α-Sulfamidoalkylation Reaction: Synthesis of 6,13-Sulfonodibenzo-[c,h][1,6]-diazecines

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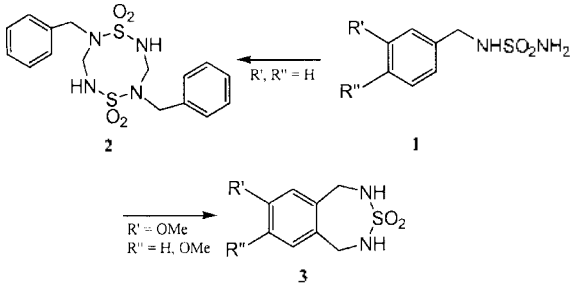
Received November 6, 2001

Keywords : Sulfamide, α-Sulfamidoalkylation reaction.

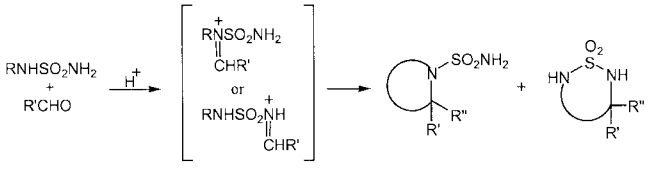
In recent years an increasing number of articles has appeared describing the synthesis, properties, and biological activities of cyclic sulfamides.[1] These compounds are the sulfonyl analogues of ureas. Two general, acid-mediated procedures have been reported for the preparation of this ring system. The first entails the reaction of a sulfamides with a 1,3-disubstituted compound (*i.e.*, dicarbonyl reagent, diacid, or diester).[2] The second reaction requires the treatment of sulfamides with two equivalents of carbonyl compound containing an acidic α-hydrogen.[3]

Previously, we have demonstrated that intra- and intermolecular α-sulfamidoalkylation transformations proceeding through the intermediacy of an iminium ion provide an expeditious route for the preparation of cyclic sulfamides (Scheme 1).[4] α-Sulfamidoalkylation reaction of benzylsulfamide **1** with formaldehyde (36% in H_2O) and water in acid gave intermolecular cyclized product **2**, but 3-methoxy- and 3,4-dimethoxybenzylsulfamide afforded intramolecular α-sulfamidoalkylation product **3** (eq.1).[5]

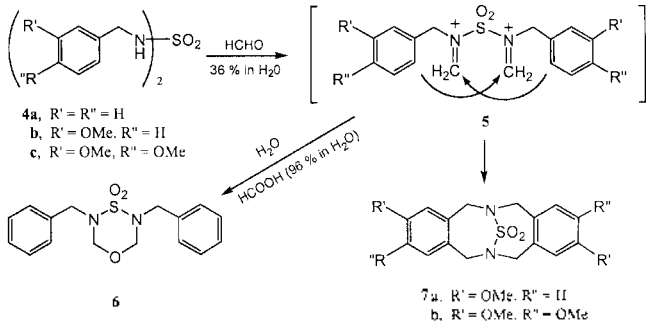


2 **1** **3** (1)

In the present study, we report on the α-sulfamidoalkylation reaction of *N,N*-dibenzylsulfamides **4** with formaldehyde in formic acid for the generation of sulfamides of novel structures (Scheme 2). The starting sulfamides **4** were



Scheme 1



Scheme 2

prepared according to established synthetic protocols.[6] Iminium ion **5** formation for the generation of products was accomplished by treatment of dibenzylsulfamides **4** with formaldehyde (36% in H_2O) in formic acid (96% in H_2O) at room temperature.

Reaction of *N,N*-dibenzylsulfamide **4a** in this protocol furnished the 1,4,2,6-thioxodiazine **6** in 85% yield. Formation of **6** is believed to proceed by the stepwise pathway depicted in Scheme 2. Compound **6** has been assigned as 1,4,2,6-thioxodiazine on the basis of the observed ^1H and ^{13}C NMR spectral data coupled with elemental analysis. Distinctive signals were observed in the ^1H NMR spectra at δ 4.55 and 4.86 ppm as a singlet, and in the ^{13}C NMR spectra

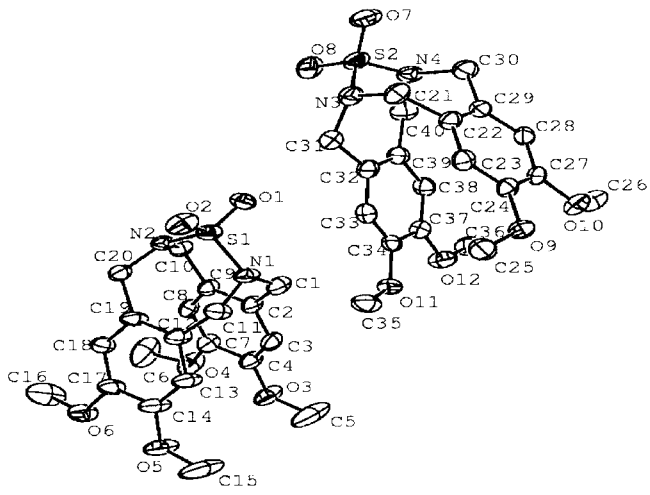


Figure 1. An ORTEP drawing of compound **7b** with atomic numbering scheme.

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Table 1. Crystal data and structure refinement for **7b**

Empirical formula	$C_{40}H_{48}N_4O_{12}S_2$
Formula weight	840.94
Temperature	293(2) K
Wavelength	0.71070 Å
Crystal system, space group	Triclinic, P-1
Unit cell dimensions	a = 10.850(2) Å α = 103.709(9)°
	b = 11.2382(12) Å β = 97.273(10)°
	c = 17.033(2) Å γ = 99.199(11)°
Volume	1962.3(4) Å^3
Z, Calculated density	2, 1.423 Mg/m^3
μ	0.206 mm^{-1}
F(000)	888
Crystal size	0.35 × 0.45 × 0.50 mm
θ range for data collection	1.25 to 25.97°
h, k, l collected	0<=h<=13, -13<=k<=13, -20<=l<=20
Reflections collected/unique	8133 / 7702 [R(int) = 0.0575]
Completeness to 2θ = 52.28	Full-matrix least-squares on F^2
Data/restraints/parameters	7702 / 0 / 540
GOF	1.729
Final R indices [I>2σ (I)]	$^aR_1$ = 0.1253, $^bwR_2$ = 0.2863
R indices (all data)	$^aR_1$ = 0.2210, $^bwR_2$ = 0.3208
Largest diff. peak and hole	0.921 and -1.399 e. Å^{-3}

$^aR_1 = \Sigma||F_o|-|F_c||$ (based on reflections with $F_o^2 \geq 2\sigma F^2$), $^bwR_2 = [\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$; $w = 1/[\sigma^2(F_o^2)+(0.095P)^2]$; $P = [\max(F_o^2, 0)+2F_c^2]/3$(also with $F_o^2 \geq 2\sigma F^2$)

at δ 51.35 and 80.78 ppm for two methylene groups of **6**. Use of the electron-rich benzylsulfamide **4b** and **4c** in place of **4a** gave the double intramolecular α-sulfamidoalkylation products **7a** and **7b** in 45% and 67%, respectively. Analysis of **7b** by X-ray crystallography confirmed the 6,13-sulfonodibenzo-[c,h][1,6]-diazecine ring structure. ORTEP view of **7b** is presented in Figure 1. The triclinic unit cell contains two parts of independent molecules. In the ^{1}H NMR spectra for **7**, two diagnostic signals were noted for the diastereotopic methylene protons at δ 3.94-4.02 and 5.20-5.24 ppm as doublets.

Key signals for methylene carbons detected in the ^{13}C NMR spectra for **7** included the resonances at δ 55.2 and 54.9 ppm. Compounds **6** and **7** exhibited characteristic absorption bands in the infrared spectrum at 1110-1170 and 1340-1390 cm^{-1} for sulfonyl group.[7]

In conclusion, we have elucidated an α-sulfamidoalkylation transformation of the electron-rich benzylsulfamide **4b** and **4c** with formaldehyde, which forms the 6,13-sulfonodibenzo-[c,h][1.6]-diazecine ring structure.

Experimental Section

General Methods. Infrared spectra were obtained on a JASCO FT/IR-5300 spectro-photometer and NMR spectra were recorded on JEOL (500 MHz) FT NMR spectrometer. Chemical shifts (δ) are given in ppm relative to TMS. Reagents and solvents were used without further purification.

General Procedure for α-Sulfamidoalkylation Transformation of *N,N*-Dibenzyl-sulfamide 4 with Formaldehyde. A formic acid (96% in H_2O, 10 mL) solution of sulfamides **4** (10 mmol) and formaldehyde (36.5% in H_2O, 33 mmol) was stirred for 24 hr at room temperature, and then the solution was quenched with excess water (50 mL). The solid that precipitated was filtered and then washed with water to give the desired products **6** and **7**.

***N,N'*-Dibenzyl-1,4,2,6-thioxodiazine 1,1-Dioxide (6)**. Beginning with *N,N'*-dibenzylsulfamide (**4a**). **6** was obtained in 85% yield (2.70 g): mp 119-122 °C; IR (KBr) 1167.04, 1363.91 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.55 (s, 4H), 4.86 (s, 4H), 7.25-7.38 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 51.35, 80.78, 128.29, 128.78, 128.90, 135.26.

Anal. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.36; H, 5.70; N, 8.80. Found: C, 60.29; H, 5.72; N, 8.83.

5,7,12,14-Tetrahydro-6,13-sulfonodi(3-methoxybenzo)-[c,h][1,6]-diazecine (7a). Beginning with *N,N'*-di(3-methoxybenzyl)sulfamide (**4b**). **7a** was obtained in 45% yield (1.62 g): mp 198-200 °C; IR (KBr) 1163.15, 1363.79 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.66 (s, 6H), 3.96 (d, 2H, J = 16.5 Hz), 4.01 (d, 2H, J = 16.5 Hz), 5.21 (d, 2H, J = 16.5 Hz), 5.22 (d, 2H, J = 16.5 Hz), 6.33-6.76 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 54.6, 55.2, 55.3, 111.4, 116.3, 130.2, 131.2, 139.7, 158.6.

5,7,12,14-Tetrahydro-6,13-sulfonodi(3,4-dimethoxybenzo)-[c,h][1,6]-diazecine (7b). Beginning with *N,N'*-di(3,4-dimethoxybenzyl)sulfamide (**4c**), **7b** was obtained in 67% yield (2.82 g): mp 240-242 °C; IR (KBr) 1163.18, 1363.80 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 12H), 3.95 (d, 4H, J = 16.5 Hz), 5.22 (d, 4H, J = 16.5 Hz), 6.34 (s, 4H); ^{13}C NMR ($CDCl_3$) δ 54.9, 56.2, 114.1, 130.9, 147.5.

X-ray Analysis of 7b. Details of the crystal data and summary of intensity data collection parameters for **7b** are given in Table 1. Crystal was grown from chloroform solution stored at room temperature. Crystal was mounted on glass fibers in random orientations, and the data were collected on a Enraf-Nonius CAD4 diffractometer equipped with graphite-monochromated Mo-K$_\alpha$ radiation (λ = 0.71073

Table 2. Selected bond lengths [Å] and bond angles [°] for **7b**

Bond lengths			
S(1)-O(2)	1.401(6)	S(1)-O(1)	1.409(6)
S(1)-N(2)	1.637(5)	S(1)-N(1)	1.643(6)
N(1)-C(1)	1.443(10)	N(1)-C(11)	1.492(10)
N(2)-C(10)	1.423(9)	N(2)-C(20)	1.488(9)
C(1)-C(2)	1.520(9)	C(2)-C(3)	1.389(10)
C(11)-C(12)	1.516(9)	C(12)-C(13)	1.396(10)
C(12)-C(19)	1.406(9)	C(13)-C(14)	1.385(10)
C(18)-C(19)	1.396(9)	C(19)-C(20)	1.509(9)
Bond angles			
O(2)-S(1)-O(1)	119.3(3)	O(2)-S(1)-N(2)	107.7(3)
O(1)-S(1)-N(2)	107.3(3)	O(2)-S(1)-N(1)	108.0(4)
O(1)-S(1)-N(1)	106.9(3)	N(2)-S(1)-N(1)	107.1(3)
C(1)-N(1)-C(11)	117.6(6)	C(1)-N(1)-S(1)	115.4(5)
C(11)-N(1)-S(1)	113.6(5)	C(10)-N(2)-C(20)	115.8(5)
C(10)-N(2)-S(1)	116.8(5)	C(20)-N(2)-S(1)	114.8(5)
N(1)-C(1)-C(2)	119.1(6)	C(9)-C(2)-C(1)	123.7(6)
C(2)-C(9)-C(10)	124.1(6)	N(2)-C(10)-C(9)	119.0(5)
N(1)-C(11)-C(12)	117.0(6)	C(19)-C(12)-C(11)	123.7(6)
C(12)-C(19)-C(20)	124.3(6)	N(2)-C(20)-C(19)	117.4(6)

Å) at room temperature. Unit cell parameters were determined by using search, center, index, and lest-square routine. Structure was solved by the application of direct methods using the SHELX-86 program[8] and least-squares refinement using SHELEX-97.[9] Anisotropic thermal parameters were used for all atoms except hydrogen. All the remaining hydrogen atoms were included in calculated positions. Some selected bond lengths and bond angles are shown in Table 2.

Supplementary material. Tables of full bond distances and bond angles, anisotropic thermal parameters, and atomic coordinates of hydrogen atoms are available from the author C. H. Lee.

Acknowledgment. This paper was supported by Wonkwang University in 2000.

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