INTERNATIONAL JOURNAL OF PURE AND APPLIED RESEARCH IN ENGINEERING AND TECHNOLOGY

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SPECIAL ISSUE FOR INTERNATIONAL LEVEL CONFERENCE "ADVANCES IN SCIENCE, TECHNOLOGY & MANAGEMENT" (IC-ASTM)

SYNTHESIS OF TRIAZOLO-DITHIADIAZINES BY SULPHUR-SULPHUR BOND FORMATION THROUGH MICROWAVE ASSISTED CYCLOCONDENSATION AND BIOLOGICAL EVALUATION

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Accepted Date: 05/09/2017; Published Date: 10/10/2017

Abstract: Synthesis of 3-arylimino-6-pyridin-4-yl-[1,2,4]-triazolo-(3,4-c)-[1,2,4,5]-dithiadiazines by sulphur-sulphur bond formation through microwave assisted cyclocondensation was performed by treating 4-amino-3-mercapto-5-pyridin-4-yl-4H-[1,2,4]-triazole with *N*-aryl-*S*-chloro isothiocarbamoyl chlorides. Synthesis of 4-amino-3-mercapto-5-pyridin-4-yl-4H-[1,2,4]-triazole was carried out by reaction of isoniazide, carbondisulphide and potassium hydroxide followed by the addition of hydrazine hydrate. Triazolo-dithiadiazines were then acetylated to afford monoacetyl derivatives. Structures of all synthesized compounds were delineated by elemental analysis, equivalent weight determination, chemical transformation, IR, ^{1}H-NMR, mass spectral studies and evaluated for biological activity against different micro-organisms.

Keywords: Triazolo-dithiadiazines, microwave cyclocondensation, biological evaluation

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Access Online On:

www.ijpret.com

PAPER-QR CODE

How to Cite This Article:

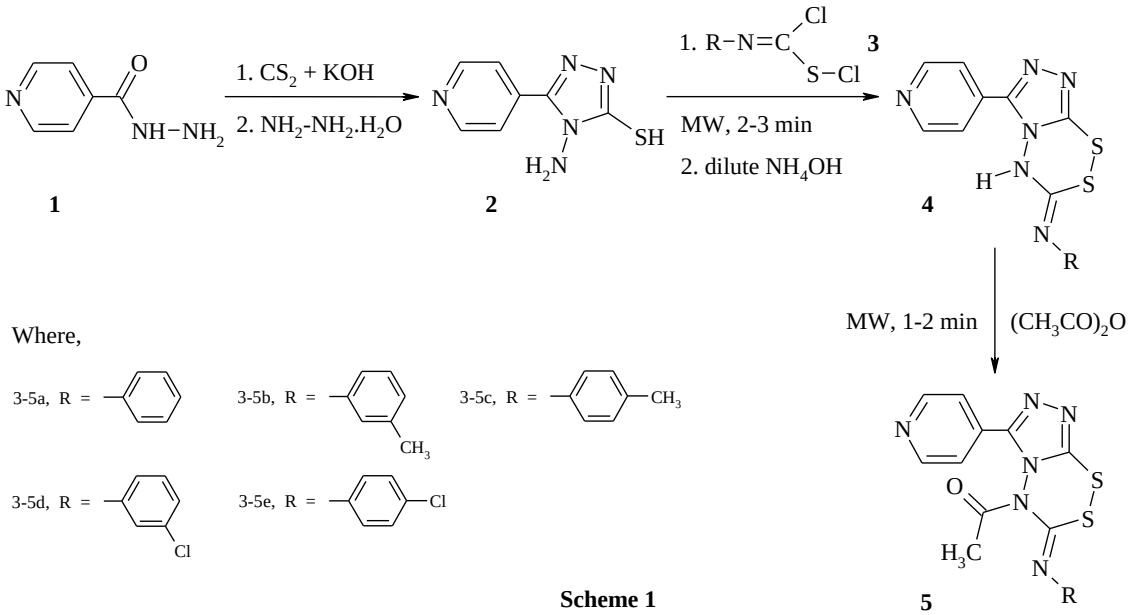
Pradip P. Deohate, IJPRET, 2017; Volume 6 (2): 233-237

INTRODUCTION

Microwave assisted synthesis of heterocyclic compounds has number of advantages over the conventional heating[1]. For accelerating time consuming reactions, high density microwave irradiation has emerged as a useful and reliable technology[2] and can be utilized for high speed parallel synthesis of bioactive compounds[3]. Compounds containing sulphur and nitrogen atoms possess variety of biological activities[4,5]. Synthesis, structural study and biological evaluation of various [1,2,4,5]-dithiadiazines was carried out earlier[6,7]. Therapeutic effect of compounds containing [1,2,4]-triazole and its derivatives have been studied for number of pathological conditions like cancer, pain, inflammation, hypertension and tuberculosis[8,9]. Fused [1,2,4]-triazoles have diverse applications in the field of medicine[10]. The *N*-aryl-*S*-chloro isothiocarbamoyl chlorides have enough potentiality in synthesis of nitrogen and sulphur containing heterocyclic compounds[11]. As a part of wider programme to provide alternative routes of synthesis[12,13] and as there is scanty work on synthesis of [1,2,4]-triazolo-[1,2,4,5]-dithiadiazines, we report herein the synthesis of [1,2,4]-triazolo-(3,4-c)-[1,2,4,5]-dithiadiazines by microwave assisted cyclocondensation method.

1 Results and Discussion

4-Amino-3-mercapto-5-pyridin-4-yl-4H-[1,2,4]-triazole **2** was synthesized by reacting isoniazide with carbondisulphide (0.01 mole) and potassium hydroxide (1M, 10 ml) followed by the addition of hydrazine hydrate (0.01 mole). The title compounds 3-arylimino-6-pyridin-4-yl-[1,2,4]-triazolo-(3,4-c)-[1,2,4,5]-dithiadiazines **4a-e** were synthesized by reacting [1,2,4]-triazole **2** with *N*-aryl-*S*-chloro isothiocarbamoyl chlorides **3a-e** (0.01 mole) under solvent free conditions by microwave irradiation. Cooling the reaction mixture afforded sticky masses. These on washing with petroleum ether gave granular solids, acidic to litmus and on equivalent weight determination found to be the hydrochlorides. These were basified with dilute ammonium hydroxide solution to afford free bases. Compounds **4a-e** were then acetylated with acetic anhydride to afford monoacetyl derivatives **5a-e (Scheme 1)**.



Scheme 1

2 Biological evaluation

Compounds **4a-e** were evaluated for biological activity using cup plate diffusion method[14,15]. The bacterial species used were *E. coli, S. typhi, B. subtilis* and *P. vulgaris*. Sensitivity plates were seeded with a bacterial innoculum of $1x10^6$ CIU ml^{-1} and each well of diameter 10 mm. was loaded with 0.1 ml of test compound solution (1000 µg ml^{-1}) in DMF, so that concentration of each test compound was 100 µg ml^{-1}. The zones of inhibition were recorded after incubation for 24 h at 37^0C, using vernier caliper. Inhibition zone record of the compounds clearly indicated that **4b** and **4c** were highly active against *E. coli* and moderately active against *S. typhi*. Majority of the compounds were found inactive against *P. vulgaris*. To determine minimum inhibitory concentration, serial dilution method[16] was used with nutrient broth medium. MIC values of compounds **4b** and **4c**, which were determined against *E. coli*, found to be 60 and 65 µg ml^{-1} respectively.

Screening of compounds **4a-e** for antifungal activity by paper disc method[17,18] with concentration 1%, showed that **4b** was highly active against *A. niger*, whereas other compounds showed low to moderate activity. The zones of inhibition were recorded after incubation for 48 h at 37^0C.

3 Experimental

Microwave assisted reactions were carried out using commercially available microwave oven (800 W). Chemicals used were of A.R. grade. Melting points of all compounds were recorded on Veego, VMP-D digital melting point apparatus and are uncorrected. ^{1}H-NMR spectra were recorded using Bruker Avance II 400 NMR spectrometer. IR spectra were recorded using Perkin-Elmer spectrophotometer in the range 4000-400 cm^{-1}. Purity of the compounds was checked using TLC.

Reagents *N*-aryl-*S*-chloro isothiocarbamoyl chlorides have been synthesized by passing chlorine gas (0.01 mole) through solution of aryl isothiocyanates (0.01 mole) in chloroform (10 ml), maintaining the temperature at 10^0C. Reaction mixtures were diluted with petroleum ether (60-80^0C) and solvent was distilled off under vacuum to obtained pale yellow oily liquids **3a-e**; ν_{max} 1652, 1703 (C=N), 840 cm^{-1} (C-S).

4-Amino-3-mercapto-5-pyridin-4-yl-4H-[1,2,4]-triazole 2.

4-Amino-3-mercapto-5-pyridin-4-yl-4H-[1,2,4]-triazole **2** was synthesized by interacting isoniazide **1** (0.01 mole) with carbondisulphide (0.01 mole) and potassium hydroxide solution (1M, 10 ml) followed by the dropwise addition of hydrazine hydrate (0.01 mole) with constant stirring. Then at room temperature mixture was stirred for 30 min., cooled and poured in distilled water to get white precipitate. It was crystallized from ethanol, **2** (85%), m.p. 145°C (Found: N, 35.82; S, 16.08. Calcd. for $C_7H_7N_5S$: N, 36.26; S, 16.58%).

3-phenylimino-6-pyridin-4-yl-[1,2,4]-triazolo-(3,4-c)-[1,2,4,5]-dithiadiazine 4a.

The mixture of 4-amino-3-mercapto-5-pyridin-4-yl-4H-[1,2,4]-triazole **2** (0.01 mole) and *N*-phenyl-*S*-chloro isothiocarbamoyl chloride **3a** (0.01 mole) was irradiated using microwave for 2 min. Acidic solid mass was obtained, it was basified with dilute ammonium hydroxide solution and crystallized from ethanol to give 3-phenylimino-6-pyridin-4-yl-[1,2,4]-triazolo-(3,4-c)-[1,2,4,5]-dithiadiazine **4a**, (92%), m.p. 162^0C (Found: N, 25.04; S, 19.66. Calcd. for $C_{14}H_{10}N_6S_2$: N, 25.76; S, 19.63%). The complete reaction was monitored by TLC and extended to synthesize the other compounds **4b** (80%), m.p. 243^0C ($C_{15}H_{12}N_6S_2$: N, 24.32; S, 18.79%); **c** (60%), m.p. 130^0C

($C_{15}H_{12}N_6S_2$: N, 24.03; S, 18.41%); **d** (65%), m.p. 122^{0}C ($C_{14}H_9N_6S_2Cl$: N, 23.05; S, 16.96%); **e** (80%), m.p. 178^{0}C ($C_{14}H_9N_6S_2Cl$: N, 22.94; S, 16.87%).

4-Acetyl-3-phenylimino-6-pyridin-4-yl-[1,2,4]-triazolo-(3,4-c)-[1,2,4,5]-dithiadiazine 5a.

Mixture of 3-phenylimino-6-pyridin-4-yl-[1,2,4]-triazolo-(3,4-c)-[1,2,4,5]-dithiadiazine **4a** (0.01 mole) and acetic anhydride (0.01 mole) was irradiated using microwave for 1.5 min. Cream solid was obtained, it was crystallized from ethanol to give compound **5a**, (95%), m.p. 201^{0}C. This reaction was extended to synthesize the other compounds **5b** (75%), m.p. 198^{0}C; **c** (65%), m.p. 204^{0}C; **d** (72%), m.p. 192^{0}C; **e** (70%), m.p. 222^{0}C.

4 Spectral data of compounds 2, 4a and 5a.

2, ν_{max} 3423, 3370 (NH), 1682 (C=N), 1298 (C-N), 1210 (N-N), 758 cm^{-1} (C-S)[19]; **4a**, ν_{max} 3416 (NH), 1667, 1608 (C=N), 1351, 1308, 1289 (C-N), 1231 (N-N), 742, 699 (C-S), 498 cm^{-1} (S-S); δ ($CDCl_3$+DMSO-d_6) 9.66 (1H, s, NH), 7.01-8.63 (9H, m, Ar-H and Py-H); MS: m/z 326 (M^+), 325 (M^+-H), 248 (M^+-C_5H_4N), 235 (M^+-C_6H_4-CH_3), 171 ($C_3HN_4S_2$-N^+)[20]; **5a**, ν_{max} 1708 (C=O), 1674, 1616 (C=N), 1340, 1318 (C-N), 1223 (N-N), 758, 715 (C-S), 494 cm^{-1} (S-S).

5 Acknowledgement

Author is thankful to Director, S.A.I.F, Punjab University, Chandigarh for providing analytical and spectral data. Thanks are also due to Dr. V. D. Nanoty, Principal, Shri R. L. T. College of Science, Akola for providing necessary facilities.

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