Imidazo[1,5-*a*]pyrazines. III. The Preparation and Chemistry of 3-(Phenylthiomethyl)imidazo[1,5-*a*]pyrazine (1,2)

E. Abushanab and A. P. Bindra

Department of Medicinal Chemistry, College of Pharmacy, University of Rhode Island Kingston, Rhode Island 02881

and

L. Goodman

Department of Chemistry, University of Rhode Island, Kingston, Rhode Island 02881

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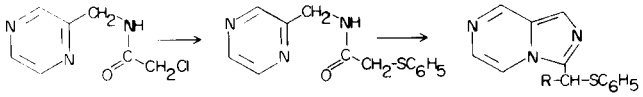
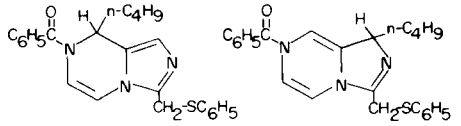
In the course of synthesizing functionally substituted imidazo[1,5-*a*]pyrazines to be investigated as potential anticancer agents, 3-(phenylthiomethyl)imidazo[1,5-*a*]-pyrazine (**3**) was prepared. Some aspects of the chemistry of **3** proved to be unique and these are the subject of this manuscript.

The reaction of the potassium salt of thiophenol with *N*-(2-pyrazinylmethyl)chloroacetamide (**1**) (2) gave an excellent yield of the amide (**2**) which could be cyclized to 3-(phenylthiomethyl)imidazo[1,5-*a*]pyrazine (**3**). The potentiality of the activated methylene group in **3** coupled with the oxidizability of the sulfur made **3** an attractive candidate for functionalization of the imidazo[1,5-*a*]-pyrazine system especially since the sulfur could be removed after functionalization.



1 2 3, R = H; 4, R = D

Reaction of **3** with *n*-butyllithium was investigated as a route to the anion of **3**. When methyl benzoate was added to the reaction mixture in an effort to intercept the anion a rather low yield of a colorless oil was obtained. The spectral data of this product strongly suggested addition of a butyl group to the nucleus followed by *N*-benzoylation of the anion formed (–C=N at 1639 cm^{-1}). An analogous reaction involving methyllithium and 2,5-dimethylpyrazine has been reported (3). The mass spectrum of this product showed a strong molecular ion (M^+, 403) and other major fragments which resulted from the loss of an *n*-butyl group ($M^+ - 57$), a phenylthio group ($M^+ - 109$) and a prominent fragment (m/e, 105) attributed to a benzoyl cation which is characteristic of aromatic benzamides (4). Four isomeric structures can be written for this product: **5**, **6**, **7**, and **8**. Structures **7** and **8** can be ruled out by nmr data since the



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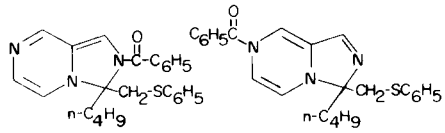

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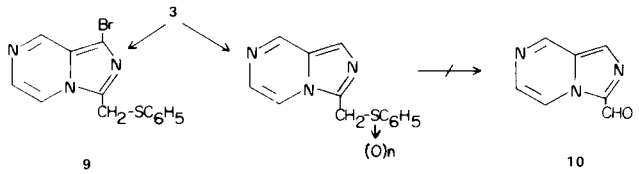
expected upfield shift of the methylene proton resonance was not observed (δ, 4.47 ppm compared to δ 4.52 for **3**). The lack of the characteristic downfield H-8 signal in the nmr spectrum favored structure **5** over **6** for this product. The chemical shift of H-1 could not be easily identified in the aromatic region which has a total of thirteen protons. Electrophilic adducts analogous to **5** have been formed from imidazo[1,5-*a*]pyrazines and acylating agents (5); microanalytical data also support such a structure.

Reaction of **3** with potassium *t*-butoxide did furnish the anion as shown by the appearance of a red color and the formation of **4** when deuterium oxide was used to quench the reaction. Both nmr and mass spectral evidence indicated a substantial incorporation of deuterium in **4**. Efforts to alkylate the anion with methyl iodide were unsuccessful; apparently the anion is too sterically hindered to react with an alkylating agent.

Oxidation of **3** with *m*-chloroperbenzoic acid gave good yields of both the sulfoxide (**11**) and the sulfone (**12**). Evidence for sulfoxide, rather than *N*-oxide formation came from infrared data which clearly showed a characteristic (6) band at 1040 cm^{-1} that was lacking in the spectrum of the parent sulfide (**3**). That a sulfone (**12**) rather than a sulfoxide *N*-oxide was formed is evidenced by the characteristic $-SO_2$ bands at 1320 and 1150 cm^{-1} (6). In addi-

tion the nmr spectrum (see experimental) showed a rather large downfield shift of the methylene group (0.9 ppm) with no significant effects on H-8 which would have experienced an upfield shift had the *N*-oxide been formed (7). When **11** was subjected to the conditions of the Pummerrer rearrangement (8) in an effort to form the aldehyde (**10**), an intractable mixture resulted.

An attempt to introduce bromine at the methylene group of **3** in a manner analogous to that reported for the preparation of α-halothioethers (**9**), did not give the desired product but furnished instead the 1-bromo derivative (**9**). The disappearance of the H-1 proton signal (10) in the nmr spectrum of **9** enabled assignment of the bromine to C-1. This substitution pattern is that noted with other electrophilic substitution reactions carried out on this system (11).



EXPERIMENTAL

Melting points (uncorrected) were determined with a Thomas-Hoover capillary apparatus. Nmr spectra were determined on a Varian A-60 apparatus in deuteriochloroform, unless otherwise indicated, using tetramethylsilane as an internal standard. Ultraviolet data were obtained on a Cary-15 spectrophotometer in ethanol. Mass spectral molecular weights were obtained from a CEC 24-104 spectrometer. Microanalyses were performed by Micro-Analysis, Inc., Marshallton, Delaware. All evaporations were carried out *in vacuo* using a water aspirator or a vacuum pump.

N-2-Pyrazinylmethyl-*S*-phenylmercaptoacetamide (**2**).

Thiophenol (1.21 g., 11 mmoles) was added to a solution of potassium hydroxide (0.65 g., 10 mmoles) in methanol (20 ml.) and the methanol was then evaporated. The residue was suspended in 1,2-dimethoxyethane (20 ml.).

A solution of *N*-2-pyrazinylmethylchloroacetamide (**1**) (2) (1.84 g., 10 mmoles) in dimethoxyethane (20 ml.) was then added and the reaction mixture was stirred at room temperature for 3 hours. The residue obtained was triturated with methylene chloride (50 ml.) and filtered. The residue obtained on evaporation of filtrate was passed over a dry alumina (90 g.) column and eluted with chloroform-methanol (98.5-1.5). The first fraction eluted a non-polar compound, presumably diphenyl disulfide. The product, obtained from the second fraction, was crystallized from ether to furnish *N*-2-pyrazinylmethyl-*S*-phenylmercaptoacetamide (1.9 g., 73%) as colorless needles; m.p. 48°.

Anal. Calcd. for $C_{13}H_{13}N_3OS$: C, 60.21; H, 5.05; N, 16.20; S, 12.36. Found: C, 60.33; H, 4.86; N, 16.02; S, 12.31.

3-(Phenylthiomethyl)imidazo[1,5-*a*]pyrazine (**3**).

Phosphorus oxychloride (50 ml.) was added to a solution of *N*-2-pyrazinylmethyl-*S*-phenylmercaptoacetamide (**2**) (5.2 g., 20 mmoles) in methylene chloride (15 ml.). After stirring overnight at room temperature, the reaction mixture was heated at 90° for an hour and phosphorus oxychloride was then removed under reduced pressure. The residue was suspended in water (25 ml.), made alkaline with aqueous 20% NaOH and extracted with methylene chloride (5 x 300 ml.). The combined methylene chloride extracts were washed with water (20 ml.), dried over anhydrous potassium carbonate and the methylene chloride evaporated under reduced pressure. The residue crystallized, from hexane, as pale yellow needles (2 g., 40%), m.p. 80°; uv: λ max 261 nm (sh), 270 (log ε, 3.90), 281 (3.95), 291 (3.94), and 338 (3.54); nmr: δ 4.5 (methylene 2H, s), 7.1-7.3 (phenyl protons, m), 7.7 (H-1, s), 7.5 (d, J = 5 Hz), and 7.7 (m), (H-5 and H-6), 8.9 (H-8, d, J = 2 Hz); mass spectrum m/e: 241 and 242 (M^+), ratio 7:2.

Anal. Calcd. for $C_{13}H_{11}N_3S$: C, 64.71; H, 4.59; N, 17.41; S, 13.29. Found: C, 64.50; H, 4.53; N, 17.27; S, 13.35.

3-Phenylthiomethyl-7-benzoyl-9-*n*-butyl-7,8-dihydroimidazo[1,5-*a*]-pyrazine (**5**).

A 2*M* solution of butyllithium in hexane (0.5 ml., 1 mmole) was added to a stirred solution of 3-(phenylthiomethyl)imidazo-[1,5-*a*]pyrazine (**3**) (96 mg., 0.4 mmole) in anhydrous tetrahydrofuran (15 ml.) under nitrogen. The reaction mixture was allowed to stir for ten minutes, methyl benzoate (68 mg., 0.5 mmole) was added and the reaction mixture refluxed for fifteen minutes. Tetrahydrofuran was then removed under reduced pressure and the residue obtained was chromatographed on alumina (Woelm dry column, 15 g.) and eluted with methylene chloride. The first fraction yielded the unreacted methyl benzoate. The second fraction furnished the product as a colorless oil (35 mg., 22%). The characteristic H-8 of **3** at δ 8.92 was absent in accord with structure **5** (the essential nmr and mass spectral data appear in the Discussion section).

Anal. Calcd. for $C_{24}H_{25}N_3OS$: C, 71.43; H, 6.24; N, 10.41; S, 7.95. Found: C, 71.48; H, 6.52; N, 10.42; S, 7.77.

3-(Phenylthiodeuteromethyl)imidazo[1,5-*a*]pyrazine (**4**).

A solution of 3-(phenylthiomethyl)imidazo[1,5-*a*]pyrazine (**3**) (96 mg., 4 mmoles) in anhydrous tetrahydrofuran (10 ml.) was added to a stirred suspension of potassium *t*-butoxide (70 mg., 62 mmoles) in THF (20 ml.) under nitrogen. After allowing the reaction mixture to stir for fifteen minutes, deuterium oxide (0.2 ml.) was added and stirring continued for another fifteen minutes. Most of tetrahydrofuran was then removed under reduced pressure and the residue extracted with chloroform (50 ml.). The chloroform extract was washed with water (5 ml.), dried over anhydrous potassium carbonate and the chloroform was then evaporated. The residue (65 mg., 69%), crystallized from hexane as pale yellow needles, m.p. 80°. The methylene peak at δ 4.61 was a singlet whose area was approximately that of one proton and in the mass spectrum the ratio of the 241 to 242 peaks was 12:11 in contrast with the situation in **3**.

3-(Phenylsulfinylmethyl)imidazo[1,5-*a*]pyrazine (**11**).

A solution of *m*-chloroperbenzoic acid (400 mg., 2 mmoles) in chloroform (15 ml.) was added dropwise to a stirred ice-cold solution of 3-(phenylthiomethyl)imidazo[1,5-*a*]pyrazine (**3**) (241 mg., 1 mmole) in chloroform (10 ml.) over a period of five minutes. The reaction mixture was allowed to stir for ten minutes and then saturated sodium bicarbonate solution (5 ml.) was added to it. The chloroform layer was separated and the aqueous layer was extracted again with chloroform (100 ml.). The combined chloroform extracts were dried over anhydrous potassium carbonate and the chloroform

was evaporated. The residue crystallized, from acetone-hexane, as colorless needles (195 mg., 76%), m.p. 118°; ir (chloroform): 1040 cm^{-1} (S → O); uv: λ max 258 nm (log ε, 3.60), 291 (3.78), and 340 (3.30); nmr: δ 4.6 (methylene, 2H, s), 7.4-7.6 (phenyl protons plus H-5 or H-6, m), 7.7 (H-1, s), 7.9 (H-5 or H-6, m), 8.9 (H-8, d, J = 2 Hz).

Anal. Calcd. for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33; S, 12.46. Found: C, 60.55; H, 4.31; N, 16.26; S, 12.28.

3-(Phenylsulfonylmethyl)imidazo[1,5-*a*]pyrazine (**12**).

A solution of *m*-chloroperbenzoic acid (1.5 g., 7 mmoles) in chloroform (2.5 ml.) was added to a stirred solution of 3-(phenylthiomethyl)imidazo[1,5-*a*]pyrazine (**3**) (483 mg., 2 mmoles) in chloroform (25 ml.) and stirring was continued for one hour. Saturated sodium bicarbonate solution (20 ml.) was then added to it. The chloroform layer was separated and the aqueous layer was extracted again with chloroform (2 x 100 ml.). The combined chloroform extracts were dried over anhydrous potassium carbonate and the chloroform evaporated. The residue was chromatographed on alumina (Woelm dry column, 50 g.) eluting with 1% methanol in chloroform. The front-moving band was collected and crystallized from chloroform-hexane as colorless needles (340 mg., 62%), m.p. 204-206° dec.; ir (potassium bromide): 1320 and 1150 cm^{-1} (SO_2); uv: λ max 261 nm (sh), 268 (log ε, 3.87), 272 (3.93), 281 (3.97), 291 (4.00), and 330 (3.60); nmr (DMSO-d-6): (s), 5.4 (methylene 2H, s), 7.5-7.7 (phenyl protons plus H-5 or H-6, m), 7.8 (H-1, s), 8.4 (H-5 or H-6, m), 9.1 (H-8, d, J = 2 Hz).

Anal. Calcd. for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37; S, 11.73. Found: C, 57.01; H, 4.27; N, 15.22; S, 11.81.

1-Bromo-3-(phenylthiomethyl)imidazo[1,5-*a*]pyrazine (**9**).

A solution of bromine (176 mg., 1.1 mmoles) in carbon tetrachloride (3.5 ml.) was added dropwise to a stirred, ice-cold, solution of 3-(phenylthiomethyl)imidazo[1,5-*a*]pyrazine (**3**) (242 mg., 1 mmole) in carbon tetrachloride (20 ml.), over a period of five minutes. The reaction mixture was allowed to stir for five minutes and then evaporated under reduced pressure. The residue was dissolved in water (5 ml.), made alkaline with aqeuous 20% sodium hydroxide and extracted with chloroform (3 x 60 ml.). The combined chloroform extracts were dried over anhydrous potassium carbonate and chloroform was then evaporated. The residue was chromatographed on alumina (Woelm dry column, 20 g.). The front-moving band furnished 1-bromo-3-(phenylthiomethyl)imidazo[1,5-*a*]pyrazine (180 mg., 56%) which crystallized from hexane as pale yellow needles, m.p. 101°; uv: λ max 242 nm (log ε, 3.88), 288 (3.96), and 350 (3.62); nmr: δ 4.5 (methylene 2H, s), 7.1-7.4 (phenyl protons, m), 7.5-7.8 (H-5 and H-6, m), 8.8 (H-8, d, J = 2 Hz). The second band gave the unreacted starting material (45 mg., 20%).

Anal. Calcd. for $C_{13}H_{10}BrN_3S$: C, 48.76; H, 3.15; N, 13.12; S, 10.01; Br, 24.96. Found: C, 48.70; H, 2.94; N, 13.05; S, 10.07; Br, 24.72.

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