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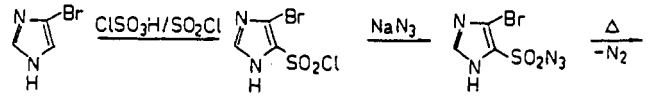
Synthesis and Some Reactions of 4-Bromoimidazole-5-sulfonyl Derivatives. A Reinvestigation

Heinz Kropf* and Felix Wöhrle

Institute of Organic Chemistry, University of Hamburg, Martin-Luther-King Platz 6, D 2000 Hamburg 13, FRG

The synthesis of 4-bromo-5-imidazolesulfonyl azide and 3-(4-bromo-5-imidazolesulfonyl)-3-azatricyclo[3.2.1.0^{2,4}]octane was reinvestigated.

In connection with our work on scission reactions of small ring heteracycloalkanes with alkyl hydroperoxides (*1–3*) we were interested in strained aziridines with electron-withdrawing substituents on the nitrogen atom as educts. So we tried to synthesize 3-(4-bromo-5-imidazolesulfonyl)-3-azatricyclo-[3.2.1.0^{2,4}]octane following a procedure which has been published recently by Obafemi and Kolawole (*4*).



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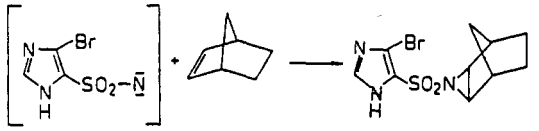

3

4-Bromoimidazole reacted with chlorosulfonic acid/thionyl chloride to produce **1** in good yields; mp 186–188 °C (decomp). This is in accordance with Bennet and Baker (*5*), who give exactly the same data. Obafemi and Kolawole claim to have observed a melting point of 190–192 °C (no mention of decomposition).

Reaction of **1** with sodium azide yielded **2** as described by Obafemi and Kolawole. In contrast to the physical data given by them, the compound evolved nitrogen at about 140 °C (depending on the rate of heating), slowly darkened, and the black residue finally melted at 178–181 °C (lit. (*4*) mp 180–181 °C, no reference to decomposition). Following the procedure given by Obafemi and Kolawole (*4*), we were unable to reproduce the synthesis of the desired aziridine **3**. Even with considerably prolonged reaction times (40 h instead of the suggested 10 h), refluxing in diethyl ether resulted only in the quantitative recovery of unchanged **2**. Nevertheless we successfully synthesized **3** refluxing the educts after 48 h in dichloromethane/methyl *tert*-butyl ether. Our product had a mp of 163–165 °C (from ethanol); lit. (*4*) 199–201 °C (decomp).

Table I

	1	2	3
mol weight calcd	245.48	252.05	226.05
expected parent peaks	244, 246, 248	251, 253	225, 227
expected rel intensity	77:100:25	100:98	100:98
parent peak obsd in this work	244, 246, 248	251, 253	225, 227
relative intensity	75:100:25	100:93	95:100
parent peak obsd by Obafemi and Kolawole	245, 247, 249	252, 254	226, 228
rel intensity	78:100:44	100:63	100:98

The constitution of **3** was confirmed by elemental analysis and ^{1}H NMR and ^{13}C NMR spectra. Reference *4* does not give any spectroscopic data. In doubt about the results reported by Obafemi and Kolawole we scrutinized the mass spectra of **1**, **2**, and the corresponding sulfonamide **4** above all with respect to the unusual parent peaks found there (Table I). A similar difference is observed for the peaks M^+–X (**1**: X = Cl; **2**: X = N_3; **4**: X = NH_2). That means, e.g., we found *m/e* 209, 211 (99:100); ref *4* gives *m/e* 210, 212 (100:99). But these observations are not due to a general shift, because distinctive peaks with smaller *m/e* values occur in both spectra (*m/e* 48 $SO^{\bullet+}$; *m/e* 64 $SO_2^{\bullet+}$; 161, 163 (1:1) M^+–Cl^+, –$SO^{\bullet+}$). For complete fragmentation schemes see ref *6*.

Experimental Section

All melting points were uncorrected. Infrared absorption spectra were measured with a Beckmann Acculab 4 spectrometer. Mass spectra were obtained on a Finnegan MAT 311 A mass spectrometer at 70 eV. ^{1}H (270 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on Bruker WH270 and WM400 spectrometers, respectively (all values in ppm). Microanalyses were performed by the microanalytical laboratory of the Institute of Organic Chemistry, University of Hamburg, on a Carlo Erba C-H-N-Analyzer 1106.

***4*-Bromo-5-imidazolesulfonyl Chloride (*1*).** Chlorosulfonic acid (8 g, 68.66 mmol, 14 mL) was cooled to –10 °C under a stream of nitrogen. 4-Bromoimidazole (10 g, 68 mmol) was added in small portions. To this reaction mixture was added dropwise thionyl chloride (3 g, 25.63 mmol, 5 mL) (not phosphorus pentachloride, as mentioned in the abstract of ref *4*).

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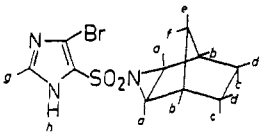
The mixture was heated at 200 °C until vapors of bromine were evolved (ca. 1 h) and then poured on crushed ice whereupon the 4-bromo-5-imidazolesulfonyl chloride precipitated. It was filtered, dried, and recrystallized from acetone/petroleum ether as chloroform/petroleum ether did not work. Yield: 6.8 g (41%) of **1**; mp 186–188 °C (decomp.)

4-Bromo-5-imidazolesulfonyl Azide (2). Compound **1** (2.0 g, 8.1 mmol) and sodium azide (0.7 g, 11 mmol) were stirred in acetone/water (95/5, v/v) at room temperature for 12 h. Solvent was removed and the resulting solid filtered, washed with water, and dried. Yield: 1.9 g of **2** (95.7%); mp 140 °C (evolution of nitrogen), 180–181 °C (decomp.)

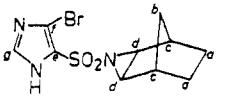
4-Bromo-5-imidazolesulfonamide (4). This compound was prepared from compound **1** and excess ammonium hydroxide as in ref *5*.

3-(4-Bromo-5-imidazolesulfonyl)-3-azatricyclo-[3.2.1.0^{2,4}]octane (3). 4-Bromo-5-imidazolesulfonyl azide (1.0 g, 10.7 mmol) and 2-norbornene (1.0 g, 10.7 mmol) were refluxed in dichloromethane/methyl *tert*-butyl ether (1/2, v/v) for 48 h. Solvent was removed and the resulting solid recrystallized from ethanol to give 450 mg of **3** (39.6%): mp 163–165 °C (Anal. Found: C, 37.75; H, 3.80; Br, 25.01; N, 13.20; S, 10.04. $C_{10}H_{12}BrN_3O_2S$ requires: C, 37.75; H, 3.80; Br, 25.11; N, 13.21; S, 10.08).

^{1}H NMR spectrum (270 MHz, DMSO-d_6, TMS): δ = 0.82 (1 H, d, J = 10.7 Hz, H_f); 1.25 (2 H, d, J = 9.6 Hz, $H_{c,d}$); 1.36 (1 H, d, J = 10.7 Hz, H_e); 1.49 (2 H, d, J = 9.6 Hz, $H_{c,d}$); 2.51 (2 H, s, H_b); 2.98 (2 H, s, H_a); 8.04 (1 H, s, H_g); 14.12 (1 H, bs, H_h).



^{13}C NMR spectrum (100.62 MHz, BB, DMSO-d_6): δ = 24.63 (s, C_a); 27.57 (s, C_b); 35.24 (t, C_c); 41.19 (t, C_d); 112.31 (q, $C_{e,f}$); 125.76 (q, $C_{e,f}$); 138.36 (t, C_g).



Abbreviations used for ^{13}C NMR spectrum: p = primary, s = secondary, t = tertiary, q = quaternary C atom.

Assignment was made by means of a DEPT spectrum.

Registry No. **1**, 99903-04-5; **2**, 99903-05-6; **3**, 115588-67-5; **4**, 34238-24-9; 4-bromoimidazole, 2302-25-2; 2-norbornene, 498-66-8.

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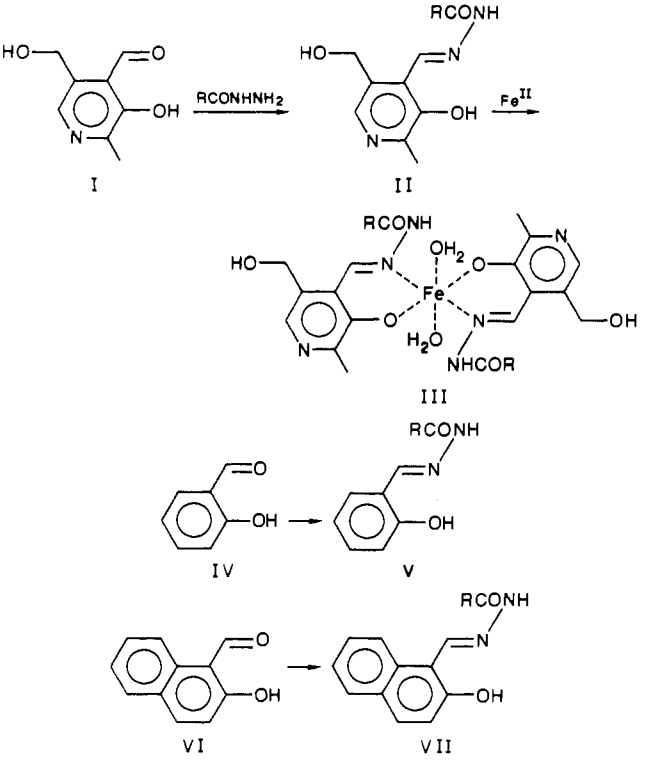
Synthesis of New Acylhydrazones as Iron-Chelating Compounds

John T. Edward,*† Mario Gauthier,† Francis L. Chubb,† and Premysl Ponka‡

Departments of Chemistry and Physiology, McGill University, Montreal, Canada H3A 2K6

Fourteen acylhydrazides have been condensed with three aromatic *o*-hydroxy aldehydes (pyridoxal, salicylaldehyde, and 2-hydroxy-1-naphthaldehyde) to give 42 acylhydrazones, of which 38 are new. These compounds complex iron and have shown varying abilities to promote the movement of iron across biological membranes. Their infrared and nuclear magnetic resonance spectra support the structures assigned to them.

Iron overload, a consequence of long-term transfusion therapy in the disease thalassemia major, may be relieved by oral administration of such iron-chelating compounds as pyridoxal isonicotinoylhydrazone (PIH; II, R = 4-pyridyl) (*1–3*), which forms a complex with Fe^{II} to which the structure III (R = 4-pyridyl) has been assigned (*4*). It complexes also with Fe^{III} (*1*). Although most biological studies have employed PIH, three other hydrazones (II, R = phenyl), (V, R = phenyl), and (V, R = 4-pyridyl) are also effective (*3*). Accordingly, for systematic study of the effect of substituents on biological activity, we have synthesized these and 38 other hydrazones having the general structures II, V, and VII by reaction of the aldehydes I, IV, and VI with 14 acylhydrazides $RCONHNH_2$ (R = methyl, phenyl, *p*-hydroxyphenyl, *p*-methylphenyl, *p*-nitrophenyl, *p*-aminophenyl, *p*-*tert*-butylphenyl, *p*-methoxyphenyl, *m*-chlorophenyl, *m*-fluorophenyl, *m*-bromophenyl, 4-pyridyl, 2-furyl, 2-thienyl).



Ten of the acylhydrazides were commercially available; the other four (*p*-*tert*-butylphenyl, *p*-methoxyphenyl, *m*-chloro-

† Department of Chemistry.
‡ Department of Physiology.

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