

A. Shafiee* and S. Shahocini

Department of Chemistry, College of Pharmacy, Tehran Medical Sciences University, Tehran Iran

Received September 26, 1988

Reaction of readily available 2-methyl-4-formylthiazole (1) with glyoxal and ammonia gave 2-(2-methyl-4-thiazolyl)imidazole (2). Nitration of 2 with a mixture of nitric acid-sulfuric acid at 100° yielded 2-(2-methyl-4-thiazolyl)-4,5-dinitroimidazole (3) as the sole reaction product, while nitration at 65° afforded 2-(2-methyl-4-thiazolyl)-4-(or 5)-nitroimidazole (4). *N*-Methylation of compound 4 in the presence of base gave 1-methyl-2-(2-methyl-4-thiazolyl)-4-nitroimidazole (6), whereas *N*-methylation with diazomethane afforded 1-methyl-2-(2-methyl-4-thiazolyl)-5-nitroimidazole (5). *N*-Methylation of compound 3 yielded 1-methyl-2-(2-methyl-4-thiazolyl)-3,5-dinitroimidazole (7) in high yield.

J. Heterocyclic Chem., **26**, 1627 (1989).

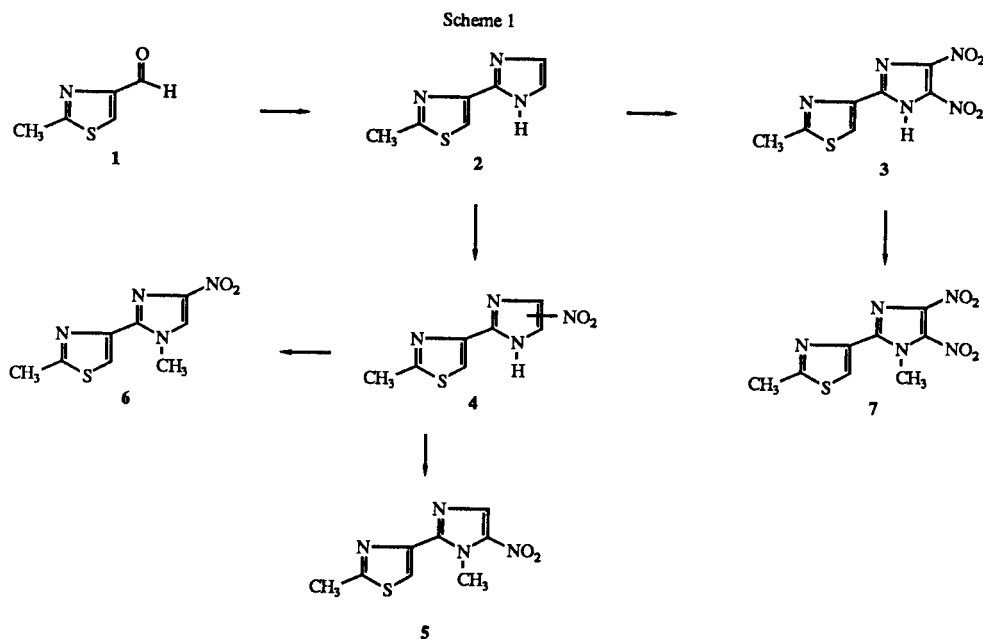
The considerable biological importance of the group of compounds incorporating an imidazole nucleus has stimulated much work on this heterocycle [2,3]. The syntheses of 1-methyl-2-(2-pyridyl)nitroimidazoles and 1-methyl-2-(2-oxazolyl)-5-nitroimidazole have recently been reported [4,5]. We would like to report the syntheses of 1-methyl-2-(2-methyl-4-thiazolyl)-5-nitroimidazole (5), 1-methyl-2-(2-methyl-4-thiazolyl)-4-nitroimidazole (6) and 1-methyl-2-(2-methyl-4-thiazolyl)-4,5-dinitroimidazole (7) as possible effective drugs against tropical diseases [6].

The title compounds were synthesized according to Scheme 1.

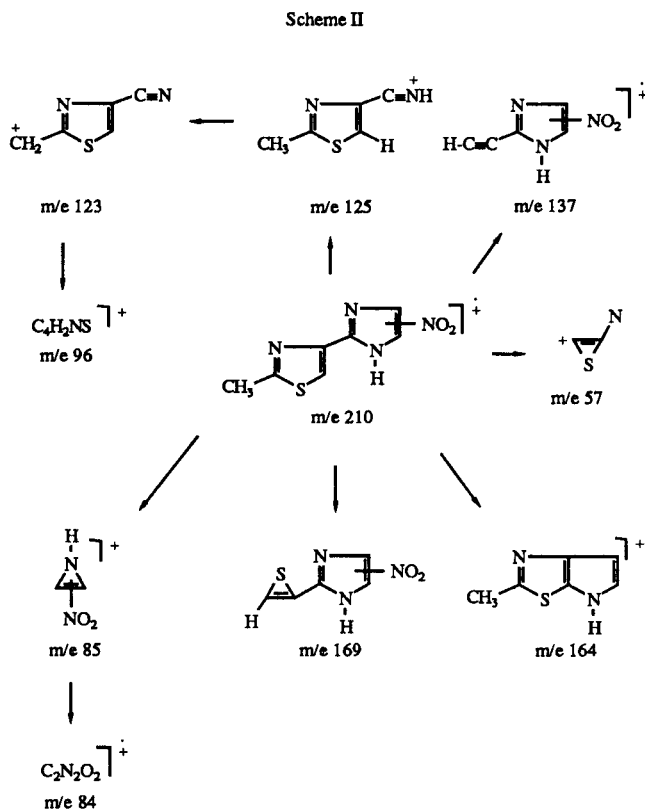
Reaction of 2-methyl-4-formylthiazole (1) [7], with glyoxal and ammonia in ethanol gave 2-(2-methyl-4-thiazolyl)imidazole (2). Nitration of imidazole with nitric acid-sulfuric acid at reflux temperature gave 4(or 5)-nitroimidazole [8], while nitration of imidazole with 98% nitric acid

and 98% sulfuric acid afforded 4,5-dinitroimidazole [9]. Nitration of 2-methylthiazole with fuming sulfuric acid and potassium nitrate at 330° was reported to give 2-methyl-5-nitrothiazole in very low yield [10], and nitration of 2-methylthiazole with nitrogen tetroxide-boron trifluoride complex afforded a mixture of 4-nitro-2-methylthiazole and 5-nitro-2-methylthiazole [11]. We observed that nitration of compound 2 with a mixture of 65% nitric acid and 95% sulfuric acid at 100° gave 2-(2-methyl-4-thiazolyl)-4,5-dinitroimidazole (3) as the sole reaction product. Nitration of compound 2 between 70-90° with the same acid mixture gave mixture of compounds 3 and 2-(2-methyl-4-thiazolyl)-4-(or 5)-nitroimidazole (4). Finally, nitration of compound 2 at 65° yielded compound 4 as the sole reaction product.

Assignment of structures of compounds 3 and 4 were made by spectroscopic data and chemical reaction.



The mass spectra fragmentation pattern of compound **4** is summarized in Scheme II is in good agreement with the suggested structure. The mass spectra fragmentation pattern of compound **3** was also similar to compound **4** (see Experimental). Peaks at m/e 125 and m/e 57 in the mass spectra of compounds **3** and **4** indicated that nitration occurred at the imidazole rings. The nmr spectrum of compound **4** was also in agreement with the suggested structure. In the nmr spectrum of compound **2**, H_4 and H_5 of imidazole ring appeared as two protons singlet at 7.06 and H_3 of thiazole as a one proton singlet at 7.73 ppm. In the nmr spectrum of compound **4**, H_4 (or H_5) of imidazole appeared at 8.17 as a one proton singlet and H_3 of thiazole was observed at 7.83 ppm.



In addition, *N*-methylation of compound **3** in the presence of base or under neutral condition, as expected, gave compound **7** as a sole reaction product. The latter experiments confirmed that the two nitro groups are in imidazole ring (see also discussion below). Compound **4** could be *N*-methylated to produce either 1-methyl-4-nitro or 1-methyl-5-nitro-derivatives depending upon reaction condition employed. *N*-Methylation of compound **4** in the presence of a base yielded compound **6**, whereas *N*-methylation with diazomethane gave compound **5** as the major product.

Assignment of structures of compounds **5** and **6** were made by analogy to similar reaction conditions [12,14] and

spectroscopic data. In the uv spectra of compounds **5** and **6**, because of the linear conjugation of compound **5** over the branched conjugated system in compound **6**, the position of the main absorption maxima in **5** had a distinct maximum at 335 nm whereas **6** had a maximum at 320 nm. In addition, as expected, the extinction coefficient at these wavelengths for **5** was greater than **6**.

It has been reported that in nmr spectrum, the δ value of 1-methyl in the 5-nitroimidazoles is greater than the 4-nitroimidazoles because of the greater deshielding effect of the 5-nitro group as compared with the 4-position [4,14,15]. In compound **5** the 1-methyl group appeared 0.25 ppm lower field relative to the 1-methyl in compound **6**. In addition, because of the linear conjugation of nitro group with H_3 of thiazole in **5**, we predicted that the latter proton in **5** should appear in lower field relative to **6**. In fact, H_3 of thiazole in **5** appeared 0.17 ppm lower field relative to H_3 of thiazole in **6**. These are in agreement with the suggested structures.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The uv spectra were recorded using a Perkin-Elmer Model 550 SE. The ir spectra were obtained using a Perkin-Elmer Model 781 spectrograph (potassium bromide disks). The nmr spectra were recorded on a Varian T-60A spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. The mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 eV.

2-(2-Methyl-4-thiazolyl)imidazole (**2**).

To a stirred solution of 2-methyl-4-formylthiazole **1** (3.81 g, 0.03 mole) in ethanol (40 ml) at 5°, a solution of 40% glyoxal in water (7 ml) and 20 *N* ammonia in water (10 ml) were added. The mixture was allowed to stand at 0-5° for 20 minutes and then at room temperature overnight. The solvent was evaporated and the residue was dissolved in water (20 ml) and extracted continuously with ether (liquid liquid extractor) for 48 hours. The solvent was evaporated and the residue is crystallized from ethyl acetate to give 2.87 g (58%) of compound **2**, mp 171-172°; 1H nmr (deuteriochloroform): 2.77 (s, 3H, CH_3), 7.06 (s, 2H, $H_{4,5}$ imidazole) and 7.73 ppm (s, 1H, H_3 thiazole); ms: m/e (relative intensity) 165 (M^+ , 26), 124 (50), 97 (63), 69 (100), 45 (60).

Anal. Calcd. for $C_7H_7N_3S$: C, 50.89; H, 4.27; N, 25.43. Found: C, 50.91 H, 4.12; N, 25.32.

2-(2-Methyl-4-thiazolyl)-4-(or 5)-nitroimidazole (**4**).

A solution of compound **2** (165 mg, 1 mmole), nitric acid (65%, 0.3 ml) and sulfuric acid (95%, 0.3 ml) was heated at 65° for 24 hours. After cooling, the solution was diluted with ice-water (5 ml). The pH of the solution was adjusted to 1.5 with sodium hydroxide solution. The precipitate was filtered and crystallized from acetone to give 63 mg (75%, based on reacted starting material) of compound **4**, mp 289-290°; 1H nmr (trifluoroacetic acid) 2.77 (s, 3H, CH_3), 7.83 (s, 1H, H_3 thiazole) and 8.17 ppm (s, 1H, H_4 or H_5 imidazole); ms: m/e (relative intensity) 210 (M^+ , 100), 169 (24), 164 (47), 137 (85), 125 (95), 123 (24), 96 (52), 85 (31), 84 (35), 69

(95), 57 (32), 52 (23), 45 (38) and 42 (50).

Anal. Calcd. for $C_7H_6N_4O_2S$: C, 40.00; H, 2.88; N, 26.67. Found: C, 40.12; H, 2.72; N, 26.51.

The pH of the filtrate was adjusted to 7 and the precipitate (starting material) was filtered, 99 mg.

2-(2-Methyl-4-thiazolyl)-4,5-dinitroimidazole (3).

A solution of compound **2** (165 mg, 1 mmole) in nitric acid (65%, 0.3 ml) and sulfuric acid (95%, 0.3 ml) was heated in an oil bath at 100° for 24 hours. After cooling, the mixture was added to ice-water (3 ml). The precipitate was filtered and crystallized from acetone to give 184 mg (72%) of compound **3**, mp 115-116° C; ¹H nmr (trifluoroacetic acid): 2.83 (s, 3H, CH₃) and 8.30 ppm (s, 1H, H₅); ms: m/e (relative intensity) 255 (M⁺, 100), 210 (64), 125 (65), 99 (27), 95 (30), 94 (29), 83 (22), 69 (23), 59 (18), 57 (22) and 42 (33).

Anal. Calcd. for $C_7H_5N_5O_4S$: C, 32.95; H, 1.97; N, 27.44. Found: C, 32.79; H, 1.81; N, 27.53.

1-Methyl-2-(2-methyl-4-thiazolyl)-5-nitroimidazole (5).

A suspension of compound **4** (210 mg, 1 mmole) with excess diazomethane in dry ether (20 ml) was stirred at room temperature overnight. The mixture was filtered. The solvent was removed under reduced pressure and the residue was crystallized from methanol to give 146 mg (65%) of compound **5**, mp 143-144°; uv (methanol): λ max 335 nm (E = 11870); ir (potassium bromide): ν = 1520, 1370 cm⁻¹ (NO₂); ¹H nmr (deuteriochloroform): 2.80 (s, 3H, CH₃), 4.42 (s, 3H, CH₃), 8.00 (s, 1H, H₅ thiazole) and 8.06 ppm (s, 1H, H₄ imidazole); ms: m/e (relative intensity) 224 (M⁺, 100), 194 (45), 178 (21), 164 (18), 137 (100), 125 (25), 96 (31), 83 (19), 69 (23), 54 (23) and 42 (22).

Anal. Calcd. for $C_8H_8N_4O_2S$: C, 42.85; H, 3.59; N, 24.99. Found: C, 42.71; H, 3.65; N, 24.86.

1-Methyl-2-(2-methyl-4-thiazolyl)-4-nitroimidazole (6).

A stirring suspension of compound **4** (210 mg, 1 mmole), dimethyl sulfate (63 mg, 0.5 mmole) and sodium carbonate (53 mg, 0.5 mmole) in acetone (40 ml) was refluxed overnight. The mixture was filtered and the solvent was removed under reduced pressure. The residue was crystallized from methanol to give 157 mg (70%) of compound **6**, mp 216-218°; uv (Methanol): λ max 320 nm (E = 6500); ¹H nmr (deuteriochloroform): 2.78 (s, 3H, CH₃), 4.17 (s, 3H, CH₃), 7.83 (s, 1H, H₅ thiazole) and 8.04 ppm (s, 1H, H₅ imidazole); ms: m/e (relative intensity) 224 (M⁺, 100), 208 (30), 132 (11), 126 (51), 85 (10) and 42 (30).

Anal. Calcd. for $C_8H_8N_4O_2S$: C, 42.85; H, 3.59; N, 24.99. Found: 42.93; H, 3.64; N, 25.04.

1-Methyl-2-(2-methyl-4-thiazolyl)-4,5-dinitroimidazole (7).

Method A.

A suspension of compound **3** (255 mg, 1 mmole) with excess diazomethane in dry ether (20 ml) was stirred at room temperature for 1 hour. The mixture was filtered. The solvent

was removed under reduced pressure and the residue was crystallized from methanol to give 188 mg (70%) of compound **7**, mp 124-125°; uv (methanol): λ max 334 nm (E = 4480); ¹H nmr (deuteriochloroform): 2.90 (s, 3H, CH₃), 4.43 (s, 3H, CH₃) and 8.16 ppm (s, 1H, H₅ thiazole); ms: m/e (relative intensity) 269 (M⁺, 100), 239 (78), 210 (19), 183 (40), 176 (12), 152 (10), 126 (99), 109 (16), 94 (39), 74 (23), 59 (40) and 47 (55).

Anal. Calcd. for $C_8H_7N_5O_4S$: C, 35.69; H, 2.62; N, 26.01. Found: 35.74; H, 2.78; N, 25.90.

Method B.

A suspension of compound **3** (255 mg, 1 mmole), dimethyl sulfate (63 mg, 0.5 mmole) in acetone (40 ml) was refluxed overnight with stirring. The mixture was filtered and the solvent was removed under the reduced pressure. The residue was crystallized from methanol to give 175 mg (65%) of compound **7** mp 124-125°. The liquor was removed under the reduced pressure and the residue purified by preparative tlc on silica gel using chloroform/ethyl acetate (9.5:0.5) as eluent. The faster moving fraction was crystallized from methanol to give 27 mg (10%) of compound **7**, total yield 75%. The slow moving fraction was crystallized from acetone to give 51 mg (20%) of starting material.

Acknowledgement.

This work was partially supported by the International Organization for Chemical Sciences in Development (IOCD).

REFERENCES AND NOTES

- [1] Part IV. A. Shafiee and M. Pirali-Hamedani, "Nitroimidazoles IV, Syntheses of 2,6-Dimethyl-3,5-dicarboalkoxy-4-(1-methyl-5-nitro-2-imidazolyl)-1,4-dihydropyridine and 2,6-Dimethyl-3,5-dicarboalkoxy-4-(2-substituted-4-thiazolyl)-1,4-dihydropyridine", *J. Sci. I. R. of Iran*, accepted for publication (1988).
- [2] K. Hofmann "Imidazole and its Derivatives," Interscience, New York, 1953.
- [3] L. B. Townsend, *Chem. Rev.*, **67**, 533 (1967).
- [4] A. Shafiee, A. Ghanbarpour and F. Ghasemian, *Synthesis*, 385 (1987).
- [5] A. Shafiee, T. Ebrahimi-Bibalan, M. E., Bakhshi-Dezfouli and A. Ghanbarpour, *Heterocycles*, **26**, 2865 (1987).
- [6] G. T. Seaborg, *Science*, **223**, 9 (1984).
- [7] A. Shafiee, A. Mazloumi and V. I. Cohen, *J. Heterocyclic Chem.*, **16**, 1563 (1979).
- [8] R. G. Fargher and F. L. Pyman, *J. Chem. Soc.*, 234 (1919).
- [9] S. S. Novikov, L. I. Khmel'nitshii, O. V. Lebedev, V. V. Sevastyanova and L. V. Epishna, *Chem. Heterocyclic Compd.*, 465 (1970).
- [10] H. V. Babo and B. Prijs, *Helv. Chim. Acta*, **33**, 306 (1950).
- [11] G. Asato, *J. Org. Chem.*, **33**, 2544 (1968).
- [12] A. Grimison, J. H. Ridd and B. V. Smith *J. Chem. Soc.*, 1352, 1357, 1363 (1960).
- [13] K. Butler, H. L. Howes, J. E. Lynch and D. K. Pirie, *J. Med. Chem.*, **10**, 891 (1967).
- [14] F. Kajfez, V. Sunjic, D. Kolbah, T. Fajdiga and M. Oklobdzija, *J. Med. Chem.*, **11**, 167 (1968).
- [15] R. N. Butler, *Can J. Chem.*, **51**, 2315 (1973).