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Microwave Promoted Synthesis of Pharmacologically Active Pyrazolidinonyl Derivatives of Benzothiazoles

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ABSTRACT

Microwave promoted synthesis of pharmacologically active N-(1,3-benzothiazol-2-yl)-2-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)amino]acetamides is described. Microwave assisted synthesis not only reduced the reaction time drastically but also gave excellent yields. The synthesized compounds are characterized by Fourier Transform Infra-Red (FTIR), Proton Nuclear Magnetic Resonance (^{1}H-NMR) and mass spectral data.

Keywords: 2-Amino benzothiazole, 4-Amino antipyrine, Microwave irradiation

INTRODUCTION

Heterocycles bearing thiazole, sulphur and nitrogen moieties constitute the core structure of a number of pharmacologically and biologically active interesting compounds [1-6]. A large number of papers and patents have been reported on 2-amino benzothiazole derivatives with significant and diverse biological activities. Benzothiazole derivatives play a vital role in biological fields such as antitubercular, antiallergic, anti-inflammatory and fungicidal activities [7-10]. The efficiency of azole as chemotherapeutic agent is well established [11,12].

Aminoantipyrine is very much used in medicine and it is believed that its amino derivatives would equally be of much use in medicine possibly as intermediate in antipyretic and analgesic drugs [13]. A major challenge in organic synthesis is to develop simple, general and efficient synthetic methods for widely used organic compounds from readily available reagents. Microwave-induced Organic Reaction Enhancement (MORE) is used for carrying out chemical transformations e.g., organic reactions and their uses in eco-friendly manner [14-16]. The microwave assisted organic reactions occur more safely and in an environmentally friendly manner with enhanced product purity and chemical yields [17]. Shorter reaction time, simple reaction conditions and higher yields render the microwave method superior [18].

MATERIALS AND METHODS

All air reactions were carried out in oven dried (120°C) or flame dried glassware. Microwave reaction were carried out in domestic microwave oven (Samsung model) Analytical thin layer chromatography was performed with Merck silica gel plates (0.25 mm thickness) with PF_{254} indicator. Compounds were visualized under UV lamp. Column chromatography was carried out using 60-120 mesh silica gel and technical grade solvents. Proton Nuclear Magnetic Resonance (^{1}H-NMR**)** spectra were recorded on at 300 MHz instruments with Tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on Shimadzu Hyper IR Instruments.

EXPERIMENTAL SECTION

Synthesis of 2-amino-1, 3-benzothiazol (Compound 1)

Compound 1 was prepared by reported method [19]. To a solution of (0.1 mol) of substituted anilines and (0.4 mol) of ammonium thiocyanate was dissolved in absolute ethanol containing 4 N HCl. To this mixture, bromine in glacial acetic acid was added and the reaction mixture was refluxed for 1 h then it was cooled in ice bath and basified with liquor ammonia to get the precipitate. The precipitate obtained was filtered washed with cold water and dried. The crude product was recrystallized from ethanol (Scheme 1).

Synthesis of N-1, 3-benzothiazol-2-yl-2-chloroacetamide (Compound 2)

Compound 1 (1 mol) dissolve in dry benzene, and K_2CO_3 (1.5 mol) was added to it. Chloroacetylchloride (1.5 mol) was added drop wise at an ice cold condition. The reaction mixture was stirred for about 6 h till the completion of the reaction. Progress of the reaction was checked with TLC (Hexane: Ethyl acetate 9:1) Then it was cooled with ice cold water. It was filtered and washed with cold water and dried the crude product was recrystallized from ethanol (Scheme 2).

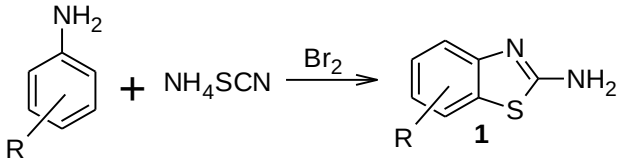
Synthesis of N-1, 3-benzothiazol-2-yl-2-[(1, 5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*h*-pyrazol-4-yl)amino]acetamide (Compound 3) (Scheme 3)

Conventional method

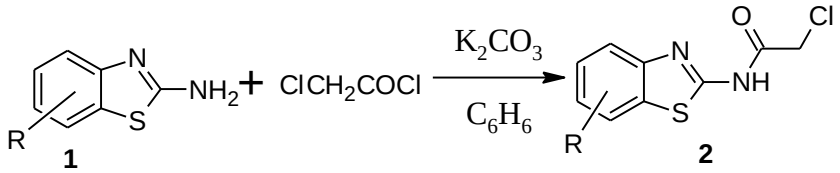
In a round bottom flask, compound 2 (1 mol), 4-amino antipyrine (1 mol), potassium carbonate (1.2 mol) and catalytic amount of tetrabutyl ammonium bromide as a phase transfer catalyst were refluxed. Completion of reaction was checked by thin layer chromatography. The reaction was cooled and poured into ice cold water. Solid Product was filtered, dried and recrystallized from ethanol (Table 1).

Microwave irradiation method

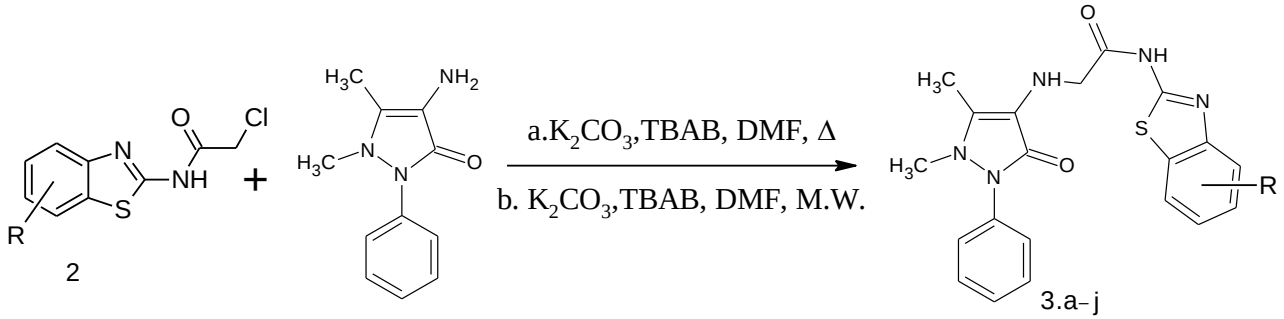
A mixture of compound 2 (1 mol), 4-amino antipyrine (1 mol), potassium carbonate (1.2 mol) and catalytic amount of tetrabutyl ammonium bromide and few drops of DMF were added in a hard glass tube and irradiated in microwave oven at appropriate power ant time till the completion of the reaction (TLC). Reaction mixture was irradiated for continuous 30 sec followed by intermittent cooling to avoid overheating. After the completion of reaction, the mixture was cooled and poured with ice cold water. Solid obtained was filtered dried and recrystallized from ethanol.



Scheme 1: Synthesis of 2-amino-1, 3-benzothiazol



Scheme 2: Synthesis of N-1, 3-benzothiazol-2-yl-2-chloroacetamide



Scheme 3: Synthesis of N-1, 3-benzothiazol-2-yl-2-[(1, 5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*h*-pyrazol-4-yl)amino]acetamide

Where, R=H, -Cl. CH_3, -Cl, $-NO_2$, $-OC_2H_5$ etc.

Table 1: Synthesis 3a-j under conventional and microwave heating

Entry	R	Conventional heating		Microwave heating		
		Time (h)	% Yields*	Microwave power (Watt)	Time (Min)	% yield
3a	H	8	55	300	8	87
3b	4-Cl	8	64	300	7.5	91
3c	6-NO_2	8	52	300	10	74
3d	6-OC_2H_5	8	56	300	7	88
3e	6-CH_3	8	59	300	6.5	90
3f	2,6,7-Tri-Cl	8	51	300	8.5	81
3g	4-CH_3	8	63	300	9	82
3h	4-NO_2	8	51	300	8	72
3i	4,6-Di-Cl	8	58	300	10	74
3j	6-OCH_3	8	54	300	12	86

Spectral data of representative compound

***N*-(1,3-benzothiazol-2-yl)-2-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)amino]acetamide (3a):** m.p: 122°C; IR (KBr) cm^{-1}: 3294 (-NH); 3053 (Ar-CH.); 1666 (CONH); 1550 (C=C), 817, 756, 694 (Ar-CH); ^{1}H-NMR (DMSO-d_6), δ=9.0 (1H, NH), 7.23-8.2 (8H, m, Ar-H),4.6(1H, t, NH), 3.69-70 (2H, s, CH_2), 3.55 (3H, s, CH_3-N), 2.20 (3H, S, CH_3-C=C), MS:- m/z=393(m+).

RESULT

As the graphic enhancements in the speed of reactions and in yield shown by the microwave assisted methods compared to conventional methods are striking, undoubtedly, microwave are going to be highly important in future synthesis of heterocycles. Also heterocyclic compounds being the most biologically active and are highly important in combinatorial chemistry to identify leads and to optimize structures.

CONCLUSION

In the present research work serious of various substituted benzothiazole derivative containing *N*-(1,3-benzothiazol-2-yl)-2-[(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazol-4-yl)amino]acetamides were synthesized as mentioned in the scheme and experimental work. Compounds were synthesized by microwave as well as conventional methods and only time factor and percentage yield were compared. Synthesized compounds were tested for their purity by TLC and melting point. The structures were confirmed by IR, NMR and GC/MS analysis. Synthesized compounds will be tested for their antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus*. The microwave assisted organic synthesis required less time and also percentage yields were more compared with conventional method.

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