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Tetrahedron Letters 44 (2003) 5483–5485

TETRAHEDRON LETTERS

Synthesis of *N*-substituted 1,2,5-thiadiazolidine and 1,2,6-thiadiazinane 1,1-dioxides from primary amines

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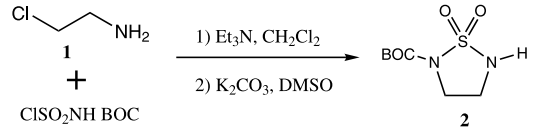
Received 24 April 2003; revised 21 May 2003; accepted 21 May 2003

Abstract—Alkyl and aryl *N*-substituted 1,2,5-thiadiazolidine and 1,2,6-thiadiazinane 1,1-dioxides **6** were synthesized in good yields from the reaction of sulfuryl chloride with 2-chloroethylamine or 3-chloropropylamine hydrochlorides, respectively, followed by treatment with a primary amine and triethylamine, and ring closure with K_2CO_3 in DMSO.

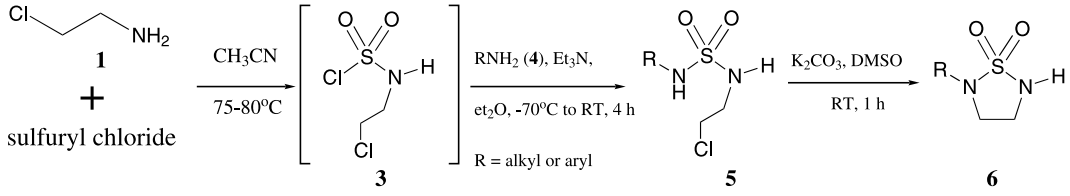
We recently required access to a wide variety of *N*-aryl 1,2,5-thiadiazolidine 1,1-dioxides. A convenient access to five-membered cyclosulfamides starting from chlorosulfonyl isocyanate and chloroethylamines followed by 5-*exo*-*tet* closure with base has been reported (Scheme 1).[1] *N*-Aryl cyclosulfamides were not reported, although they may be available by this route if the requisite *N*-aryl nitrogen mustards or *N*-aryl glycine esters were available. Older methods are not general and the reaction conditions are usually harsh and yields are low.[2]

We envisioned that an attractive approach to a general synthesis of the title compounds would involve the reaction of mono(chloroalkyl)sulfamyl chlorides with aryl amines followed by ring closure of the resulting chloroalkyl sulfamide, vida supra. We report herein a versatile synthesis of five- and six-membered *N*-alkyl and *N*-aryl cyclosulfamides from readily available primary amines.



Scheme 1.

Monoalkylsulfamyl chlorides have been reported to be prepared from primary alkylamine hydrochlorides and a large excess of sulfuryl chloride.[3] We found that when 2-chloroethylamine hydrochloride or 3-chloropropylamine hydrochloride were heated at 75–80°C for about 18 h with 6 equiv. of sulfuryl chloride in acetonitrile the corresponding mono(chloroalkyl)sulfamyl chlorides **3** were obtained (Scheme 2). Concentration in vacuo and extraction with diethyl ether separated the product **3** from any unreacted amine hydrochloride. This ether solution was added dropwise to a solution of 0.6 equiv. of a primary amine **4** and 2 equiv. of triethylamine in diethyl ether at −70°C. The mixture was stirred at room temperature for 4 h, then washed with water and dried to give the *N*-alkyl or *N*-aryl (chloroalkyl)sulfamides **5**.



Scheme 2.

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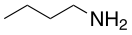
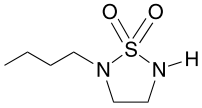
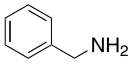
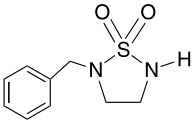
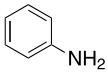
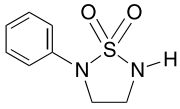
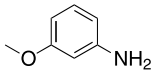
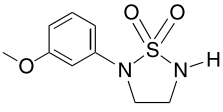
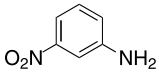
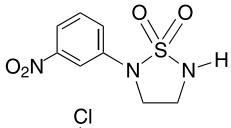
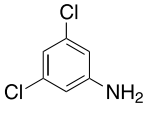
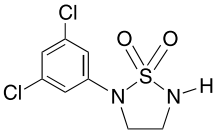
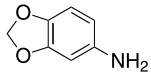
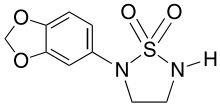
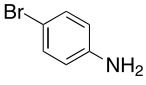
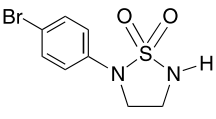
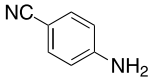
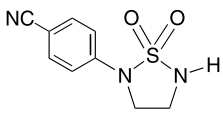
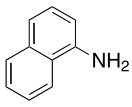
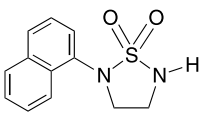
doi:10.1016/S0040-4039(03)01269-3

Treatment of **5** with 1 equiv. of potassium carbonate in DMSO gave the final products **6**. Isolated yields of 22–67% for the thiadiazolidine 1,1-dioxides over the three steps (Table 1) were obtained.

In the first step, lower yields are obtained with less than 5 equivalents of sulfuryl chloride, when the reaction is conducted at 65°C, or if solvents other then acetonitrile are used. The volatiles were removed by rotary evaporation and no attempt was made to further purify or characterize the intermediate monoalkylsulfamyl chlorides, which were used immediately in the next step. Diethyl ether is the preferred solvent in the formation of the sulfamides and other than the aqueous workup

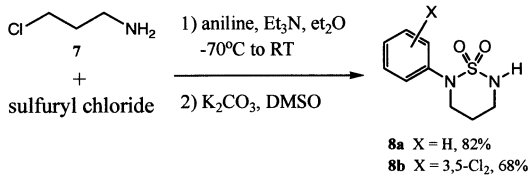
Table 1. The synthesis of 1,2,5-thiadiazolidine 1,1-dioxides[a]

Entry	Amine (**4**)	Product[b] (**6**)	Yield (%)[c]
a			41
b			45
c			56
d			26
e			44
f			45
g			22
h			64
i			32
j			67

[a] The reaction was carried out following the general procedure in the text.

[b] All products were fully characterized by ^{1}H NMR, LC/MS, and CHN.

[c] Isolated yields after flash chromatography and crystallization.



Scheme 3.

no further purification was necessary. The resulting product **5** was characterized by LC/MS and was generally quite clean. The ring closure of **5** to **6** may be accomplished with triethylamine in acetonitrile, although the formation of the cyclosulfamide is slower and yields are somewhat diminished. The final product was purified by flash chromatography.

In addition, 1,2,6-thiadiazinanes may be prepared by this method in similar yields (Scheme 3).[4]

In conclusion, we have developed a simple, efficient synthesis of *N*-alkyl or *N*-aryl 1,2,5-thiadiazolidine and 1,2,6-thiadiazinane 1,1-dioxides from readily available chloroalkylamines, sulfuryl chloride, and primary alkyl or aryl amines.

References

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3. Hansen, N. C. *Acta. Chem. Scand.* **1963**, *17*, 2141.
4. Selected data: **2-phenyl-1,2,5-thiadiazolidine 1,1-dioxide**, **4c**: mp 128–129°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 2H), 7.24 (m, 2H), 7.15 (t, $J=6.0$ Hz, 1H), 4.57 (bs, 1H), 3.93 (t, $J=5.3$ Hz, 2H), 3.71 (m, 2H); $C_8H_{10}N_2O_2S$, calcd C, 48.57; H, 5.08; N, 14.13. Found: C, 48.47; H, 5.11; N, 14.13. **2-phenyl-1,2,6-thiadiazinane 1,1-dioxide**, **8a**: mp 154-155°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.2–7.4 (m, 5H), 4.37 (t, $J=6.0$ Hz, 1H), 3.76 (t, $J=6.3$ Hz, 2H), 3.6–3.7 (m, 2H), 1.97 (m, 2H); $C_9H_{12}N_2O_2S$, calcd C, 50.93; H, 5.70; N, 13.20. Found: C, 50.96; H, 5.77; N, 13.20.