Notes

Novel Synthesis of *N*-Methyl-1,2-benzosultams, an Unsuspected Demethylative Intramolecular Cyclization Reaction

Chengde Wu*

Texas Biotechnology Corporation, 7000 Fannin, Suite 1920, Houston, Texas 77030

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During work on the synthesis of endothelin receptor antagonists,[1−3] we sought to study the structure−activity relationships of benzene sulfonamides, in particular the 2,5-disubstituted system (Figure 1). To synthesize 2-(dimethylamino)-5-methylbenzenesulfonamides, we needed to make 2-(dimethylamino)-4-methylbenzenesulfonyl chloride (Figure 1).

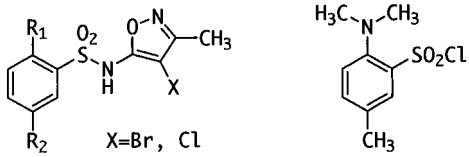

Figure 1.

Typical ways of synthesizing aromatic sulfonyl chlorides are by reacting the sulfonic acid with $SOCl_2$,[4] $POCl_3$,[5] PCl_5,[6] $PCl_5/POCl_3$,[7] or chlorosulfonic acid.[8] In our hands, the $PCl_5/POCl_3$ method had been most effective and appeared to be applicable to aromatic systems substituted with a dimethylamino group.

We attempted to make the sulfonyl chloride from commercially available 2-amino-4-methylbenzenesulfonic acid (Scheme 1). The aniline **1** was dimethylated with aqueous formaldehyde under catalytic hydrogenation conditions in essentially quantitative yield, while the other standard procedures failed on this substrate.[9] When this sulfonic acid **2** was heated at 60−80 °C for 4−6 h with phosphorus oxychloride in the presence of phosphorus pentachloride,[10] we did not obtain any of the desired (dimethylamino)benzenesulfonyl chloride. Instead, the dimethylamino group was monodemethylated and the four-membered-ring sultam **3** was obtained in good yield. Sultam **3** is insoluble in water and can be stored at −20 °C for at least 1 week. This demethylation reaction was not expected because under the same experimental conditions 5-(dimethylamino)-2-methylbenzenesulfonic acid (**6**) was converted to the corresponding sulfonyl chloride **7** rather uneventfully. Compound **7** was coupled with the bromoisoxazole[2] to afford sulfonamide **8**.

We speculated that the following mechanisms might be operative. The sulfonic acid group of **2** first reacted with phosphorus pentachloride to give intermediate **13**, which then formed a six-membered ring with the neighboring dimethylamino group with the release of a molecule of chloromethane (Scheme 2). This intermediate **14** then upon heating extruded phosphorus oxytrichloride to give the sultam **3**. Alternatively, the expected dimethylamino sulfonyl chloride **15** maybe did form but underwent an internal nucleophilic attack on the sulfonyl chloride to produce intermediate **16**, which upon demethylation led to **3**. This represents a novel synthesis of such a four-membered benzosultam, the literature methods of synthesis being by extrusion of dinitrogen from a 1,1-dioxo-1,2,3,4-thiatriazole formed via intramolecular capturing of an aromatic diazonium with an *ortho* sulfonamide[11,12] or by intramolecular radical cyclization.[13]

Considering the strain of this four-membered ring sultam, it is probable that it may be opened by the attack of a nucleophile. Indeed, when the sultam **3** was treated with 5-amino-4-chloro-3-methylisoxazole,[2] the ring was opened to give the corresponding sulfonamide **4**, which was fully characterized. To show that this was a general reaction, we subjected both 2-(dimethylamino)benzenesulfonic acid (**9**) and 2-aminobenzenesulfonic acid (**11**) to the cyclization conditions, and the corresponding sultams **10** and **12** were obtained. Compound **10** had essentially no solubility in water and was quite stable when stored at −20 °C, while compound **11** was moderately soluble in warm water but prolonged storage at −20 °C caused significant decomposition. Sultam **12** could not be coupled with an amine and was only destroyed.

In summary, we have serendipitously discovered a facile synthesis of benzosultams via a demethylative cyclization. This sultam ring can be readily opened by coupling with an amine and functions as a sulfonyl chloride substitute.

Experimental Section

General Methods. For compounds **3**, **10**, and **12**, melting points were determined using a Fisher-Johns hot-stage apparatus and are uncorrected. Proton NMR (^{1}H NMR) spectra

* To whom correspondence should be addressed. Tel.: (713) 796-8822. Fax: (713) 796-8232. E-mail: cwu@tbc.com.

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(9) Procedures tried: $NaCNBH_3$/THF/HCHO, HCHO/HCO_2H/reflux, MeI/K_2CO_3/THF/MeOH, MeOH/concd H_2SO_4/sealed tube, or MeI/NaOH/MeOH/100−110 °C.

(10) Even when the reaction was stirred at room temperature, **3** was the sole product only with lower yield; higher temperature also gave **3** but with lower purity.

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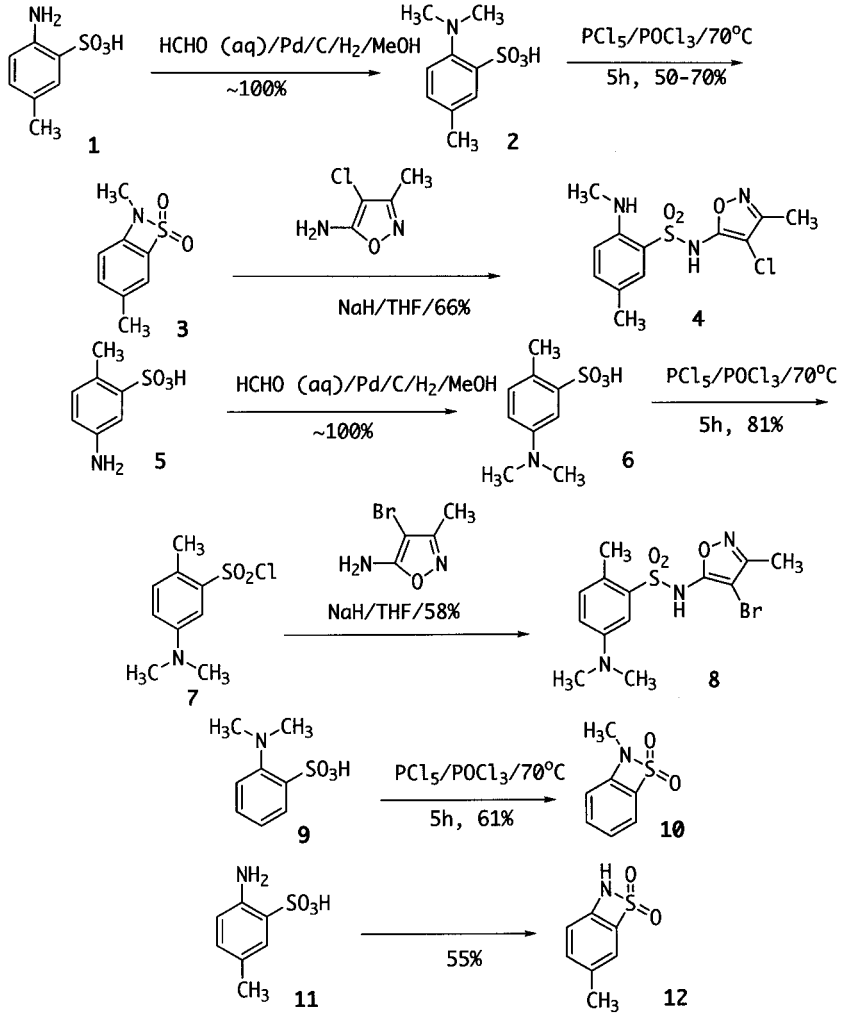
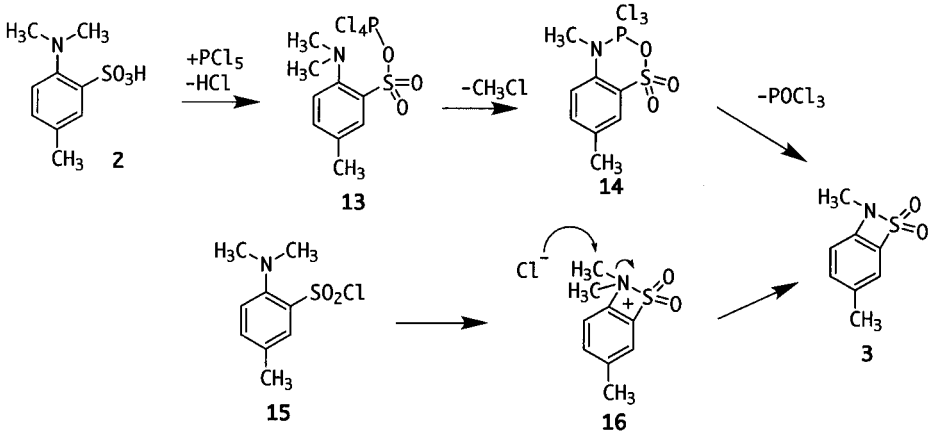
Scheme 1



Scheme 2



were recorded on a JEOL 400 MHz spectrometer. Elemental analyses were performed by Oneida Research Services, Inc. (Whitesboro, NY) and were within 0.4% of theoretical values unless otherwise indicated. For descriptions of analytical instruments for other compounds, spectral data formats, and standard calibrations, see ref 1.

2-(Dimethylamino)-5-methylbenzenesulfonic Acid (2). To a suspension of **1** (10 g, 53.4 mmol) in methanol (100 mL) was added formaldehyde (17 mL, 37% in water, 213.7 mmol). The mixture was subjected to catalytic hydrogenation conditions (Pd/C, 40 psi) overnight. The solids were filtered off, and the filtrate was concentrated to give **2** as a white powder (8.94 g, 78% yield): mp 220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.37 (m, 2H), 3.42 (s, 6H), 2.42 (s, 3H). Anal. Calcd for $C_9H_{13}NO_3S$: C, 50.22; H, 6.09; N, 6.51. Found: C, 49.84; H, 6.12; N, 6.46.

***N*-5-Dimethyl-1,2-benzosultam (3).** To a suspension of **2** (8.94 g, 41.6 mmol) in $POCl_3$ (50 mL) was slowly added PCl_5 (44 g, 213.6 mmol). The resulting mixture was heated at 70 °C for 5 h before it was allowed to cool to room temperature and poured onto crushed ice. The icy aqueous mixture was stirred vigorously at 0 °C for 40 min, and the resulting yellow precipitate was filtered, washed with water and dried on lyopholyzer. This material was chromatographed (10% CH_2Cl_2 in hexanes) to give **3** as a bright yellow solid (3.8 g, 49% yield): mp 68−69 °C; R_f = 0.45 in 10% CH_2Cl_2 in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.59 (d, 1H, J = 1.6 Hz), 7.34 (dd, 1H, J = 8.6, 1.6 Hz), 6.71 (d, 1H, J = 8.6 Hz), 2.97 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 145.66, 138.98, 129.11, 125.23, 124.94, 112.90, 29.76 (NCH_3), 19.40 ($ArCH_3$); HRMS for $C_8H_{10}NO_2S$ $(M + H)^+$ calcd 184.0432, found 184.0449.

It should be noted that if this procedure is followed, a violent exotherm may result depending on the amount of ice present. A safer method for quenching these quantities of $POCl_3$ is to add the reaction mixture slowly to warm water (35−45 °C) with good agitation, thus hydrolyzing the $POCl_3$ almost instantaneously.

***N*-(4-Chloro-3-methyl-5-isoxazolyl)-2-(aminomethyl)-5-methylbenzenesulfonamide (4).** To a solution of 4-chloro-5-amino-3-methylisoxazole[2] (1.74 g, 13.1 mmol) in anhydrous THF (30 mL) was added sodium hydride (874 mg, 21.9 mmol, 60% dispersion in mineral oil) at 0 °C. The mixture was stirred for 30 min at 0 °C before the addition of **3** (800 mg, 4.4 mmol). The resulting mixture was stirred for 30 min at 0 °C and an additional 3 h at room temperature. The reaction was quenched with saturated NH_4Cl (aqueous, 10 mL), and THF was evaporated in vacuo. The aqueous residue was extracted with EtOAc, and the organic layer was concentrated. A fraction of the residue was subjected to HPLC purification to give **4** as a brown powder (60 mg, ∼66% yield): mp 132−135 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.39 (1H, d), 7.26 (1H, dd), 7.69 (1H, d), 2.80 (3H, s), 2.19 (3H, s), 2.12 (3H, s); HRMS for $C_{12}H_{14}ClN_3O_3S$ (M^+) calcd 315.0444, found 315.0466; IR (KBr pellet) 3416, 1634, 1522, 1341, 1412, 1154 cm^{-1}. Anal. Calcd for $C_{12}H_{14}ClN_3O_3S$: C, 45.64; H, 4.47; N, 13.31. Found: C, 45.59; H, 4.43; N, 13.09.

5-(Dimethylamino)-2-methylbenzenesulfonyl Chloride (7). Compound **7** was synthesized in the same fashion as for **2** with the exception that **5** and **6** were used instead of **1** and **2**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, 1H), 7.26 (dd, 1H), 7.05 (d, 1H), 3.05 (s, 6H), 2.68 (s, 3H). Anal. Calcd for $C_9H_{12}ClNO_2S$: C, 46.25; H, 5.18; N, 5.99. Found: C, 45.95, H, 5.14; N, 5.95.

***N*-(4-Bromo-3-methyl-5-isoxazolyl)-5-(dimethylamino)-2-methylbenzenesulfonamide (8).** Compound **8** was synthesized in the same fashion as for **4** except that 4-bromo-5-amino-3-methylisoxazole and **7** were used in place of 4-chloro-5-amino-3-methylisoxazole and **3**, respectively. Compound **8** was obtained as a white powder (76 mg, 58% yield): mp 128−129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, 1H), 7.16 (d, 1H), 6.81 (dd, 1H), 2.95 (s, 6H), 2.55 (s, 3H), 2.20 (s, 3H); HRMS for $C_{13}H_{16}BrN_3O_3S$ (M^+) calcd 373.0096, found 373.0095. Anal. Calcd for $C_{13}H_{16}BrN_3O_3S$: C, 41.72; H, 4.31; N, 11.23; S, 8.57. Found: C, 41.80; H, 4.43; N, 11.03; S, 8.65.

***N*-Methyl-1,2-benzosultam (10).** Compound **10** was synthesized in the same fashion as for **3** except that **9** was used instead of **2** and the crude material was chromatographed (10% CH_2Cl_2 in hexanes): 56% yield; mp 60−62 °C; R_f = 0.45 in 10% CH_2Cl_2 in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, 1H, J = 1.5, 8.1 Hz), 7.52 (ddd, 1H, J = 1.5, 6.2, 8.1 Hz), 6.79 (d, 1H, J = 8.4 Hz), 6.74 (ddd, 1H, J = 1.1, 5.8, 8.1 Hz), 3.00 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 147.53, 137.73, 129.81, 125.29, 115.65, 112.75, 29.68 (NCH_3); HRMS for $C_7H_8NO_2S$ $(M + H)^+$ calcd 170.0276, found 170.0280.

5-Methyl-1,2-benzosultam (12). Compound **12** was synthesized in the same fashion as for **3** except that **11** was used instead of **2** and this material was chromatographed (10% EtOAc in hexanes): 48% yield; mp 38−40 °C; R_f = 0.3 in 10% EtOAc in hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 0.7 Hz, 1H), 7.23 (dd, J = 8.4, 0.7 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 143.52, 138.58, 128.40, 127.71, 125.79, 118.76, 19.56 ($ArCH_3$); HRMS for $C_7H_8NO_2S$ $(M + H)^+$ calcd 170.0276, found 170.0315.

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Supporting Information Available: NMR spectra of **3** and **10** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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