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MICROWAVE ASSISTED SYNTHESIS OF SOME PYRIMIDINE LINKED THIADIAZOLIDINES AND EVALUATION OF THEIR BIOLOGICAL ACTIVITIES

Kalpana A. Palaspagar and Pradip P. Deohate *

Department of Chemistry, Shri Radhakisan Laxminarayan Toshniwal College of Science, Akola-444001, India.

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***Corresponding Author**
Dr. Pradip P. Deohate
Department of Chemistry,
Shri Radhakisan
Laxminarayan Toshniwal
College of Science,
Akola-444001, India.

ABSTRACT

In the present work efforts are made for microwave assisted synthesis and characterization of series of 1-(5-aryl/alkylimino-2-phenylimino-[1,3,4]-thiadiazolidin-3-yl)-2-(4,6-dimethyl-pyrimidin-2-yl-amino)-ethanones. The reaction initiated by reacting 2-amino-4,6-dimethyl-pyrimidine with ethyl chloroacetate to give ethyl (4,6-dimethyl-pyrimidin-2-yl-amino)-acetate which on further reaction with hydrazine hydrate afforded (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid hydrazide. The hydrazide was reacted with N-aryl/alkyl isothiocyanates and further with N-phenyl isocyanodichloride and basified to afford the title compounds exhibiting differently substituted constrained pharmacophores. The purity of compounds was checked by TLC and constituents of compounds delineated by chemical transformations, IR, ^{1}H-NMR and mass spectral studies. The title compounds were assayed for their biological activities.

KEYWORDS: Microwave, pyrimidine linked thiadiazolidines, biological activities.

INTRODUCTION

The heterocyclic compounds especially with distinguished pharmacological activities have proved to be excellent and versatile drugs in the field of medicinal chemistry.[1] Pyrimidine as a heterocyclic compound is an excellent core structure with diversified therapeutic applications.[2] Its fascinating use as a medicinally important compound is evidential from its varied biological properties.[3] Similar to pyrimidine; thiadiazolidines[4-8] also shows remarkably unique properties like antibacterial, anti-inflammatory, antifungal, anti-tubercle,

antiviral etc.[9-11] The fusion of pyrimidine nucleus with thiadiazolidine derivatives proved to be excellent biological compounds.[12]

In the present work efforts are made for microwave assisted synthesis[13-14] and characterization of series of 1-(5-aryl/alkylimino-2-phenylimino-[1,3,4]-thiadiazolidin-3-yl)-2-(4,6-dimethyl-pyrimidin-2-yl-amino)-ethanones.

MATERIALS AND METHODS

Melting points of all the synthesized compounds were determined on a digital melting point apparatus (Veego, VMP-D) and are uncorrected. All chemicals used were of AR grade. The C, H and S analysis was carried out on Carlo-Erba analyser, N estimation was carried out on Colman-N-analyser-29. Purity of the title compounds were checked by TLC. All the reactions carried out in GMG20E-08-SLGX microwave oven at 800 W. IR spectra were recorded on Perkin-Elmer spectrophotometer using KBr disc. ^{1}H-NMR spectra were obtained on a Bruker-DRX-600 spectrophotometer in $CDCl_3$ with TMS as internal standard using $CDCl_3$ and DMSO-d_6 as solvents. Mass spectral measurements were carried out by EI method on a Jeol-JMC-300 spectrometer at 70 eV. The reagents used in the synthesis of 1-(5-aryl/alkylimino-2-phenylimino-[1,3,4]-thiadiazolidin-3-yl)-2-(4,6-dimethyl-pyrimidin-2-yl-amino)-ethanones (7a-h) have been prepared as follows.

Synthesis of ethyl (4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (2)

The parent compound ethyl (4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (2) was prepared by irradiating the mixture of 2-amino-4,6-dimethyl-pyrimidine (1) (0.01 mole) and ethyl chloroacetate (0.01 mole) in 1,4-dioxane under microwave for 4 min. 10 sec. using anhydrous potassium carbonate as a catalyst. When 1,4-dioxane was evaporated, crude solid mass was obtained, it was crystallised from absolute ethanol and identified as ethyl (4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (2), yield 88%, m.p. 142^{0}C (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%).

Synthesis of (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 prepared by irradiating the 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 for 1 min. 30 sec., progress of the reaction was monitored by TLC. The crude solid mass obtained was crystallised from absolute ethanol in cold condition (3), yield 88%, m.p. 138^{0}C (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), 1705 (C=O), 1628 (C=N), 1336 (C-N), 1156 cm^{-1} (N-N); ^1H NMR ($CDCl_3$+DMSO-d_6): 7.38 (1H, s, CO-NH), 6.46 (1H, s, Pyrm-NH), 6.32 (1H, s, Pyrm-H), 3.57 (2H, s, CO-CH_2), 2.52 (2H, s, NH_2), 2.17 (6H, s, Pyrm-CH_3).

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

The 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 was irradiated in a microwave oven for 1 min. 30 sec., progress of the reaction was monitored by TLC. The crude solid mass obtained was crystallized from ethanol in cold condition and identified as (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid N-(N'-phenyl-thioamido)-hydrazide (5a), yield 79%, m.p. 134^{0}C (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); ^1H 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). This reaction was extended to synthesize other compounds (5b-h) using different N-aryl/alkyl isothiocyanates (4a-h): (5b) (84%), m.p. 118^{0}C; (5c) (87%), m.p. 112^{0}C; (5d) (88%), m.p. 111^{0}C; (5e) (79%), m.p. 64^{0}C; (5f) (91%), m.p. 149^{0}C; (5g) (88%), m.p. 210^{0}C; (5h) (90%), m.p. 94^{0}C. The reactions were monitored on silica gel-G plates by TLC.

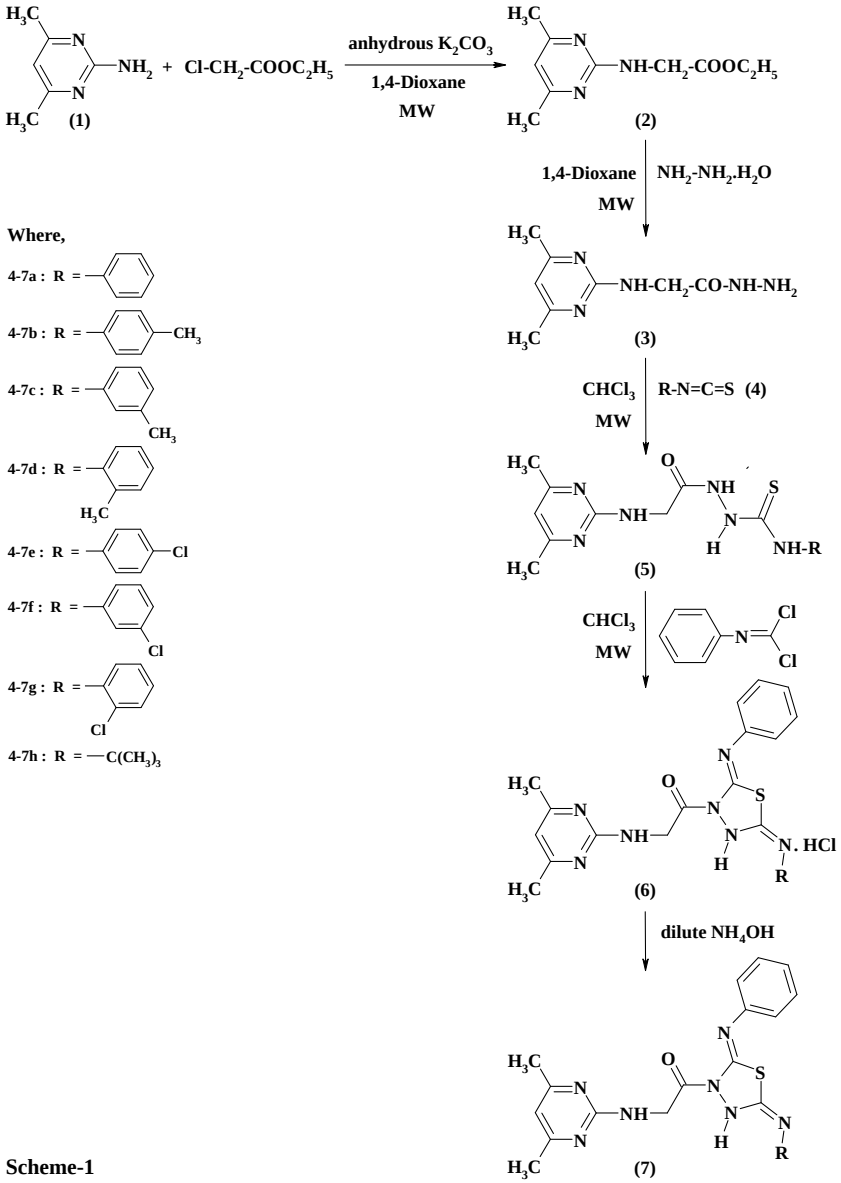
Synthesis of 2-(4,6-dimethyl-pyrimidin-2-yl-amino)-1-(2,5-diphenylimino-[1,3,4]-thiadiazolidin-3-yl)-ethanone (7a)

The mixture of (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid N-(N'-phenyl-thioamido)-hydrazide (5a) (0.01 mole) and N-phenyl isocyanodichloride (0.01 mole) in chloroform was irradiated under microwave for 1 min. 30 sec., which leads to the formation of sticky mass. It was repeatedly washed with petroleum ether (60-80^{0}C). The separated solid was acidic to litmus and identified as 2-(4,6-dimethyl-pyrimidin-2-yl-amino)-1-(2,5-diphenylimino-[1,3,4]-thiadiazolidin-3-yl)-ethanone hydrochloride (6a). It on basification with dilute ammonium hydroxide solution afforded a free base (7a). It was crystallized from ethanol, yield 83%, m.p. 139^{0}C (Found: C, 59.91; H, 4.66; N, 22.68; S, 7.11. Calcd. for $C_{22}H_{21}N_7OS$: C, 61.25; H, 4.87; N, 22.72; S, 7.42%); IR: 3414, 3309 (NH), 1757 (C=O), 1649 (C=N), 1311 (C-N), 1170 (N-N), 773 cm^{-1} (C-S); ^1H NMR ($CDCl_3$+DMSO-d_6): 6.89-7.76 (10H, m, Ar-H), 6.36 (1H, s,

Pyrm-NH), 6.30 (1H, s, Pyrm-H), 3.68 (2H, s, CO-CH_2), 2.43 (1H, s, Thdz-H), 2.18 (6H, s, Pyrm-CH_3); MS: m/z 431 (M^+), 416 (M^+-CH_3), 324 (M^+-$(CH_3)_2.C_4HN_2$), 295 (M^+-$(CH_3)_2.C_4HN_2.NH.CH_2$), 267 (M^+-$(CH_3)_2.C_4HN_2.NH.CH_2.CO$), 164 $(CH_3)_2.C_4HN_2.NH.CH_2.CO^+$), 122 $(CH_3)_2.C_4HN_2.NH^+$), 107 $(CH_3)_2.C_4HN_2^+$). This reaction was extended to synthesize other compounds (7b-h): (7b) (72%), m.p. 116^0C (Found: C, 61.43; H, 5.02; N, 21.88; S, 6.82. Calcd. for $C_{23}H_{23}N_7OS$: C, 62.02; H, 5.16; N, 22.02; S, 7.19%); IR: 3400, 3307 (NH), 1755 (C=O), 1639 (C=N), 1311 (C-N), 1170 (N-N), 775 cm^{-1} (C-S) ; ^{1}H NMR ($CDCl_3$+DMSO-d_6): 6.92-7.75 (9H, m, Ar-H), 6.30 (1H, s, Pyrm-NH), 6.22 (1H, s, Pyrm-H), 3.37 (2H, s, CO-CH_2), 2.44 (1H, s, Thdz-H), 2.29 (3H, s, Ar-CH_3), 2.23 (6H, s, Pyrm-CH_3); (7c) (87%), m.p. 135^0C; (7d) (90%), m.p. 144^0C; (7e) (82%), m.p. 80^0C; (7f) (87%), m.p. 105^0C; (7g) (92%), m.p. 120^0C; (7h) (84%), m.p. 91^0C. The reactions were monitored on silica gel-G plates by TLC.

RESULTS AND DISCUSSION

The starting product ethyl (4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (2) was prepared by the reaction of 2-amino-4,6-dimethyl pyrimidine (1) and ethyl chloroacetate in 1,4-dioxane medium using anhydrous potassium carbonate as a catalyst[2]. The product ethyl (4,6-dimethyl-pyrimidin-2-yl-amino)-acetate (2) was reacted with hydrazine hydrate in 1,4-dioxane to give (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid hydrazide (3) and further reacted with N-phenyl isothiocyanate (4a) to afford (4,6-dimethyl-pyrimidin-2-yl-amino)-acetic acid N-(N'-phenyl-thioamido)-hydrazide (5a). The compound (5a) was reacted with N-phenyl isocyanodichloride in chloroform medium to yield 2-(4,6-dimethyl-pyrimidin-2-yl-amino)-1-(2,5-diphenylimino-[1,3,4]-thiadiazolidin-3-yl)-ethanone hydrochloride (6a). It on basification with dilute ammonium hydroxide solution afforded a free base 2-(4,6-dimethyl-pyrimidin-2-yl-amino)-1-(2,5-diphenylimino-[1,3,4]-thiadiazolidin-3-yl)-ethanone (7a). All these reactions were carried by microwave irradiation. These reactions were extended to synthesize 1-(5-aryl/alkylimino-2-phenylimino-[1,3,4]-thiadiazolidin-3-yl)-2-(4,6-dimethyl-pyrimidin-2-yl-amino)-ethanones (7b-h) (Scheme-1).



Scheme-1

The products obtained were characterized by spectral method.[15-17] The elemental analysis[18] satisfied the structural properties of the synthesized compounds. To conclude, the chemistry of the reactions employed together with their chemical behaviour was discussed exhibiting the importance of novel molecular templates.

Antimicrobial activity

Various methods have been proposed and adopted for the measurement of antimicrobial activity.[19] In present antimicrobial study the newly synthesized compounds were screened for their antibacterial activity using Kirby-Baeur method.[20-22] Sensitivity plates were seeded with a bacterial inoculum of 1×10^6 CIU/mL and each well diameter 10 mm was loaded with 0.1 mL of test compound solution 1000 µg/mL. The zones of inhibition were recorded after

incubation for 24 hr at 37ºC, using Vernier caliper. The bacterial organisms used included both gram-positive as well as gram-negative strains. The medium used for the study of antibacterial activity of newly synthesized compounds was Hi-media Laboratories Pvt. Ltd., India make nutrient agar. It was of bacteristatic grade and found to be suitable for the growth of all bacterial strains used in the present study.

The antibacterial activity and inhibition effect of the compounds (7a-h) on the growth of various bacterial organisms is summarised in table given below along with the inhibition effect of standard drug streptomycin for comparison purpose. The compound (7e) was found to be highly sensitive (bactericidal) against the microorganisms *E. coli* and *P. vulgaris* whereas moderately sensitive against *B. subtilis*. Majority of the compounds were found to be moderately sensitive against *S. aureus* and slightly sensitive against *B. subtilis*. Compound (7h) was resistant against almost all the microorganisms. To determine the minimum inhibitory concentration (MIC), the serial dilution technique was followed using nutrient broth medium. The MIC [23] values of compounds (7e) against *E. coli* and *P. vulgaris* were found to be 60 and 64 µg/mL respectively.

Antibacterial activity of 1-(5-aryl/alkylimino-2-phenylimino-[1,3,4]-thiadiazolidin-3-yl)-2-(4,6-dimethyl-pyrimidin-2-yl-amino)-ethanones (7a-h)

Compounds	Microorganisms				
	E. coli	***S. aureus***	***S. typhi***	***B. subtilis***	***P. vulgaris***
7a	S 14	S 16	S 16	S 14	S 11
7b	S 13	S 18	S 11	S 11	R
7c	S 15	S 17	R	S 12	S 12
7d	S 18	S 19	R	S 15	R
7e	S 22	S 15	S 11	S 17	S 23
7f	S 19	S 14	S 17	S 12	S 15
7g	R	S 16	S 19	S 14	S 14
7h	R	S 13	R	R	R
Streptomycin	S 23	S 20	S 22	S 18	S 13

(Concentration 100 µg/ml) (Diameter of inhibition zone in mm)

R (Resistant) : (11 mm and below)

S (Sensitive) (Bactericidal) : (11 mm above)

Slightly Sensitive : (11 mm above to 15 mm)

Moderately Sensitive : (15 mm above to 20 mm)

Highly Sensitive : (20 mm above)

CONCLUSION

In present work microwave irradiative synthesis of 1-(5-aryl/alkylimino-2-phenylimino-[1,3,4]-thiadiazolidin-3-yl)-2-(4,6-dimethyl-pyrimidin-2-yl-amino)-ethanones has been reported. The compounds obtained were of good quality and purity with high % yield. Microwave assisted method applied for the synthesis is quite simple, efficient, fast, clean, economic and eco-friendly.

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