Vol. 1, No. 1
Fall 1989

*J. Sci. I. R. Iran*

# NITROIMIDAZOLES III. [1]. SYNTHESIS, ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF 2-METHYL-SULFONYL-5-(1-METHYL-5-NITRO-2-IMIDAZOLYL) 1,3,4-THIADIAZOLE

Abbas Shafiee, Monireh Anaraki, Sima Sadrai and Fattemeh Kamal

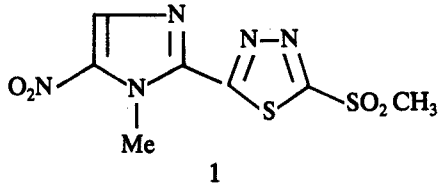
*Department of Chemistry, College of Pharmacy, Tehran Medical Sciences University, Tehran, Iran.*

**Abstract**

2-Methylsulfonyl-5-(1-methyl-5-nitro-2-imidazolyl) 1,3,4-thiadiazole (**1**) was prepared by two independent routes. 1) reaction of 1-methyl-2-formyl-5-nitroimidazole (**3**) with methyl hydrazinecarbodithioate gave the hydrazone **4.** Reaction of compound **4** with acetic anhydride followed by potassium permanganate oxidation of the intermediate **5** gave the desired compound **1.** 2) Reaction of thiourea with 2-chloro-5-(1-methyl-5-nitro-2-imidazolyl) 1, 3, 4-thiadiazole (**7**) gave the thiol **8.** Reaction of the latter with methyl iodide in alkaline medium followed by potassium permanganate oxidation afforded also compound **1.** The antibacterial and antifungal activity of compound **1** against a number of microorganisms were determined. Compound **1** showed significant antibacterial and antifungal activity.

## Introduction

The considerable biological importance of nitroimidazoles has stimulated much work on this heterocycle [2 – 6]. It was also shown that substituted nitroimidazolylthiadiazoles and nitroimidazolyloxadiazoles have antiprotozoal activity [7 – 9]. We would like to report the synthesis, antibacterial and antifungal activity of 1-methylsulfonyl-5-(1-methyl-5-nitro-2-imidazolyl) 1, 3, 4-thiadiazole (**1**).



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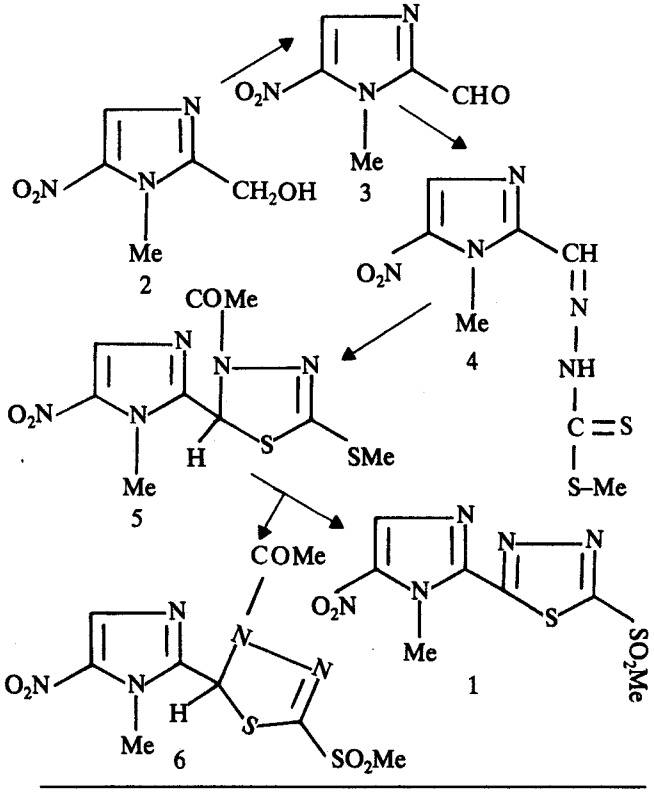
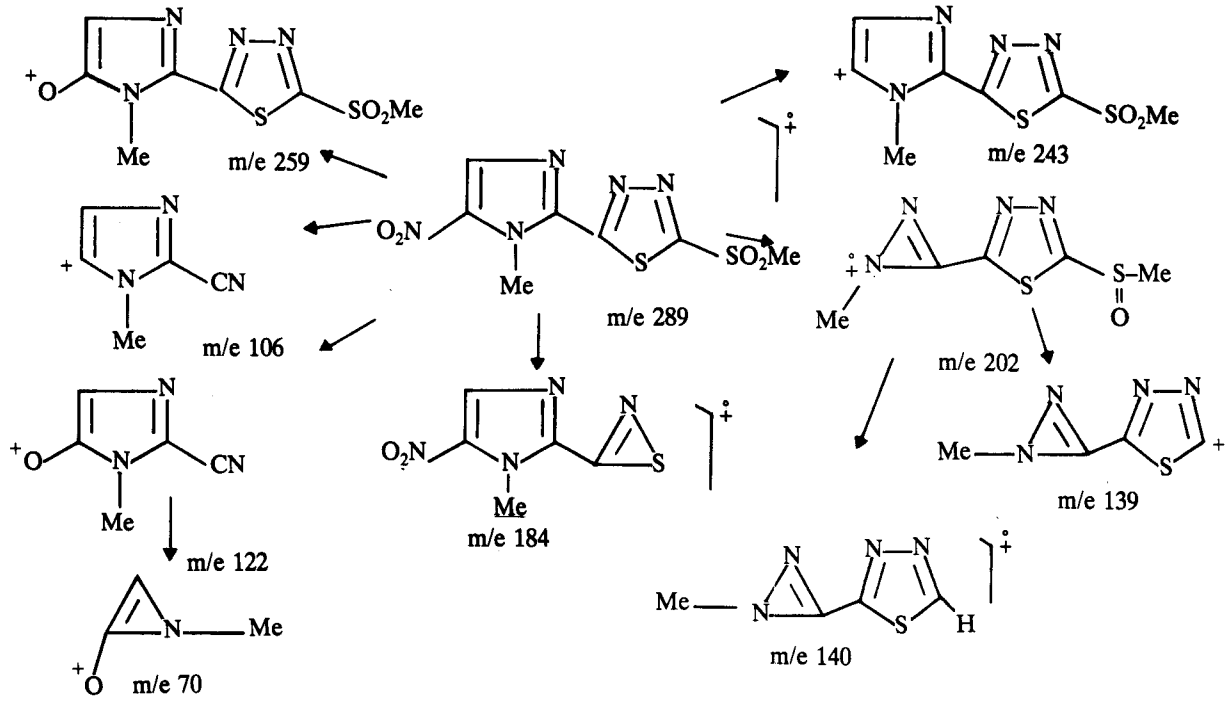
## Results and Discussion

The synthesize of compound **1**, was studied according to the method for the preparation of 1-methylsulfonyl-5-phenyl-1, 3, 4-thiadiazole [10] (scheme 1).

Manganese dioxide oxidation of 1-methyl-2-hydroxymethyl-5-nitroimidazole (**2**) [11] afforded 1-methyl-2-formyl-5-nitroimidazole (**3**) [12]. Reaction of me-



**Scheme 1**



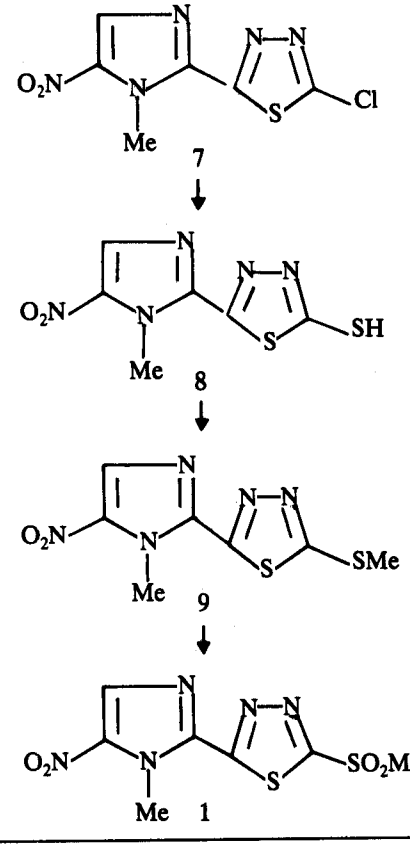

**Scheme 2**

thyl hydrazinecarbodithioate [13] with compound **3** afforded 1-methyl-5-nitro-2-imidazolylmethylene hydrazinecarbodithioic acid methyl ester (**4**). Treatment of compound **4** with acetic anhydride gave 2-methylthio-4-acetyl-5-(1-methyl-5-nitro-2-imidazolyl)-$\Delta^2$-1,3,4- thiadiazolin (**5**) in 30% yield. Potassium permanganate oxidation of compound **5** gave two compounds which were separated by preparative tlc. The fast moving fraction was the desired compound **1** (35% yield). The mass fragmentation pattern was in agreement with the suggested structure and is summarized in Scheme 2. The nmr spectrum was also in agreement with the suggested structure (see experimental).

The slow moving fraction was 2-methylsulfonyl-4-acetyl-5-(1-methyl-5-nitro-2-imidazolyl)-$\Delta^2$-1,3,4-thiadiazoline (**6**, 15% yield). Since over all yield of compound **1** was not satisfactory, we decided to study the preparation of compound **1** according to Scheme 3.

Reaction of thiourea with 2-chloro-5-(1-methyl-5-nitro-2-imidazolyl)1,3,4-thiadiazole (**7**) [11] in boiling ethanol afforded 2-mercapto-5-(1-methyl-5-nitro-2-imidazolyl) 1, 3,4-thiadiazole (**8**) in 80% yield. Reaction of compound **8** in alkaline solution with methyl iodide gave 2-methylmercapto-5-(1-methyl-5-nitro-2-imidazolyl)1,3,4-thiadiazole (**9**). Potassium permanganate oxidation of compound **9** gave the desired compound 1.

The potent antibacterial and antiviral activity of 1,3,4-thiadiazolylcarbamic acid esters were reported [14, 15]. In the present work, antibacterial and antifungal activities of compound **1** are summarized in Tables 1, and 2.




**Scheme 3**

| Concentration | 1 | 5 | 10 | Gentamycin (10) |
|---|---|---|---|---|
| *B. Subtilis* | 11 | 15 | 17 | 22 |
| *E. Coli* | 9 | 11 | 18 | 21 |
| *K. Pneumonia* | — | — | — | 18 |
| *P. Vulgaris* | — | — | — | 19 |
| *P. Aeruginosa* | — | — | — | 18 |
| *Salmonela Paratyphi B* | — | — | 8 | 18 |
| *S. Aureus* | 8 | 15 | 17 | 21 |
| *S. Epidermids* | — | 11 | 15 | 11 |

**Table 1. Antibacterial activity of compound 1 - The amount of compound 1 in a disk in μg; average zone size, mm.**

| Concentration | 1.25 | 12.5 |
|---|---|---|
| *M. Canis* | — | + |
| *M. Gypseum* | + | + |
| *Penicillium sp* | — | + |
| *A. Niger* | — | — |
| *C. Albicans* | — | + |

**Table 2. Antifungal activity of compound 1, concentration in μg/ml**

## Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The IR spectra were obtained using a Perkin-Elmer Model 267 spectrograph (potassium bromide disks). The nmr spectra were recorded on a Varian T-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 ev.

1-Methyl-2-formyl-5-nitroimidazole (**3**).

To a stirred solution of 1-methyl-2-hydroxymethyl-5-nitroimidazole (**2**, 15.7 g, 0.1 mol) in chloroform (1 l) at r.t. is added manganese dioxide (100 g). The stirring is continued for 2 hrs and filtered. The filterate is evaporated and the residue is crystallized from acetone to give 13.5 g (87%) of **3**; m.p. 97-98°C; IR 3118 (H–$C_4$ imidazole), 1705 (C=O), 1530, 1350 $cm^{-1}$ ($NO_2$); NMR ($CDCl_3$) δ 9.90 (s, 1H, HCO), 8.10 (s, 1H, $H_4$) and 4.40 ppm (s, 3H, $CH_3$).

Anal Calcd. for $C_5H_5N_3O_3$: C, 38.71; H, 3.25; N, 27.09. Found: C, 38.55; H, 3.15; N, 27.21.

1-Methyl-5-nitro-2-imidazolylmethylene hydrazinecarbodithioic Acid Methyl Ester (**4**).

To a stirring solution of methyl hydrazinecarbodithioate (1.22 g, 0.01 mol) in methanol (25 ml) at r.t. a solution of compound **3** (1.55 g, 0.01 mol) in methanol (5 ml) was added. After 2 hrs the precipitate was filtered and crystallized from ethanol to give 2.07 g (80%) of **4**; m.p. 209-211°C.

Anal. Calcd. for $C_7H_9N_5O_2S_2$: C, 32.43; H, 3.47; N, 27.03. Found: C, 32.55; H, 3.56; N, 27.18.

2-Methylthio-4-acetyl-5-(1-methyl-5-nitro-2-imidazolyl)-$\Delta^2$-1,3,4-thiadiazoline (**5**).

A stirring mixture of compound **4** (2.59 g, 0.01 mol) and acetic anhydride (13.5 mg) was heated at 100° in an oil bath for 1 hr. The solvent was evaporated and the residue was purified by preparative tlc on silica gel using chloroform-ethyl acetate (8:2) as eluent. The desired compound was an oily product: It was let to stand at 0° for 2 days. The crystals were separated and recrystallized from ethyl acetate-ether to give 0.9 g (30%) of **5**; m. p. 65-68°C; IR: 3120 (H – $C_4$ imidazole), 1670 (C = O), 1540, 1380 $cm^{-1}$ ($NO_2$); NMR ($CDCl_3$)δ 7.90 (s, 1H, $H_4$ imidazole), 7.06 (s,1H,$H_5$), 4.06 (s,3H, N–$CH_3$), 2.67 (s, 3H, $COCH_3$) and 2.33 ppm (s, 3H, $SCH_3$); ms: m/e (%) 301 ($M^+$, 70), 259 (88), 212 (19), 184 (100), 168 (10), 138 (11), 91 (11), 85 (49), 83 (78), 47 (15), and 43 (26).

Potassium permanganate oxidation of compound **5**.

To a stirring solution of compound **5** (3.01 g, 0.01 mol) in acetic acid (20 ml) at 5° potassium permangante (3.16 g, 0.02 mol) was added. The stirring was continued for 1 hr. water (20 ml) was added. Hydrogen peroxide (30%) was added to the mixture dropwise until the violet color disappeared. The mixture was let to stand at 0 – 5° overnight. The precipitate was filtered and purified by preparative tlc on silica gel using chloroform-aceton (96:4) as eluent. The fast moving fraction was crystallized from ethanol to give 0.87g(30%) of 1-methylsulfonyl-5-(1-methyl-5-nitro-2-imidazolyl)1,3,4-thiadiazole (**1**); m.p. 209 – 212°C; IR: 3120 (H – $C_4$ imidazole), 1530, 1330 ($NO_2$), 1360, 1150 $cm^{-1}$ ($SO_2$); NMR($CDCl_3$) δ 8.10(s, 1H, $H_4$), 4.60 (s, 3H, $NCH_3$) and 3.50 ppm (s, 3H, $SO_2CH_3$); ms: m/e (%) 289 ($M^+$, 73), 259 (100), 243 (11), 229 (11), 210 (15), 202 (27), 190 (13), 184 (16), 140 (11), 139 (14), 122 (30), 106 (22), 97 (12), 85 (18), 70 (21), 67 (47), 63 (19), 54 (56) and 42 (61).

Anal. Calcd. for $C_7H_7N_5S_2O_4$: C, 29.07; H, 2.42; N, 24.22. Found: C, 29.23; H, 2.35; N, 24.10.

The slow moving fraction was crystallized from ethanol to give 0.5 g (15%) of 2-methylsulfonyl-4-acetyl-5-(1-methyl-5-nitro-2-imidazolyl)-$\Delta^2$ -1,3,4-thiadiazoline(**6**);m. p. 198-201°C; IR: 3120 (H – $C_4$ imidazole), 1680 (carbonyl), 1530, 1350 ($NO_2$), 1380, 1150 $cm^{-1}$ ($SO_2$); NMR ($CDCl_3$) δ7.91 (s, 1H, $H_4$ imidazole), 7.23 (s, 1H, $H_5$), 4.10 (s, 3H, $NCH_3$), 3.32 (s, 3H, $SO_2$ $CH_3$) and 2.40 ppm (s, 3H, $COCH_3$); ms: m/e (%) 333 ($M^+$, 30), 291 (74), 212 (99), 184 (77), 154 (57), 138 (31), 137 (46), 127 (16), 96 (12), 81 (20), 71 (15), 69 (14), 57 (26), 55 (20), 52 (20) and 43 (100).

Anal. Calcd. for $C_9H_{11}N_5O_5S_2$: C, 32. 43; H, 3.30; N, 21. 02. Found: C, 32.29; H, 3.43; N, 21. 15.

Antibacterial and Antifungal Assay* – Compound I was tested against *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 6538 p), *Staphylococcus epidermidis* (ATCC 12228) *Escherichia coli, Klebisella pneumoniae, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella paratyphi B, Candida albicans, Aspergillus niger, Penicillium sp, Microsporum canis* and *Microsporum gypseum.*

For antibacterial assay compound 1 was dissolved in methanol and diluted to 1mg/1ml concentration with

methanol. To standard paper disk of 6 mm. diameter the latter solution was added until the desired amount of compound was absorbed by the disk (see table 1). The disks were then placed on an inoculated assay medium surface. Gentamycin was used for comparison. Compound 1 showed significant activity against B. subtilis E. coli, S. aureus and S. epidermidis and no or small activity against other microorganisms.

For antifugal assay, compound **1** was dissolved in methanol diluted with hot culture medium to the desired concentration and autoclaved at 120° for 1 hr (table 2). Compound **1** inhibited the growth of all microorganisms except A. niger at 12.5 mg/ml concentration against the blank.

*Acknowledgement:* This work was partially supported by the International Organization of Chemical Sciences in Development (IOCD).

* Unless otherwise specified the microorganism was obtained from the department of Parasitology, Public Health Institute, Tehren Medical Sciences University, Tehran, Iran.

## References

1. For part II see A. Shafiee, T. Ebrahimi-Bibalan, M. E. Bakhshi-Dezfouli, and A. Ghanbarpour, *Heterocycles* 26, 2865 (1987).
2. H. Horie, *J. Antibiot,* (Tokyo) A9, 168 (1981).
3. G. C. Lancini, E. Lazzari and R. Pallanza, *Farmaco., Ed, Sci.*, **21,** 278 (1966).
4. A. G. Beaman, W. Tautz, T. Gabriel, O. Keller, V. Toome and R. Duschinsky, *Antimicrobial Agents Chemotherapy,* 469 (1965).
5. G. Grunberg and E. Tisworth, *ibid.*, 478 (1965).
6. G. C. Lancini, E. Lazzari, V. Arioli and P. Bellani, *J. Med, Chem.*, **12,** 775 (1969).
7. G. Asato and G. Berkelhammer, *ibid.*, **15,** 1086 (1972).
8. G. Berkelhammer and G. Asato, *U. S. Patent* 3, 740, 434 (1973) American Cyanamid Co.; *C. A.* 66365k (1973).
9. G. Asato and G. Berkelhammer, *U. S. Patent* 3,658, 832 (1972) American Cyanamid Co.; *C. A.* 77, 48468a (1972).
10. S. Kubota, K. Toyook, J. Ikeda, N. Yamamoto and M. Shibuya, *J. Chem. Soc.*, 967 (1983).
11. J. Kollonitsch, *U. S. Patent* 3, 290, 328 (1966) Merck & Co,. Inc.; *C. A.* 66, 55488h (1967).
12. P. F. Fabio, A. S. Tomcufzik and A. M. Hoffman, *Ger. Offen* 1,800, 362 (1969) American Cyanamid Co.; *C. A.* 71, 38968a (1969).
13. E. S. Scott and L. F. Audrieth, *J. Org. Chem.*, **19,** 742 (1954).
14. H. Mirshamsi, I. Lalezari, M. Kamal, G. Niloufari and N. Rezvani, *Arch. Virusforsch.*, 29,267 (1970).
15. I. Lalezari and A. Vahdat, *J. Med, Chem.*, 14, 59 (1971).