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MW INDUCED SYNTHESIS OF SOME PYRIMIDINE LINKED THIADIAZOLES AND STUDY OF THEIR ANTIMICROBIAL PROPERTIES

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ABSTRACT

The series of some interesting heterocyclic scaffolds (5-aryl/alkyl-amino-[1,3,4]-thiadiazol-2-yl-methyl)-(4,6-dimethyl-pyrimidin-2-yl)-amines (6) has been synthesized by the intramolecular cyclization of (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid N-(N'-aryl/alkyl-thioamido)-hydrazides (5) using *o*-phosphoric acid. The required hydrazides (5) were prepared by the interaction of (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid hydrazide (3) with differently substituted N-aryl/alkyl-isothiocyanates (4) under microwave conditions at 800 W. The hydrazide (3) was synthesized by reacting 2-amino-4,6-dimethyl-pyrimidine (1) with ethyl chloroacetate to give ethyl-(4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (2) followed by its condensation with hydrazine hydrate in ethanol medium by microwave irradiation. The formation of desired compounds was checked by TLC and their structural interpretation was done by chemical transformations, elemental analysis, equivalent weight determination and spectral studies viz. IR, ^{1}H-NMR, mass spectroscopy. The synthesized compounds were assayed for their antimicrobial properties.

KEYWORDS: Microwave, pyrimidine linked thiadiazolidines, biological activities.

INTRODUCTION

Mostly five membered aromatic systems having three hetero-atoms at symmetrical position have been studied because of their physiological properties. Thiadiazole is a member of azole class of heterocycle with di-unsaturated ring containing two carbons, two nitrogens and one

sulphur atom.[1] During recent years there has been extensive investigation of different classes of thiadiazole compounds, many of which known to possess interesting biological properties such as antimicrobial[2], antituberculosis[3], anticonvulsants[4], anti-inflammatory, antihypersensitive[5], antioxidant[6], human adenosine A3 antagonist[7], anticancer[8] and antifungal activity.[9] Thiadiazole exists in four isomeric forms viz. 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole and 1,3,4-thiadiazole.[10] The 1,3,4-thiadiazole are core skeletons subjected to various substitution reactions to afford various drugs.[11] The substituted 1,3,4-thiadiazole nucleus is particularly ubiquitous and found in some marketed drugs such as acetazolamine, methazolamine and antibacterial such as sulphamethazole, antibiotic like cefazoline[12]. The synthesis of 1,3,4-thiadiazole derivatives has been allured widespread attention due to their biological activities. Prompted by the abundance in literature reviews and as a part of our study to develope novel biologically potent molecules, synthesis of (5-aryl/alkyl-amino-[1,3,4]-thiadiazol-2-yl-methyl)-(4,6-dimethyl-pyrimidin-2-yl)-amines have been performed by environmentally benign MW induced technique.

MATERIALS AND METHODS

The melting points of all synthesized compounds were determined using Veego, VMP-D digital melting point apparatus and are uncorrected. The chemicals used were of AR grade. The elemental analysis of carbon, hydrogen and sulphur was done using Carlo-Erba analyser whereas nitrogen estimation was carried using Colman-N-analyser-29. The purity of synthesized compounds was checked by TLC. The reactions were performed at 800 W in GMG20E-08-SLGX microwave oven. IR spectra were recorded using Perkin-Elmer spectrophotometer whereas ^{1}H-NMR spectra using Bruker-DRX-600 spectrophotometer with TMS as internal standard and $CDCl_3$ and DMSO-d_6 as solvents. Mass spectra were obtained by using Jeol-JMC-300 spectrometer by EI method at 70 eV. The synthesis of title compounds was done as follows.

Ethyl-(4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (2)

The compound ethyl-(4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (2) was synthesized by irradiation of mixture of 2-amino-4,6-dimethyl-pyrimidine (1) (0.01 mole) and ethyl chloroacetate (0.01 mole) in 1,4-dioxane under microwave conditions for 4 min. 10 sec. in presence of anhydrous potassium carbonate as a catalyst. The formation of ethyl-(4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (2) was confirmed by TLC. The product obtained was crystallized from ethanol (2), m.p. 142^{0}C, yield 88% (Found: C, 55.11; H, 6.98; N,

20.10. Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.41; H, 7.17; N, 20.09%).

(4,6-Dimethyl-pyrimidin-2-yl-amino)-acetic acid hydrazide (3)

The compound (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid hydrazide (3) was synthesized by irradiation of mixture of ethyl-(4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (2) (0.01 mole) and hydrazine hydrate (0.01 mole) in 1,4-dioxane under microwave conditions for 1 min. 30 sec. The progress of reaction was monitored by TLC. The solid mass obtained was crystallized from ethanol (3), m.p. 138^0C, yield 88% (Found: C, 48.17; H, 6.38; N, 35.01. Calcd. for $C_8H_{13}N_5O$: C, 49.22; H, 6.71; N, 35.87%); IR: 3401, 3310 (NH), 1729 (C=O), 1628 (C=N), 1336 (C-N), 1156 cm^{-1} (N-N); ^{1}H NMR ($CDCl_3$+DMSO-d_6): 7.38 (3H, bs, NH-NH_2), 6.46 (1H, s, Pyrm-NH), 6.32 (1H, s, Pyrm-H), 3.57 (2H, s, CO-CH_2), 2.17 (6H, s, Pyrm-CH_3).

(4,6-Dimethyl-pyrimidin-2-yl-amino)-acetic acid N-(N'-phenyl-thioamido)-hydrazide (5a)

The compound (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid N-(N'-phenyl-thioamido)-hydrazide (5a) was synthesized by irradiation of mixture of (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid hydrazide (3) (0.01 mole) and N-phenyl-isothiocyanate (4a) (0.01 mole) in chloroform under microwave conditions for 1 min. 20 sec. The progress of reaction was monitored by TLC. The solid mass separated out was crystallized from ethanol (5a), m.p. 134^0C, yield 79% (Found: C, 53.77; H, 5.05; N, 25.40; S, 9.08. Calcd. for $C_{15}H_{18}N_6OS$: C, 54.54; H, 5.45; N, 25.45; S, 9.69%); IR: 3402, 3311 (NH), 1764 (C=O), 1649 (C=N), 1311 (C-N), 1246 (C=S), 1170 cm^{-1} (N-N); ^{1}H NMR ($CDCl_3$+DMSO-d_6): 7.99 (1H, s, CO-NH), 7.75 (1H, s, Ar-NH), 7.73 (1H, s, CS-NH), 7.09-7.58 (5H, m, Ar-H), 6.41 (1H, s, Pyrm-NH), 6.29 (1H, s, Pyrm-H), 3.64 (2H, s, CO-CH_2), 2.21 (6H, s, Pyrm-CH_3). The other compounds (5b-h) were synthesized by extending the above reaction using substituted N-aryl/alkyl-isothiocyanates (4b-h): (5b) (84%), m.p. 118^0C; (5c) (87%), m.p. 112^0C; (5d) (88%), m.p. 111^0C; (5e) (79%), m.p. 64^0C; (5f) (91%), m.p. 149^0C; (5g) (88%), m.p. 210^0C; (5h) (90%), m.p. 94^0C. The formation of products was verified on silica gel-G plates by TLC.

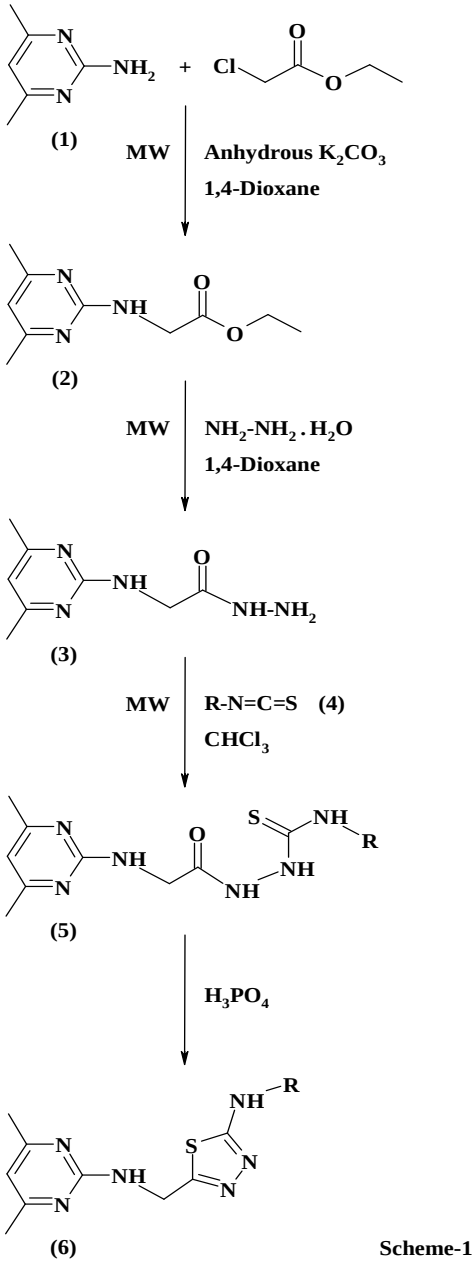
(4,6-Dimethyl-pyrimidin-2-yl)-(5-phenyl-amino-[1,3,4]-thiadiazol-2-yl-methyl)-amine (6a)

The compound (4,6-dimethyl-pyrimidin-2-yl)-(5-phenyl-amino-[1,3,4]-thiadiazol-2-yl-methyl)-amine (6a) was synthesized by intramolecular cyclization of (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid N-(N'-phenyl-thioamido)-hydrazide (5a) using *o*-

phosphoric acid. The formation of compound was confirmed by TLC. During synthesis, *o*-phosphoric acid (10 ml) was added to the compound (5a) (0.01 mole) dropwise with constant stirring for 30 min. The reaction mixture was left for 3 hr. at room temperature and poured in distilled water, the solid separated was crystallized from ethanol (6a), m.p. 107^0C, yield 94%. (Found: C, 56.60; H, 5.07; N, 26.83; S, 10.20. Calcd. for $C_{15}H_{16}N_6S$: C, 57.69; H, 5.12; N, 26.92; S, 10.25%); IR: 3396, 3186 (NH), 1628 (C=N), 1312 (C-N), 1165 (N-N), 749 cm^{-1} (C-S); ^{1}H NMR ($CDCl_3$+DMSO-d_6): 6.87-7.99 (5H, m, Ar-H), 6.40 (1H, s, Ar-NH), 6.32 (1H, s, Pyrm-H), 6.30 (1H, s, Pyrm-NH), 2.51 (2H, s, CH_2), 2.16 (6H, s, CH_3); MS: m/z 312 (M^+), 297 (M^+-CH_3), 220 (M^+-C_6H_5.NH), 176 (M^+-$(CH_3)_2$.C_4HN_2.NH.CH_2), 136 $(CH_3)_2$.C_4HN_2.NH.CH_2^+), 122 $(CH_3)_2$.C_4HN_2.NH^+). This reaction was extended to synthesize other compounds (6b-h): (6b) (88%), m.p. 111^0C (Found: C, 57.44; H, 5.48; N, 24.91; S, 9.70. Calcd. for $C_{16}H_{18}N_6S$: C, 58.89; H, 5.52; N, 25.76; S, 9.81%); IR: 3394, 3193 (NH), 1631 (C=N), 1310 (C-N), 1162 (N-N), 746 cm^{-1} (C-S); ^{1}H NMR ($CDCl_3$+DMSO-d_6): 6.79-7.95 (4H, m, Ar-H), 6.56 (3H, s, Pyrm-NH, Ar-NH, Pyrm-H), 2.53 (2H, s, CH_2), 2.42 (3H, s, Ar-CH_3), 2.28 (6H, s, CH_3); MS: m/z 325 (M^+-H), 311 (M^+-CH_3), 235 (M^+-C_6H_4.CH_3), 204 (M^+-$(CH_3)_2$.C_4HN_2.NH), 122 $(CH_3)_2$.C_4HN_2.NH^+), 106 (CH_3.C_6H_4.NH^+), 91 (CH_3.$C_6H_4^+$); (6c) (84%), m.p. 128^0C; (6d) (82%), m.p. 179^0C; (6e) (84%), m.p. 120^0C; (6f) (90%), m.p. 188^0C; (6g) (95%), m.p. 162^0C; (6h) (90%), m.p. 132^0C. The formation of products was verified on silica gel-G plates by TLC.

RESULTS AND DISCUSSION

The compound ethyl-(4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (2) was synthesized by reacting 2-amino-4,6-dimethyl-pyrimidine (1) with ethyl chloroacetate in 1,4-dioxane medium using anhydrous potassium carbonate as a catalyst. The product (2) was reacted with hydrazine hydrate in 1,4-dioxane to obtain (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid hydrazide (3) and further reacted with N-phenyl-isothiocyanate (4a) to give (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid N-(N'-phenyl-thioamido)-hydrazide (5a). The compound (5a) was reacted with *o*-phosphoric acid to undergo intramolecular cyclization to produce (4,6-dimethyl-pyrimidin-2-yl)-(5-phenyl-amino-[1,3,4]-thiadiazol-2-yl-methyl)-amine (6a). All these reactions were performed by MW induced technique. The other compounds (5-aryl/alkyl-amino-[1,3,4]-thiadiazol-2-yl-methyl)-(4,6-dimethyl-pyrimidin-2-yl)-amines (6b-h) were synthesized by extending the above reaction (Scheme-1). All the synthesized compounds were characterized using spectral techniques[13-15]. The structural properties of these compounds were confirmed by elemental analysis[16].



Where,

4-6a: R =

4-6b: R = CH_3

4-6c: R = CH_3

4-6d: R = H_3C

4-6e: R = Cl

4-6f: R = Cl

4-6g: R = Cl

4-6h: R =

Scheme-1

Antimicrobial activity

To do the antimicrobial screening, various methods are proposed[17]. In present study the synthesized compounds were evaluated for antibacterial activity by Kirby-Baeur method[18-20]. Sensitivity plates were seeded with bacterial inoculums of $1x10^6$ CIU/mL. Each well of diameter 10 mm was loaded with 0.1 mL of test solution of 1000 µg/mL concentration in DMF. After incubation at 37ºC for 24 hr, the zones of inhibition were recorded using Vernier caliper. Both gram-positive and gram-negative bacteria were used. The medium used for antibacterial study was Hi-media Laboratories Pvt. Ltd., India make nutrient agar of bacteristatic grade and found to be suitable for the growth of all bacteria used in the present study.

The antibacterial screening and inhibition effect of the compounds (6a-h) on the growth of various bacteria showed that, the compound (6b) was found to be most sensitive (bactericidal) against the microorganisms *E. coli*, *S. typhi* and *S. aureus* whereas the compound (6h) was found to be resistant. Majority of the compounds were found to be moderately sensitive against these bacteria. The drug ofloxacin was used as standard for comparison purpose. For determination of minimum inhibitory concentration, the serial dilution technique using nutrient broth medium was used. The MIC[21] values of compounds (6b) against *E. coli* and *S. aureus* were found to be 80 and 90 µg/mL respectively.

CONCLUSION

In present work, MW induced synthesis of some interesting heterocyclic scaffolds (5-aryl/alkyl-amino-[1,3,4]-thiadiazol-2-yl-methyl)-(4,6-dimethyl-pyrimidin-2-yl)-amines has been reported. This technique of heterocyclic synthesis was found to be most simple, efficient, eco-friendly and products obtained were of high purity and good quality with high percent yield.

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