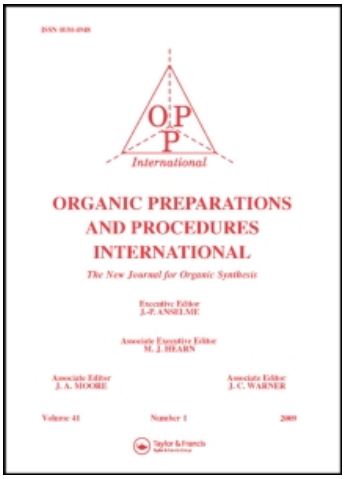

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PREPARATION OF 6-, 7- AND 8-MEMBERED SULTAMS BY FRIEDEL-CRAFTS CYCLIZATION OF ω-PHENYLALKANESULFAMOYL CHLORIDES

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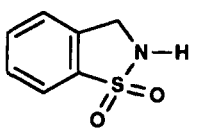
5-Membered benzosultams, especially 2,3-dihydro-1,2-benzisothiazole-1,1-dioxide (**1**) and its derivatives, are well known due to their relation to saccharin.[1-4] Several N-substituted and 3-substituted derivatives[5,6] or derivatives with substituents on the carbocyclic ring[7,8] have been extensively studied as biologically active compounds. 2-Alkyl-7-sulfonamido derivatives of **1** have been found to be effective herbicides.[9] Sultam **1** can be easily prepared by bromination of 2-methylbenzenesulfonyl chloride followed by treatment with ammonia.[5] The simplest route to 3,4-dihydro-2H-benzothiazine-1,1-dioxide (**2**) involves hydrogenation of 2-nitrobenyl cyanide,[10] diazotization of the obtained 2-aminobenzyl cyanide,[11] treatment with sulfur dioxide in the presence of copper(I) chloride, treatment of the obtained 2-cyanomethylbenzenesulfonyl chloride[11] with ammonia and hydrogenation of the 2-cyanomethylbenzenesulfonamide intermediate.[12]



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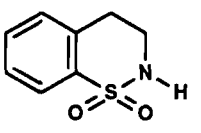

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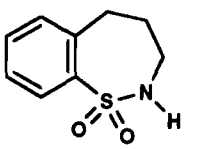

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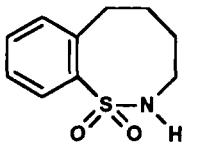
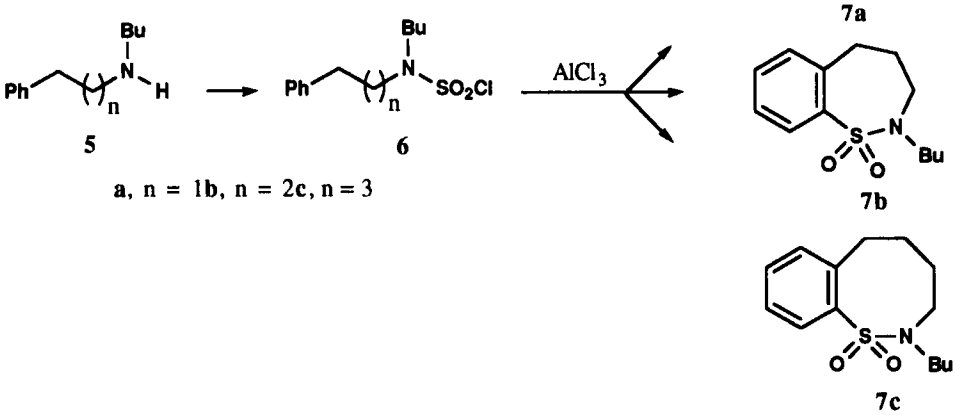


4

Two alternative synthetic methods for **2** (one or two steps longer) have also been reported.[12] Several derivatives of **2** are of interest for their anticonvulsant,[13] diuretic[14] and sedative[15] activities. A 4-iodo derivative of 2,3,4,5-tetrahydrobenzo-1,2-thiazepine-1,1-dioxide (**3**) was obtained from iododediazonization of *o*-(N-2-propenylsulfamoyl)benzenediazonium tetrafluoroborate.[16] We now report a convenient synthetic method for N-akyl derivatives of **2**, **3** and **4** by a Friedel-Crafts cyclization of the corresponding (ω-phenylalkanesulfamoyl chlorides. The related Friedel-Crafts cyclization of ω-phenylalkanesulfonyl chlorides[17] gives cyclic sulfones in yields of 37, 76, 31 and 0%, for the 5-, 6-, 7- and 8-membered rings, respectively.

N-Butyl-ω-phenylalkylamines **5** were prepared in almost quantitative yields by hycdrogenation of mixtures of butyraldehyde and the appropriate amines (**4a** and **4c**), or a mixture of butylamine and hydrocinnamaldehyde (**4b**) with 1% platinum on alumina as the catalyst. Upon treatment with sulfuryl chloride at 20°, amines **5** were converted in a simple operation to the corresponding sulfamoyl chlorides **6** in 30, 42 and 29% yields, **6a**, **6b** and **6c**, respectively. The products were satisfactorily pure (> 95%, by NMR) and did not require vacuum distillation which was applied in the original procedure for preparation of N,N-dialkylsulfamoyl chlorides.[18]

Friedel-Crafts intramolecular reactions of sulfamoyl chlorides **6** were carried out in nitrobenzene as previously described for ω-phenylalkanesulfonyl chlorides.[17] After aqueous work-up, sultam



7b (69% yield) was obtained in high purity and did not require further purification, whereas sultams **7a** (46% yield) and **7c** (7% yield) had to be purified by column chromatography.

EXPERIMENTAL SECTION

The ^1H and ^{13}C NMR spectra were recorded on a Varian 300 MHz spectrometer in $CDCl_3$. Coupling constants (*J* values) are in Hz. Both proton and carbon chemical shifts are reported in ppm downfield from internal TMS. High resolution mass spectra were recorded on a Finnigan MAT 95Q instrument. Microanalyses were performed by the Atlantic Microlab, Norcross, Georgia.

N-Butyl-(ω-phenylalkylamines (5). General Procedure.- Butyraldehyde (8.8 mL, 100 mmol) was added portionwise to a solution of the appropriate amine (100 mmol) in methanol (150 mL) at 0°. The solution was placed in a Parr autoclave with the platinum catalyst (1% Pt on Al_2O_3, 0.5 g) and the autoclave was charged with hydrogen to a pressure 1000 psi and the reduction was allowed to proceed overnight at 25°. The catalyst was filtered off and the solvent evaporated under reduced pressure to give pure amine **5a** or **5c**. Amine **5b** was obtained in a similar manner from butylamine and 3-phenylpropanal.

N-Butyl-2-phenylethylamine (5a), oil, bp. 73-74°/0.5 mm, lit.[19] bp. 85°/8 mm. ^{1}H NMR: δ 7.16-7.30 (m, 5H), 2.82 (m, 4H), 2.59 (t, 3H, *J* = 7.4), 1.42 (quintet, 2H, *J* = 7.1), 1.29 (sextet, 2H, *J* = 7.1), 0.89 (t, 3H, *J* = 7.2). ^{13}C NMR: δ 139.9, 128.4 (2C), 128.1 (2C), 125.8, 51.0, 49.2, 36.2, 32.0, 20.2, 13.7.

N-Butyl-3-phenylpropylamine (5b), oil. ^{1}H NMR: δ 7.24-7.30 (m, 2H), 7.15-7.20 (m, 3H), 2.55-2.68 (m, 6H), 1.81 (quintet, 2H, *J* =7.8), 1.46 (quintet, 2H, *J* = 7.3), 1.34 (quintet, 2H, *J* = 7.4), 1.22 (s, 1H, NH), 0.91 (t, 3H, *J* = 7.3). ^{13}C NMR: δ 142.1, 128.3 (2C), 128.2 (2C), 125.7, 49.7, 49.6, 33.7, 32.3, 31.7, 20.5, 14.0.

Hydrochloride, mp. 218-219°, lit.[20] mp. 218-219°

N-Butyl-4-phenylbutylamine (5c), oil. ^{1}H NMR: δ 7.24-7.32 (m, 2H), 7.15-7.20 (m, 3H), 2.54- 2.72 (m, 6H), 1.25-1.70 (m, 9H), 0.91 (t, 3H, *J* = 7.3). ^{13}C NMR: δ 142.4, 128.3 (2C), 128.2 (2C), 125.6, 49.9, 49.7, 35.8, 32.2, 29.8, 29.2, 20.5, 14.0.

Hydrochloride, mp. 199-201°.

Anal. Calcd. for $C_{14}H_{24}NCl$: C, 69.54; H, 10.00; N, 5.79. Found: C, 69.68; H, 10.20; N, 5.74

Sulfamoyl Chlorides 6. General Procedure.- To a stirred solution of SO_2Cl_2 (16.2 mL, 200 mmol) in $CHCl_3$ (50 mL) cooled in an ice bath was added a mixture of triethylamine (13.9 mL, 100 mmol) and the appropriate amine **5** (100 mmol) at such a rate as to keep the temperature below 20°. After the addition was complete, the mixture was stirred at 25° for 2 hrs and then poured into 100 mL of ice-water. The organic phase was separated, washed with 10% HCl (50 mL) followed by ice-cold water (2 x 50 mL) and dried over anhydrous $CaCl_2$. After evaporation of the solvent, the residue was triturated with hexane, the hexane solution filtered and the solvent evaporated to give sulfamoyl chloride **6** of good purity, which was used directly in the next step. Sulfamoyl chlorides **6** were not stable enough to give CHN analyses, however, their HRMS were satisfactory.

N-Butyl-2-phenylethanesulfamoyl chloride (6a), oil, 30% yield. ^{1}H NMR: δ 7.19-7-32 (m, 5H), 3.50 (t, 2H, *J* = 8.0), 3.26 (t, 2H, *J* = 7.5), 2.99 (t, 2H, *J* = 8.0), 1.57 (quintet, 2H, *J* = 7.5), 1.29 (sextet, 2H, *J* = 7.5), 0.90 (t, 3H, *J* = 7.2). ^{13}C NMR: δ 137.3, 128.7 (2C), 128.6 (2C), 126.8, 52.3, 51.3. 34.1, 29.0. 19.6, 13.4.

HRMS Calcd. for $C_{12}H_{18}ClNO_2S$: 275.0714. Found: 275.0710.

N-Butyl-3-phenylpropanesulfamoyl chloride (6b), oil, 42%, yield. ^{1}H NMR: δ 7.29 (t, 2H, *J* = 7.6), 7.15-7.20 (m, 3H), 3.21-3.35 (m, 4H), 2.66 (t, 2H, *J* = 7.8), 2.02 (quintet, 2H, *J* = 7.5), 1.62 (quintet, 2H, *J* = 7.3), 1.33 (sextet, 2H, *J* = 7.8), 0.92 (t, 3H, *J* = 7.2). ^{13}C NMR: δ 140.4, 128.5 (2C), 128.2 (2C), 126.2, 50.9, 50.5, 32.7, 29.3, 28.9, 19.7, 13.5.

HRMS Calcd. for $C_{13}H_{20}ClNO_2S$: 289.0903. Found: 289.0905.

N-Butyl-4-phenylbutanesulfamoyl chloride (6c), oil, 29% yield. ^{1}H NMR: δ 7.15-7.35 (m, 5H), 3.21-3.35 (m, 6H), 2.65 (t, 2H, *J* = 7.1), 1.58-1.80 (m, 4H), 1.33 (sextet, 2H, *J* = 7.6), 0.93 (t, 3H, *J* = 7.4). ^{13}C NMR: δ 144.5, 128.4 (2C), 128.3 (2C), 125.9, 50.9, 50.8, 35.2,29.3, 28.2, 26.8, 19.8, 13.5.

HRMS Calcd. for $C_{14}H_{22}NClOS$: 304.1138. Found: 304.1139.

Sultams 7. General Procedure.- A solution of sulfamoyl chloride **6** (10 mmol) and anhydrous $AlCl_3$ (2.67 g, 20 mmol) in nitrobenzene (30 mL) was heated on an oil bath at 90° for 14 hrs. The reaction

mixture was poured into ice-cold 10% HCl (50 mL) and extracted with ether (3 x 50 mL). The combined extracts were washed with water, 5% $NaHCO_3$, water again and dried over $MgSO_4$. The ether was evaporated and the nitrobenzene was distilled off under a pressure of 0.5 mm (from a water bath) to give sultam **7**. Compound **7b** was analytically pure, but **7a** and **7c** required purification by column chromatography (silica gel, chloroform).

2-Butyl-1,2-benzothiazine-1,1-dioxide (7a), oil, 46% yield. ^{1}H NMR: δ 7.77 (d, 1H, *J* = 7.7), 7.42 (t, 1H, *J* = 7.6), 7.33 (t, 1H, *J* = 7.3), 7.22 (d, 1H, *J* = 7.7), 3.84 (t, 2H, *J* = 6.3), 3.14 (t, 2H, *J* = 7.2), 3.00 (t, 2H, *J* = 6.2), 1.58 (quintet, 2H, *J* = 7.3), 1.37 (sextet, 2H, *J* = 7.3), 0.92 (t, 3H, *J* = 7.0). ^{13}C NMR: δ 136.5, 134.9, 131.5, 129.2, 126.9, 124.0, 46.2, 44.6, 29.9, 23.0, 19.4, 13.3.

Anal. Calcd. for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 60.17; H, 7.14; N, 5.81

2-Butyl-1,2-benzothiazepine-1,1-dioxide (7b), oil, 69% yield. ^{1}H NMR: δ 7.90 (d, 1H, *J* = 7.8), 7.41 (t, 1H, *J* = 7.4), 7.24-7.34 (m, 2H), 3.79 (s, 2H), 3.28 (s, 2H), 2.79 (s, 2H), 1.76 (quintet, 2H, *J* = 6.1), 1..52 (quintet, 2H, *J* = 8.4), 1.31 (sextet, 2H, *J* = 8.0), 0.89 (t, 3H, *J* = 7.3). ^{13}C NMR: δ 139.7, 139.4, 132.4, 131.3, 128.9, 126.2, 48.8, 45.8, 35.2, 30.6, 22.4, 19.6, 13.6.

Anal. Calcd. for $C_{13}H_{19}NO_2S$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.71; H, 7.57; N, 5.53

3,4,5,6-Tetrahydro-2H-1,2-benzothiazocine-1,1-dioxide (7c), oil, 7% yield. ^{1}H NMR: δ 7.96 (dd, 1H, *J* = 8.4 and 1.7), 7.45 (dt, 1H, *J* = 7.4 and 1.7), 7.27-7.35 (m, 2H), 3.51-3.59 (m, 2H), 3.34 (t, 2H, *J* = 6.7), 2.87 (t, 2H, *J* = 7.3), 1.83 (quintet, 2H, *J* = 6.8), 1.56 (quintet, 2H, *J* = 7.8), 1.28-1.48 (m, 4H), 0.92 (t, 3H, *J* = 7.3). ^{13}C NMR: δ 140.9, 139.6, 132.3, 132.0, 129.1, 125.9, 45.9, 43.9, 30.5, 30.3, 28.9, 21.9, 19.8, 13.7.

Anal. Calcd. for $C_{44}H_{21}NO_2S$: C, 62.89; H, 7.92; N, 5.24. Found: C, 62.91; H, 7.91; N, 5.26

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