SYNTHESIS AND CHARACTERIZATION OF 4-AMINO-1,2,4-TRIAZOLE-3-THIOLS

Savita Choudhary* and Vibha Shrivastav#

*Department of Chemistry, S. K. Govt. College, Sikar

#Department of Chemistry, S. K. Govt. College, Sikar

Abstract

Heterocycles bearing a symmetrical triazole or 1,2,4-triazole scaffold are the structural element of many drugs that have diverse pharmacological activities. The triazole nucleus is an important part of the therapeutically interesting drugs. The 1,2,4-triazole derivatives are being used extensively in medicine, namely alprazolam (tranquilizer), estazolam (hypnotic, sedative, and tranquilizer), rilmazafone (hypnotic, anxiolytic, used in the case of neurotic insomnia), benatradin (diuretic), trapidil (hypotensive), trazodone (antidepressant, anxiolytic), etoperidone (antidepressant), nefazodone (antidepressant, 5-HT2A-antagonist), anast-rozole (antineoplastic, nonsteroidal aromatase inhibitor), letrozole (anti-neoplastic, aromatase inhibitor), ribavirin (antiviral), fluconazole, itraconazole, terconazole (antifungal), and so forth.

Key Words : 2-Mercapto-1,3,4-Oxadiazoles, Thiocarbohydrazides.

Introducion

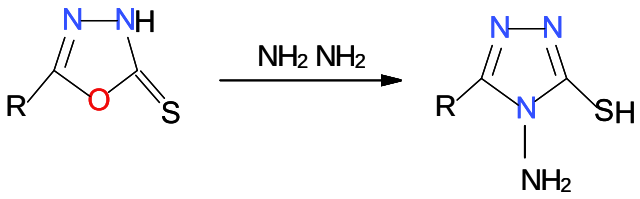
The biological profile of triazole derivatives is very extensive[1-4]. Compounds bearing a symmetrical triazole moiety are reported to show a broad spectrum of pharmacological activities such as antibacterial[5-8], antifungal[9-15], antimicrobial[16-20], antimycobacterial[21-22], antioxidant[23], analgesic[24-25], antipyretic[26], anticancer[27-32], anticonvulsant[33-34], antinfla-mmatory[35-39], CNS stimulants, sedatives, antianxiety etc.

In addition to these important biological applications, mercapto-1,2,4-triazoles have been reported to have their importance in the preparative organic chemistry and have been used to synthesize structurally diverse therapeutically interesting compounds such as, triazolothiadiazines and triazolobenzothiadiazines.

In the present investigation we have synthesized the intermediate 5-substituted-4-amino-1,2,4-triazole-3-thiols required for synthesis of thiadiazine derivatives . Different synthetic methods have been reported in the literature for the synthesis of 5-substituted-4-amino-1,2,4- triazole-3-thiol. Some recently reported important methods have been presented briefly.

2.7 FROM 2-MERCAPTO-1,3,4-OXADIAZOLES

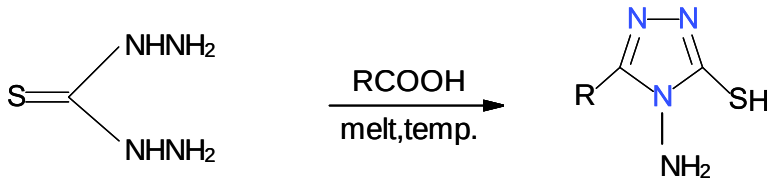
5-Substituted-4-amino-1,2,4-triazole-3-thiols were prepared by the reaction of 5-substituted-2-mercapto-1,3,4-oxadiazoles with hydrazine hydrate. The reaction is considered to proceed[40-43] with the recyclization of 5-substituted-1,3,4-oxadiazole-2-thiol (scheme 2.15).



(Scheme: 2.15)

2.8 FROM THIOCARBOHYDRAZIDES

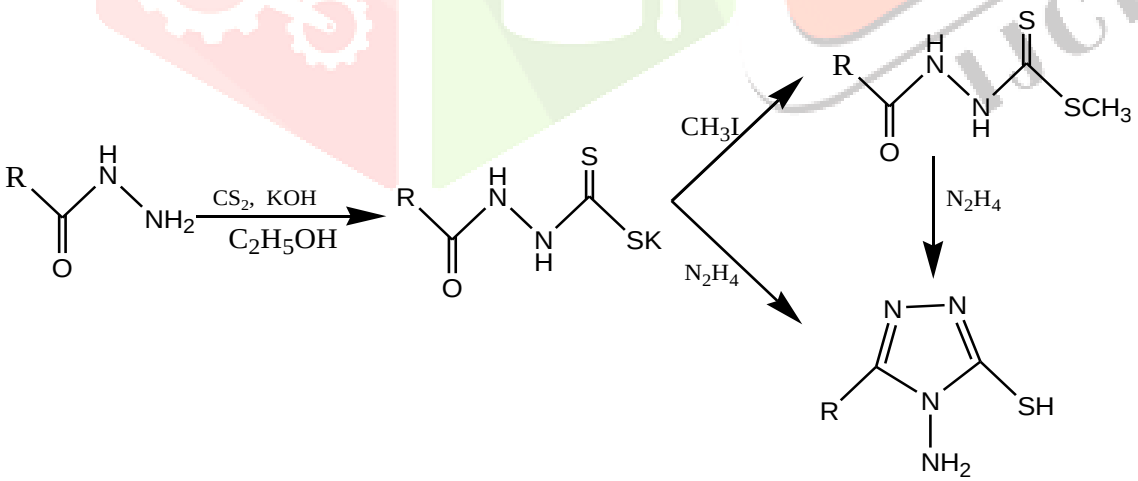
The condensation of thiocarbohydrazides with aliphatic and aromatic carboxylic acids is the widely used method[44-48] for the preparation of 5-alkyl/aryl-4-amino-1,2,4-triazole-3-thiols. The reaction was improved by using carboxylic acids at their melting points (scheme 2.16).



(Scheme: 2.16)

2.9 FROM CARBOXYLIC ACID HYDRAZIDES

In this method, the condensation of carboxylic acid hydrazides with carbon disulphide in ethanolic KOH yields potassium-3-aroyldithiocar-bazates and the latter was directly converted to 4-amino-1,2,4-triazole-3-thiol by the reaction with an excess of hydrazine[49]. The methylation of 3-aroyldithiocarbazates with methyl iodide provided the S-alkylated derivatives that also cyclised to 4-amino-1,2,4-triazole-3-thiol with hydrazine (scheme 2.17).



(Scheme: 2.17)

The increasing importance of 1,2,4-triazoles as agrochemicals inspired us to synthesize a new series viz 5-substituted-4-amino-1,2,4-triazole-3-thiol. In the present investigation entirely new solvent free environment friendly microwave assisted method is used for the synthesis of

substituted 4-amino-1,2,4-triazole-3-thiols. The conventional method is also used to compare the results.

2.10 EXPERIMENTAL

Melting points of all the synthesized compounds were determined on open aluminum block and are uncorrected. Purity was checked by thin layer chromatography using Merck silica gel G-60. IR spectra were recorded in KBr on Shimdzu Affinity-1 FTIR spectrophotometer. ^{1}H NMR spectra were recorded on Varian Gemini 400 spectrometer (300 MHz) using TMS as an internal standard.

CONVENTIONAL METHOD

1. Synthesis of Arylhydrazides

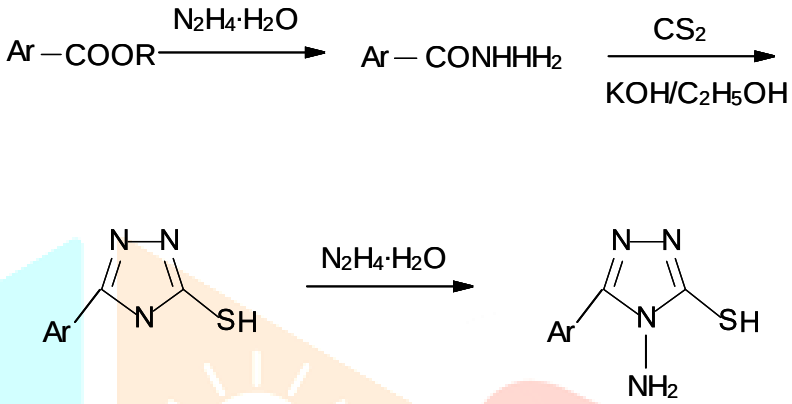
Hydrazine hydrate (10 mmol) was added to the esters of substitu-ted aromatic acids (10 mmol) and refluxed the solution for 30 min. To the refluxing mixture, 20 ml of ethanol was added as a solvent in order to homogenize the contents. The resulting mixture was further allowed to reflux for 6 hrs. Excess ethanol was distilled out and the contents were allowed to cool. The crystals formed were filtered, washed thoroughly with water and dried.

2. Synthesis of 5-(4-Substitutedphenyl)-1,3,4-oxadiazole-2-thiols

To a solution of aryl hydrazide **1** (10 mmol) in ethanol (30 ml), potassium hydroxide (10 mmol) in absolute ethanol (50 ml) and carbon disulfide (20 mmol) were added and refluxed for about 5 hrs. till evolu-tion of hydrogen sulfide ceased. The reaction mixture was cooled at room temperature and diluted with water. On acidification with dilute hydrochloric acid, the required oxadiazole derivative was precipitated out. It was filtered, washed thoroughly with cold water and recrystallized from ethanol.

3. Synthesis of 4-Amino-1,2,4-triazole-3-thiols

A mixture of compound **2** (10 mmol) and hydrazine hydrate (10 mmol) in dry pyridine (15 ml) was refluxed for about 4 hrs. The reaction mixture was cooled at room temperature and neutralized with dilute hydrochloric acid. The solid precipitated out was filtered, washed thoroughly with cold water and recrystallized from ethanol (scheme 2.18).



(Scheme: 2.18)

MICROWAVE ASSISTED METHOD

4-Amino-5-substituted-1,2,4-triazole-3-thiols were prepared in three steps by new environmentally benign solvent free methods using microwave irradiation. The conventional methods for synthesis of these intermediates require hazardous chemicals like pyridine etc and long heating systems. The yield obtained from microwave methods was better as compared to conventional method.

1. Synthesis of Arylhydrazides

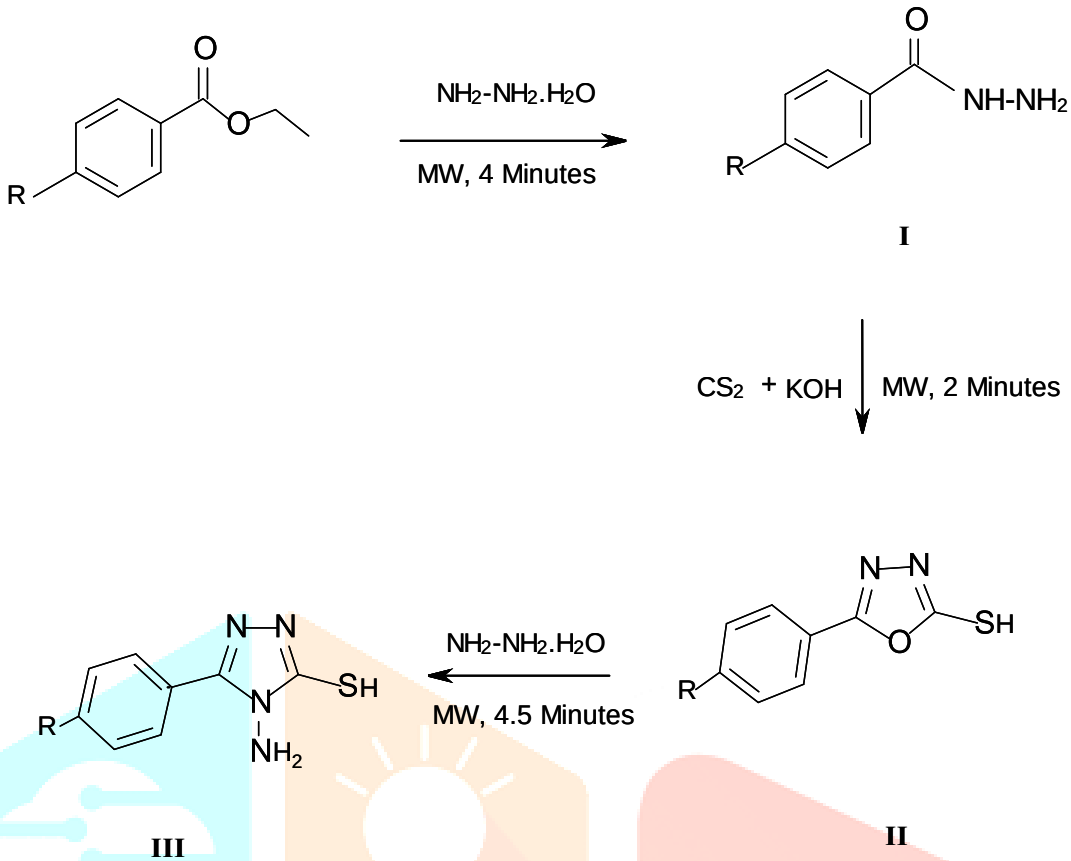
A mixture of esters of substituted aromatic acids (10 mmol) and hydrazine hydrate (10 mmol) exposed to microwave irradiations intermit-tently at 30 seconds for four minutes in microwave oven. After completion of reaction, the contents were allowed to cool at room temperature. The crystals separated out were filtered, washed thoroughly with water and dried to get aryl hydrazide (I).

1. Synthesis of 5-(4-Substitutedphenyl)-1,3,4-oxadiazole-2 thiols

A mixture of aryl hydrazide I (10 mmol) and potassium hydroxide (10 mmol) was well grinded to make a fine homogeneous powder. To this powder carbondisulfide (20 mmol) was added and exposed to microwave irradiations intermittently at 20 seconds for two minutes. The reaction mixture was cooled and neutralized with dilute hydrochloric acid. The solid separated out on neutralization was filtered, washed with cold water and dried. There is no need to purify the product 1,3,4-oxadiazole-2-thiol derivatives (II) for further reaction.

2. Synthesis of 4-Amino-1,2,4-triazole-3-thiols

A mixture of compound 2 (10 mmol) and hydrazine hydrate (10 mmol) was exposed to microwave irradiations intermittently at 30 seconds for 4.5 minutes. After completion of reaction as monitored by TLC, the hot reaction mixture was cooled at room temperature and neutralized with dilute hydrochloric acid. The solid separated out was filtered, washed thoroughly with water and crystallized from ethanol (scheme 2.19).



(Scheme: 2.19)

Following 4-amino-1,2,4-triazole-3-thiols have been synthesized

(1). 4-Amino-5-(4-methoxyphenyl)-1,2,4-triazole-3-thiol

(2). 4-Amino-5-(4-flurophenyl)-1,2,4-triazole-3-thiol

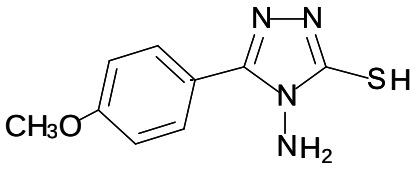
(3). 4-Amino-5-(4-chlorophenyl)-1,2,4-triazole-3-thiol

(4). 4-Amino-5-(4-bromophenyl)-1,2,4-triazole-3-thiol

(5). 4-Amino-5-(4-nitrophenyl)-1,2,4-triazole-3-thiol

(1). 4-Amino-5-(4-methoxyphenyl)-1,2,4-triazole-3-thiol

Molecular Formula : $C_9H_{10}N_4OS$



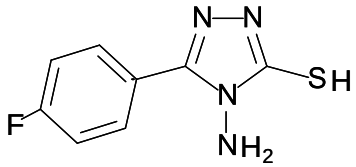
Yield : 68%, M.P. 204 ºC.

IR (KBr, ν_{max}, cm^{-1}): 3335, 3280 (N-H), 2570 (S-H), 1610 (C=N), 3010 (C-H, Ar).

^1H NMR ($CDCl_3$) δ: 5.45 (2H, s, NH_2), 12.50 (1H, s, SH), 7.45-7.80 (4H, m, H-Ar), 3.80 (3H, s, OCH_3).

(2). 4-Amino-5-(4-flurophenyl)-1,2,4-triazole-3-thiol

Molecular Formula : $C_8H_7FN_4S$



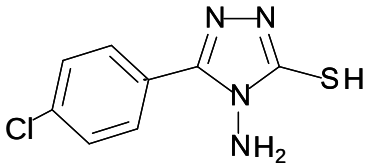
Yield : 65% , M.P. 139ºC.

IR (KBr, ν_{max}, cm^{-1}): 3420, 3315(N-H), 2590 (S-H), 1615 (C=N), 2980 (C-H, Ar).

^1H NMR ($CDCl_3$) δ: 5.40 (2H, s, NH_2), 12.15 (1H, s, SH), 6.75-7.30 (4H, m, H-Ar).

(3). 4-Amino-5-(4-chlorophenyl)-1,2,4-triazole-3-thiol

Molecular Formula : $C_8H_7ClN_4S$



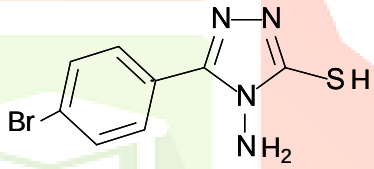
Yield : 70%, M.P. 212 ^{o}C.

IR (KBr, ν_{max}, cm^{-1}): 3350, 3270 (N-H), 2560 (S-H), 1545 (C=N), 695 (C-Cl).

^{1}H NMR ($CDCl_3$) δ: 5.75 (2H, s, NH_2), 12.5 (1H, s, SH), 7.60-8.10 (4H, m, Ar-H)

(4). 4-Amino-5-(4-bromophenyl)-1,2,4-triazole-3-thiol

Molecular Formula : $C_8H_7BrN_4S$



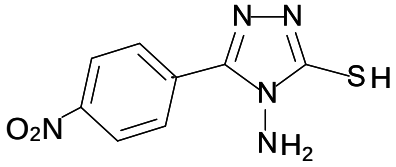
Yield : 70%, M.P. 205 ^{o}C.

IR (KBr, ν_{max}, cm^{-1}): 3350, 3260 (N-H), 2559 (S-H), 1545 (C=N), 1340 (C-N, Ar), 640 (C-Br).

$_{1}$H NMR ($CDCl_3$) δ: 5.70 (2H, s, NH_2), 13.0 (1H, s, SH), 7.70 (4H, m, Ar-H).

(5). 4-Amino-5-(4-nitroyphenyl)-1,2,4-triazole-3-thiol

Molecular Formula : $C_8H_7N_5O_2S$



Yield : 62%, M.P. 213 ^{o}C.

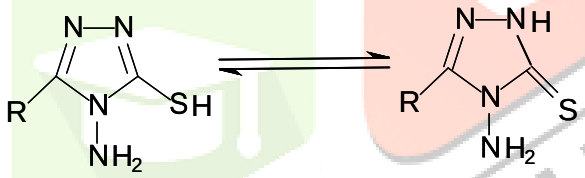
IR (KBr, ν_{max}, cm^{-1}): 3345,3275 (N-H), 2560 (S-H), 1555 (C=N), 1385 (C-NO_2).

^{1}H NMR ($CDCl_3$) δ: 5.20 (2H, s, NH_2), 12.5 (1H, s, SH), 8.00-8.25 (4H, m, Ar-H).

Spectral Analysis:

The structures of synthesized compounds have been confirmed by their spectral characteristics. In IR spectra, the position of characteristic absorption bands for NH_2, C=N and SH groups are in accordance with their assigned structures. The two sharp absorption bands in the regions 3420-3350 cm^{-1} and 3310-3250 cm^{-1} are observed due to the asymmetric and symmetric stretching vibrations of the primary amino group. An absorption band in the region 1540-1620 cm^{-1} is observed due to C=N stretching vibrations, and at 2550-2600 cm^{-1} due to SH group.

In the ^{1}H NMR spectra characteristic peaks for protons in NH_2 and SH groups are in accordance with the structure of synthesized 1,2,4-triazoles. The signal for the S-H proton on triazole ring was observed in these compounds as a singlet at 11.50-13.00 ppm and signal for the NH_2 was observed as a singlet between 5.20-5.80 ppm.



Thiol (1) Thione (2)

The absence of absorption band /peak corresponding to N-H and presence of S-H absorption confirm the thiol form (1) of triazole ring.

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