Studies of Heterocyclic Compounds. 8. The Synthesis and Some Reactions of 4-Bromoimidazole-5-sulfonyl Derivatives

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The chloride, azide, and amides of 4-bromoimidazole-5-sulfonic acid were prepared by the reaction of the sulfonic acid with phosphorus pentachloride and the treatment of the resulting imidazolesulfonyl chloride with sodium azide and various aromatic and heteroaromatic amines. The sulfonyl azide was further reacted with trisubstituted phosphines, norbornene, indole, and *N*-methylindole to give new compounds of expected biological activity. The infrared and mass spectra of some of the compounds are presented.

Introduction

Organosulfonamides have been of tremendous value since the late 1930s due to their great antibacterial powers; the famous M and B 693 is an example. Some heteroaromatic sulfonamides have been shown to exhibit some antifungal and antibacterial properties (*1*, *2*) and in continuation of our studies on the synthesis, reactions, and antimicrobial properties of heteroaromatic sulfonyl derivatives (*1*, *3*), the 4-bromoimidazole-5-sulfonyl derivatives have been synthesized and the infrared and mass spectra of some of them recorded.

Results and Discussion

The synthesis and reactions of the 4-bromoimidazole-5-sulfonyl chloride (**2**) and its corresponding azide, **3**, are shown in Scheme I, following known procedures, while the properties of the sulfonamides (**5–20**, **27**, **28**) are given in Table I. In the infrared spectra of the compounds, the NH_2 stretching of the 5-imidazolesulfonamide (**5**) is split into two bands located at 3345 and 3270 cm^{-1}, as usually observed for a sulfonamides (*4*), while in the secondary sulfonamides, **7–20**, the SO_2N-H stretching vibrations (associated form) showed in the range 3340–3220 cm^{-1}. The stretching vibration of the sulfonyl group, asymmetric and symmetric, showed, respectively, in the range 1370–1325 and 1170–1115 cm^{-1} in accordance with the literature data (*5*). Generally, these absorptions often exhibit complex spectra probably due to rotational isomerism and/or Fermi resonance. The difference between the asymmetric and symmetric absorptions ranges between 220 and 165 cm^{-1}, the highest differences occurring for the heterocyclic amines. There is no correlation between these absorption differences and the σ parameters and this is not unexpected.

Data for the relative intensities of the major ion fragments, (≥2.9%) for the sulfonyl chloride, **2**, the sulfonyl azide, **3**, and the sulfonamide, **5**, are listed in Table II. The mass spectra of the compounds are dominated by the loss of the Cl, NH_2, and N_3 (major pathway) from the molecular ions, chlorine atom migration from sulfur to carbon in the imidazolesulfonyl chloride, and imidazole-S → imidazole-O rearrangement, all in accordance with the reported fragmentations of simple alkane- and arylsulfonyl chlorides (*6*), aryl sulfones, and several thiophenesulfonyl derivatives (*7*, *8*).

Table I. Experimental Data of the 4-Bromoimidazole-5-sulfonamides[a]

compd no.	X	yield, %	mp, °C	formula
5	NH_2	59	245–247	
6	$NHNH_2$	48		$C_3H_5BrN_4O_2S$
7	NHPh	52	197–200	$C_9H_8BrN_3O_2S$
8	$NPh(CH_3)$	65	193–195	$C_{10}H_{10}BrN_3O_2S$
9	NHPh-4′-Cl	75	210–213	$C_9H_7BrClN_3O_2S$
10	NHPh-2′-OCH_3	62	172–174	$C_{10}H_{10}BrN_3O_3S$
11	NHPh-4′-OCH_3	55	215–217	$C_{10}H_{10}BrN_3O_3S$
12	NHPh-3′-CH_3	68	224–227	$C_{10}H_{10}BrN_3O_2S$
13	NHPh-4′-CH_3	70	209–210	$C_{10}H_{10}BrN_3O_2S$
14	NHPh-3′-NO_2	58	207–210	$C_9H_7BrN_4O_4S$
15	NHPh-4′-NO_2	66	235–238	$C_9H_7BrN_4O_4S$
16	$NHCH_2Ph$	80	126–128	$C_{10}H_{10}BrN_3O_2S$
17	NHPh-4′-Br	65	220–223	$C_9H_7Br_2N_3O_2S$
18	NH-pyridyl-α	70	230–232	$C_8H_7BrN_4O_2S$
19	NH-pyridyl-β, α-Cl	68	210–213	$C_8H_6BrClN_4O_2S$
20	NH-isoquinolyl-4′	65	217–220	$C_{12}H_9BrN_4O_2S$
27	*N*-imidazolyl	40	207–210	$C_6H_5BrN_4O_2S$
28	*N*-indolyl	48	199–203	$C_{11}H_8BrN_3O_2S$

[a] Correct elemental analyses were found. [b] Lit. (*9*) 246–247 °C.

Experiment Section

All melting points were uncorrected. Infrared absorption spectra were measured with a Perkin-Elmer 727B spectrometer. Mass spectra were obtained on an AE1 MS12 mass spectrometer at 70 eV. Microanalyses were performed by Mr. O. Aladegbami, Department of Chemistry, University of Ife, Nigeria.

4-Bromo-5-imidazolesulfonyl Chloride (2). A mixture of 4-bromoimidazole (10.0 g, 68 mol), chlorosulfonic acid (14.0 mL), and thionyl chloride (5.0 mL) was heated at 200 °C for 2 h and then poured into crushed ice when the 4-bromo-5-imidazolesulfonyl chloride precipitated out. This was filtered, dried, and recrystallized from chloroform–petroleum ether to give 11.6 g (70%) of **2**: mp 190–192 °C. [lit. (*9*), 186–188 °C).

4-Bromo-5-imidazolesulfonyl Azide (3). Compound **2** (2.0 g, 8.1 mol) and sodium azide (0.7 g, 11 mmol) were stirred in acetone–water (95/5, v/v) at room temperature for 6 h. Solvent was removed and the resulting solid filtered, washed with water, dried, and recrystallized from petroleum ether to give 1.6 g of **3** (80%): mp 180–182 °C. (Anal. Found: C, 14.28; H, 0.90, N, 27.70. $C_3H_2BrN_5O_2S$ requires: C, 14.29; H, 0.80; N, 27.78.)

4-Bromo-5-imidazolesulfonamide (5). This compound was prepared from compound **2** and excess ammonium hydroxide. Property, as in Table I.

4-Bromo-5-imidazolesulfonamides (6–20). The imidazolesulfonamides (**6–20**) were prepared by refluxing the sulfonyl

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Scheme I. The Reactions of 4-Bromoimidazole-5-sulfonyl Chloride

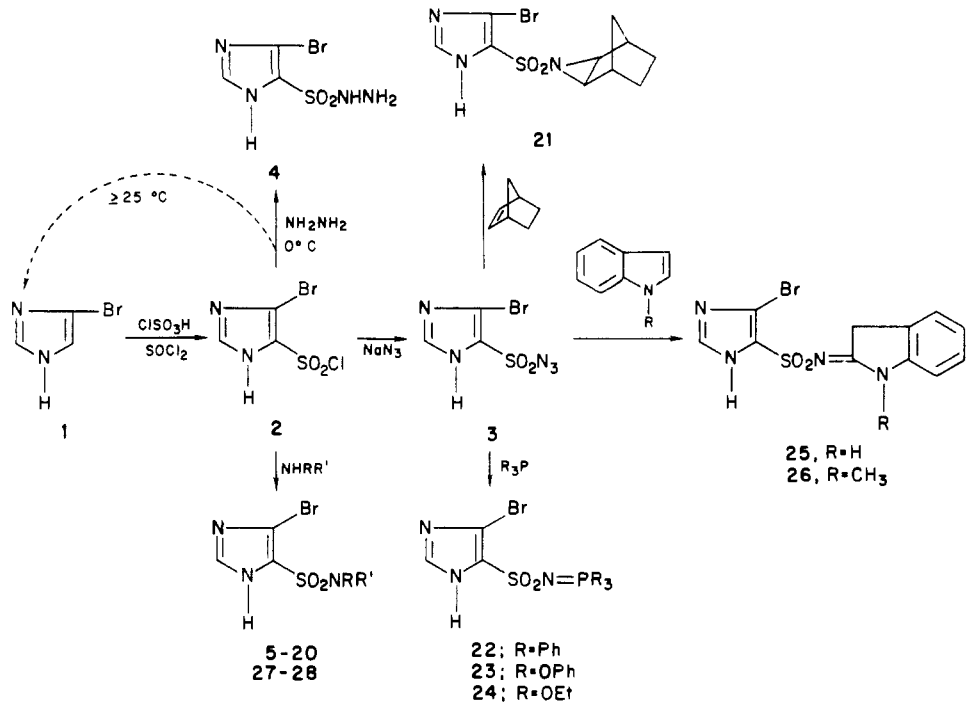

Table II. Mass Spectra of Three of the 4-Bromoimidazole-5-sulfonyl Derivatives at 70 eV[a]

m/e[a]	X = Cl	X = NH_2	X = N_3
36	100		
38	39.2	19.7	16.5
39	10.8	23.5	22.6
40	5.9	6.1	6.5
48	25.5	58.6	56.5
52		51.8	53.5
64	41.6	100	100
80		15.1	15.7
82		15.1	15.4
91	8.6	21.6	15.2
93	8.2	21.2	14.9
106	5.9	16.8	16.1
108	5.7	16.6	15.9
118	15.7	35.8	30.4
120	15.5	34.7	30.3
145	6.5	17.5	13.0
146	6.5		
147	6.5	15.3	12.8
148	6.1		
153	3.9		
155	4.9		
161	2.9	10.2	8.7
163	2.9	10.0	8.7
180	4.3		
182	5.9		
210	27.5	48.1	52.2
212	27.1	47.3	51.1
225			8.6
226		34.4 $(M)^+$	
227			8.7
228		33.8	
245	6.9 $(M)^+$		
247	8.8		
249	3.9		
252			13.9 $(M)^+$
254			8.7

[a] Parent peak is denoted by $(M)^+$. All peaks ≥2.9% of base peak are included.

chloride (**2**) with the appropriate amine in acetonitrile for about 3 h. The solvent was removed and the residue washed 3 times with warm water and then recrystallized from aqueous ethanol. Their physical properties are given in Table I.

Reactions of 4-Bromoimidazole-5-sulfonyl Azide (3). (I) With Norbornene. The sulfonyl azide (1.0 g, 4 mmol) was reacted with norbornene (1 M equiv) in ether under reflux for 10 h. It was recrystallized from ethanol to give 0.5 g of **21** (40%): mp 199–201 °C (dec). (Anal. Found: C, 37.62; H, 3.71; N, 13.01. $C_{10}H_{12}BrN_3O_2S$ requires: C, 37.75; H, 3.80; N, 13.21.)

(II) With Indole and 1-Methylindole. (a) Indole (1.0 g, 8.5 mmol) and 4-bromo-5-imidazolesulfonyl azide (2.2 g, 8.5 mmol) in acetonitrile (1 mL) was heated gently for 36 h. The solvent was removed and the solid left recrystallized from methanol–chloroform (2/1) to give compound **25** (1.6 g, 55%): mp 252–254 °C (dec). (Anal. Found: C, 38.64; H, 2.65; N, 16.51. $C_{11}H_9BrN_4O_2S$ requires: C, 38.72; H, 2.66; N, 16.42.) IR ν_{max} 1580 (C=NSO_2) cm^{-1} (*7*). (b) Compound **26** was similarly prepared in 65% yield: mp 229–230 °C (dec). IR ν_{max} 1571 (C=NSO_2) cm^{-1} (*7*). (Anal. Found: H 3.12; N, 15.80. $C_{12}H_{11}BrN_4O_2S$ requires: C, 40.58; H, 3.12, N, 15.77.)

(III) With Trisubstituted Phosphines. (a) 4-Bromoimidazole-5-sulfonyl azide (1.0 g 4 mmol) and triphenylphosphine (1.0 g, 1 M equiv) in dry tetrahydrofuran was boiled for 5 h. The solvent was removed and the residue recrystallized from ethyl acetate to give 4-bromoimidazole-5-sulfonyliminophosphorane (**22**) (1.1 g, 60%): mp 230–234 °C (dec). Anal. Found: C, 51.67; H, 3.58; N, 8.39. $C_{21}H_{17}BrN_3O_2PS$ requires: C, 51.86; H, 3.52; N, 8.64.

(b) 4-Bromoimidazole-5-sulfonyl(triphenoxy)iminophosphorane (**23**) was prepared as in (a) in 55% yield: mp 210–213 °C (dec). (Anal. Found: C, 47.13; H, 3.11; N, 7.60. $C_{21}H_{17}BrN_3O_5PS$ requires: C, 47.21; H, 3.21, N, 7.86.)

(c) 4-Bromoimidazole-5-sulfonyl(triethoxy)iminophosphorane (**24**) was obtained as an oil. (Anal. Found: C, 27.51; H, 4.38; N, 10.69. $C_9H_{17}BrN_3O_5PS$ requires; C, 27.70; H, 4.39; N, 10.77.)

Registry No. **1**, 2302-25-2; **2**, 99903-04-5; **3**, 99903-05-6; **5**, 34238-24-9; **6**, 99903-06-7; **7**, 99903-07-8; **8**, 99903-08-9; **9**, 99903-09-0; **10**, 99903-10-3; **11**, 104-94-9; **12**, 99903-11-4; **13**, 99903-12-5; **14**, 99903-13-6; **15**, 99903-14-7; **18**, 99903-15-8; **17**, 99903-16-9; **18**, 99922-97-1; **19**, 99903-17-0; **20**, 99903-18-1; **21**, 99903-19-2; **22**, 99903-20-5; **23**, 99903-21-6; **24**, 99903-22-7; **25**, 99903-23-8; **26**, 99903-24-9; **27**, 99903-25-0; **28**, 99903-26-1; $HONH_4$, 1336-21-6; H_2NNH_2, 302-01-2; H_2NPh, 62-53-3; H_3CNHPh, 100-61-8; 4-NH_2PhCl, 106-47-8; 2-NH_2PhOCH_3,

90-04-0; 4-NH_2PhOCH_3, 104-94-9; 3-NH_2PhCH_3, 108-44-1; 4-NH_2PhCH_3, 106-49-0; 3-NH_2PhNO_2, 99-09-2; 4-NH_2PhNO_2, 100-01-6; H_2NCH_2Ph, 100-46-9; 4-NH_2PhBr, 106-40-1; Ph_3P, 603-35-0; $(PhO)_3P$, 101-02-0; $(EtO)_3P$, 122-52-1; 2-aminopyridine, 504-29-0; 2-chloro-3-aminopyridine, 6298-19-7; 4-aminoisoquinoline, 23687-25-4; imidazole, 51741-29-8; 1-aminoindole, 56480-48-9; norbornene, 498-66-8; indole, 120-72-9; 1-methylindole, 603-76-9.

Literature Cited

(1) Part 7: Fagun, Y. O.; Kolawole, D. O.; Obafemi, C. A. Submitted for publication in *Eur. J. Med. Chem.*
(2) Carter, G. A.; Dawson, G. W.; Garraway, J. L. *Pestic. Sci.* **1975**, *6*, 43.
(3) Obafemi, C. A. *Phosphorus Sulfur* **1982**, *12*, 189.
(4) Flett, M. ST. C. *Spectrochim. Acta* **1982**, *18*, 1537.
(5) Lutski, A. E.; Ishchenko, I. K. *Zh. Obshch. Khim.* **1968**, *38*, 1618.
(6) Daries, P. P.; Grossert, J. S.; Langler, R. F.; Mantle, W. S. *Org. Mass. Spectrom.* **1977**, *12*, 659.
(7) Obafemi, C. A. *Phosphorus Sulfur* **1982**, *13*, 119.
(8) Khodair, A. I.; Swelim, A. A.; Abdel-Wahab, A. A. *Phosphorus Sulfur* **1976**, *2*, 173 and references therein.
(9) Bennet, L. L.; Baker, H. T. *J. Am. Chem. Soc.* **1957**, *79*, 2188.

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Reaction of Azomethine *N*-Oxides. 6. Spectroscopic Study of Lewis Acid Catalyzed Reactions of Nitrones with *N*-Phenylmaleimide

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The effect of the Lewis acid $AlCl_3$ on the reactivity and stereoselectivity of the 1,3-dipolar cycloaddition reactions of some azomethine *N*-oxides with *N*-phenylmaleimide in benzene at room temperature has been spectroscopically investigated. Decrease of the reactivity and increase of the stereoselectivity of the cycloaddition reactions are observed.

The effect of Lewis acids on the reactivity, regioselectivity, and stereoselectivity of Diels-Alder reactions have been thoroughly investigated. (*1-9*) In general, large rate accelerations (*1-3*) and greatly increased regioselectivity (*4*, *7*) and stereoselectivity (*8*, *9*) are observed.

Frontier orbital theory also predicts that Lewis acids like BF_3 and $AlCl_3$ will affect rates and selectivities in 1,3-dipolar cycloadditions. Lewis acids catalyzed 1,3-dipolar cycloaddtions of both diphenylnitrilimine (*10*) and benzonitrile oxide (*11*) have been studied. The two examples undergo rapid 1,3-dipolar cycloadditions in the presence of the Lewis acids $AlCl_3$ and BF_3, respectively. In conjunction with our interest in the reactions of azomethine *N*-oxides with electron-deficient compounds, (*12-17*) we now wish to report the spectroscopic study of the effect of the Lewis acid $AlCl_3$ on the reactivity and stereoselectivity of the 1,3-dipolar cycloaddition reactions of the azomethine *N*-oxides (nitrones) (**1a-e**) with the symmetrical electron-poor dipolarophile **2** in benzene as a solvent. The aldonitrones (**1a-e**) react with the *N*-phenylmaleimide (**2**) in dry benzene at room temperature to give two stereoisomers, the *cis*-isoxazolidines (**3a-e**) and the *trans*-isoxazolidines (**4a-e**) (Figure 1). The major adducts formed were the thermodynamically more stable trans adducts (**4a-e**) (51-69%). The configuration of the isoxazolidines were determined on the basis of the magnitude of the coupling constant between H_3 and H_4 of the isoxazolidine ring (Figure 1); the larger values (J = 7-9 Hz) were assigned to the cis coupling constants H_3 and H_4 of **3a-e**, and the smaller values (J = 1-2 Hz) to the trans coupling constants between the corresponding protons of **4a-e** (*18*, *19*) (Table I). On the other hand, heating of the cis isomers **3a-e** in *p*-xylene gave the thermodynamically more stable trans isomers **4a-e** in very good yield (100%).

However, in the presence of an $^1/_{10}$ M ratio of $AlCl_3$, the reactions of the nitrones **1a-e** with **2**, under the same conditions, slow down and the cis stereoisomer ratio was increased (3-17%). The ratio of the cis and trans products were determined from the integration of the resonance of the H_3 proton nuclear magnetic resonance spectra of the reaction mixtures.

The decrease of the reactivity of the reactions has been attributed to the complexation between the Lewis acid $AlCl_3$ and the nitrones **1a-e**. This assumption has been confirmed by observation of the UV spectra of the mixtures of each of the nitrones **1a**, **1d**, as well as **1e** and $AlCl_3$ in benzene (Table II). A new broad band in the UV spectrum, 317-365 nm, is observed immediately on mixing equimolar solutions of the Lewis acid $AlCl_3$ with each of the nitrones **1a**, **1d**, and **1e** in benzene (Table II). These absorptions were ascribed to the complex formation. However, the reaction of the nitrone **1c** with **2**, in the presence of $^1/_{10}$ M ratio of $AlCl_3$, in benzene led to formation of more trans isomer. This behavior may be ascribed to the difficulty of the complexation of the nitrone **1c** with the Lewis acid $AlCl_3$.

Attempts to study the effect of an equimolar ratio of $AlCl_3$ to both reactants **1a-e** and **2** on the reactions failed because of the difficulty of the solubility of aluminum chloride in benzene.

Experimental Section

Melting points are uncorrected. IR spectra were taken on a Shimadzu-408 spectrophotometer as KBr disk. UV-vis spectra were recorded on a Beckman Model 26 recording spectrophotometer. ^1H NMR spectra were measured in $CDCl_3$ or CD_3SOCD_3 as solvents by using Varian XL 100 (100 MHz) and EM 390 (90 MHz) with Me_4Si as internal standard. Elemental analyses were performed by the microanalytical Unit of Cairo University. The nitrones **1a-e** (*20*) were prepared according to literature procedures.

General Procedure of the Cycloaddition of the Nitrones (1a-e) and N-Phenylmaleimide (2). A solution of 1 mmol of nitrone (**1a-e**) in 3 mL of dry benzene was added to a solution of 173 mg (1 mmol) of *N*-phenylmaleimide in 2 mL of dry benzene. The reaction mixture was stirred at room temperature until the thin-layer chromatogram (TLC) showed the disappearance of the starting compounds. The solvent was then removed at room temperature with a rotary evaporator. The NMR spectrum of the residue showed two cycloaddition adducts in different ratios (Table I). The isomers were separated by

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