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Microwave Assisted Synthesis and Biological Evaluation of Some Novel Pyrimidine Linked Pyrazoles

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Abstract

Microwave assisted synthesis and characterization of some heterocycles containing pyrimidine linked pyrazole derivatives has been carried out. A series of (2-aryl/H-5-methyl-pyrazol-3-yl)-(4,6-dimethyl-pyrimidin-2-yl)-amines has been synthesized by microwave assisted method. The starting material N-(4,6-dimethyl-pyrimidin-2-yl)-3-oxo-butyramide has been synthesized by the reaction of 2-amino-4,6-dimethyl pyrimidine and ethyl acetoacetate. The title compounds were synthesized from N-(4,6-dimethyl-pyrimidin-2-yl)-3-oxo-butyramide and substituted hydrazines. The structural evaluation of synthesized compounds has been performed by IR, ^{1}H-NMR and mass spectroscopic data with elemental analysis.

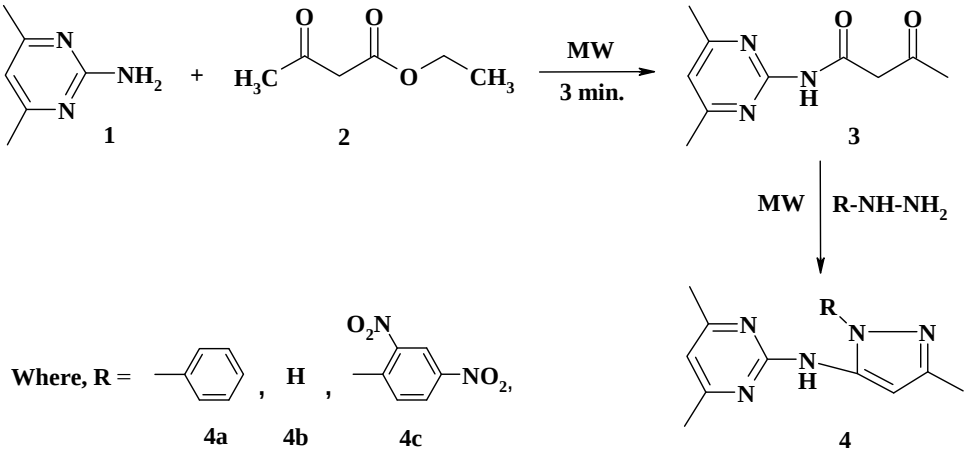
Keywords: Microwave synthesis, pyrimidine linked pyrazoles.

Introduction

Heteroaromatics are a class of exceedingly important compounds to organic chemists. Pyrimidine has emerged in its usage as a core structure in the diversified therapeutic applications. Similar to it pyrazoles are gaining much attention from the field of therapeutics due to its fascinating applications in medicinal chemistry. These promising nuclei serve to be a basic moiety for a number of bioactive compounds[1-9]. In present work the microwave assisted synthesis[1] and characterization of some heterocycles containing pyrimidine linked pyrazoles[4] have been carried out. The series of compounds (2-aryl/H-5-methyl-pyrazol-3-yl)-(4,6-dimethyl-pyrimidin-2-yl)-amines has been synthesized.

Experimental

The starting product N-(4,6-dimethyl-pyrimidin-2-yl)-3-oxo-butyramide was prepared by microwave induced reaction of 2-amino-4,6-dimethyl pyrimidine and ethyl acetoacetate. The product N-(4,6-dimethyl-pyrimidin-2-yl)-3-oxo-butyramide was further treated with phenyl hydrazine to afford (4,6-dimethyl-pyrimidin-2-yl)-(5-methyl-2-phenyl-2H-pyrazol-3-yl)-amine. This product obtained exhibited a single spot in TLC[10] and was crystallized from absolute alcohol. The reaction was further extended to afford the (2-aryl/H-5-methyl-pyrazol-3-yl)-(4,6-dimethyl-pyrimidin-2-yl)-amines by reacting N-(4,6-dimethyl-pyrimidin-2-yl)-3-oxo-butyramide with substituted hydrazines. The synthesized products were further acetylated with acetic acid and acetic anhydride.



The products obtained were characterized by spectral method.[11] The IR spectrum of the compounds showed characteristic peak at 3018 cm^{-1} indicated amino group for **4a** and 1672 cm^{-1} characteristic peak of nitro group for **4c**. ^1H NMR spectrum of the compounds indicated signal at δ 7.39-9.11 and δ 6.1-6.37 for the presence of aromatic ring linked to pyrazole nucleus and pyrimidine ring respectively. In mass spectrum base peak observed at *m/z* 279 for **4a** and elemental analysis fully agrees with the structures of all compounds. The elemental analysis satisfies 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

The synthesized compounds **4a** and **4c** were screened for their antibacterial activity using cup plate diffusion method (Kirby-Baur method)[12]. The bacterial organisms used included both gram-positive as well as gram-negative strains like *E. coli*, *S. aureus*, *S. typhi*, *B. subtilis* and *A. aerogenes*. 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. Inhibition zone record of the compounds indicated that **4a** and **4c** were highly active against *E.coli* and *B. subtilis* and moderately active against *S. aureus*. The compounds were inactive against *A. aerogenes*. To determine the minimum inhibitory concentration (MIC), the serial dilution technique was followed using nutrient broth medium. The MIC values of compounds **4a** and **4c** were determined against *E. coli* and *B. subtilis* which were found to be 68 and 72 µg/mL respectively.

Results and Discussion

The melting points were determined on a digital melting point apparatus (Veego, VMP-D) and are uncorrected. The starting material (Sigma-Aldrich) and all chemicals used were of AR grade, synthesized compounds were monitored on silica gel-G plates using chloroform-methanol (7:2) as a mobile phase. IR

spectra were recorded on Perkin-Elmer spectrophotometer using KBr disc. ^{1}H-NMR spectra were obtained on a Bruker Avance-II, 400-NMR spectrophotometer in $CDCl_3$ using TMS as internal standard. The chemical shifts are expressed in δ (ppm). Mass spectral measurements were carried out on a LC-MS spectrometer at 70 eV.

Synthesis of N-(4,6-dimethyl-pyrimidin-2-yl)-3-oxo-butyramide (3)

A mixture of 2-amino-4,6-dimethyl pyrimidine and ethyl acetoacetate was charged in microwave for 3 minutes. On cooling the solid product separated out and was checked for purity by the TLC method. The product was crystallized from absolute alcohol and identified as N-(4,6-dimethyl-pyrimidin-2-yl)-3-oxo-butyramide, 78%, m.p. 128^{0}C.

Synthesis of (4,6-dimethyl-pyrimidin-2-yl)-(5-methyl-2-phenyl-2H-pyrazol-3-yl)-amine (4a)

The product N-(4,6-dimethyl-pyrimidin-2-yl)-3-oxo-butyramide was further mixed with phenyl hydrazine and charged in microwave for 3 minutes 30 seconds. On cooling the solid separated out and identified as 4,6-dimethyl-pyrimidin-2-yl)-(5-methyl-2-phenyl-2H-pyrazol-3-yl)-amine. It was checked for purity by TLC and crystallized from absolute alcohol, yield 85%, m.p. 118^{0}C.

Compounds 4b and 4c were prepared in similar manner using substituted hydrazines.

Spectral data of (4,6-dimethyl-pyrimidin-2-yl)-(5-methyl-2-phenyl-2H-pyrazol-3-yl)-amine (4a)

IR: 3408 (NH), 3018 (C-H), 1604cm^{-1} (C=N); ^{1}H NMR: δ 6.12 (s, 1H, Pyrimidin-H), 3.87 (s, 1H, NH), 2.26 (s, 3H, Pyraz-CH_3), 7.39-7.41 (m, 5H, Phenyl-H); ESI-MS: *m/z* 279.4 (M^+), 172.8.

Spectral data of (4,6-dimethyl-pyrimidin-2-yl)-[2-(2,4-dinitro-phenyl)-5-methyl-2H-pyrazol-3-yl]-amine (4c)

IR: 3404 (NH), 3005 (C-H), 1517 cm^{-1} (C=N), 1672 cm^{-1} (NO_2); ^{1}H NMR: δ 6.37 (s, 1H, Pyrimidin-H), 4.09 (s,1H,NH), 7.03-9.11 (m, 3H, 2,4-Dinitrophenyl-H), 2.28 and 2.08 (s, 3H, Pyrimidin-CH_3); ESI-MS: *m/z* 368 (M^+-H), 122.

Table: Physical characterization data of synthesized compounds

Compd.	M.P. (^{0}C)	Mol. Formula	Yield (%)	Elemental analysis Found (Calcd) (%)		
				C	H	N
3	128	$C_{10}H_{13}N_3O_2$ 78	55.13	5.02 (57.96)	18.92 (6.32)	(20.28)
4a	118	$C_{16}H_{17}N_5$	85	66.66 (68.80)	5.63 (6.13)	22.87 (25.07)
4b	132	$C_{16}H_{15}N_7O_4$ 76	49.06	2.56 (52.03)	21.35 (4.09)	(26.55)
4c	138	$C_{10}H_{13}N_5$	70	57.07 (59.10)	4.93 (6.45)	32.29 (34.46)

Conclusion

In the present work the synthesis of (2-aryl/H-5-methyl-pyrazol-3-yl)-(4,6-dimethyl-pyrimidin-2-yl)-amines has been reported. The method applied for the synthesis is quite simple, efficient and in compliance with the green chemistry protocols, requires extremely mild reaction conditions and completed within a short period of time with high yield.

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