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Microwave Irradiation Versus Conventional Method: Synthesis of some Novel 2-Substituted benzimidazole derivatives using Mannich Bases.

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Abstract: The benzimidazole is synthesized by reaction between o-phenylenediamine with twice molar quantities of formic acid .The compound (I) will be subjected to sulphonation which results in the formation of 2-mercaptobenzimidazole then the products obtained were treated with secondary amines in the presence of formaldehyde in order to synthesize Mannich bases. Both conventional and microwave irradiated synthesis of derivatives has been carried out to compare their yield and reaction time.
Keywords: Benzimidazole, Formaldehyde, Formic acid, Mannich bases, microwave, synthesis.

Introduction

Chemistry is critical to drug discovery especially at the lead optimization phase, but methods for synthesis of organic compounds have remained unchanged for decades. It takes long time with high manpower requirement, new ways required to improve efficiency, output and quality. The solution is microwave assisted synthesis, which is very superior reactions are completed in minutes; with high yield temperature is controlled so reaction can be more easily repeated[(1)]. Microwave-assisted organic synthesis (MAOS) is an acknowledged quick alternative & green technology in synthetic organic chemistry[(2)]. Attempt was made to synthesize benzimidazole and their derivatives, it is well known that Benzimidazole possess antimicrobial, anthelmintic, analgesic and anti inflammatory activities[(3)]. The synthesis of substituted Benzimidazole derivatives in the presence of ring closing agents and the synthesized compounds were screened for their anthelmintic activity [(4)].in recent years, Mannich bases have gained importance because of their pharmaceutical importance in this investigation, an attempt was made on incorporation of some selected compounds having secondary amine with 2-mercaptobenzimidazole reaction that this modification would improve the efficacy of the basic moiety [(5)].

Experimental

TMS as an internal All the melting point were determined in open capillary tubes and were found uncorrected. Silica gel G plates of SD-Fine were used for TLC and spots located in iodine chamber. The IR spectra were recorded in the 4000-400 cm^{-1} range on FT-IR spectrometer (BRUKER) using KBR disc method. ^{1}H NMR

spectra were recorded on BRUKER AVANCE II 400 NMR spectrometer in DMSO standard and chemical shift values are expressed in δ ppm.

Synthesis of Benzimidazole:

Conventional method

2 gm of o-phenylendiamine was placed in 250 ml of R.B.F and 12 ml of 90% formic acid added mixture was refluxed on a water bath at 100℃ for 2hr after the solution become cool 10% NaoH solution added slowly with constant rotation of the flask until the mixture is just alkaline to litmus. Cured benzimidazole filtered off washed with ice cold water again with 25 ml of cold water. The crude product was added in 200 ml of decolorizing carbon added and digested for 15 min and filtered off the benzimidazole washed with 25 ml of cold water and dried at 100℃. the product recrystallised with methanol to obtained white crystalline product. The solvent system used for TLC chloroform: methanol (9:1).

Microwave Irradiation Method:

O-phenylenediamine (0.01 mol) and formic acid (0.01mol) was subjected to microwave irradiation at 350W at 25 minutes. Completion of the reaction was monitored by TLC. The reaction mixture was cooled and basified by addition of sodium hydroxide solution. The separated benzimidazole was filtered and washed with ice cold water. It was recrystallised from boiling water. TLC: Chloroform: Methanol (9:1).

Synthesis of 2-mercaptobenzimidazole:

Conventional Method

Potassium hydroxide (1.9g, 0.03ml) was dissolved in a mixture of ethanol (30ml) and water 30ml.The CS_2 (2.7 g, 0.03 ml) was added with stirring. This mixture was boiled and then the solution of o-phenylenediamine (0.03mol) in ethanol (20 ml) was added drop wise to it the mixture was refluxed for $3_{1/2}$ hr after the reflux the white residue is obtained and dissolved in water the product was ppt. by the addition of dil. Acetic acid and then recrystallised from a mixture of water-ethanol (1:1) solvent is chloroform: methanol (9:1).

Microwave Irradiation Method:

Potassium hydroxide (0.03mol) and carbon disulphide (0.03mol) were dissolved in ethanol and water (1:1). To this o-phenylenedamine added and the reaction mixture was placed in microwave oven 350W for 5 minute. In between the completion of reaction was monitored by TLC. After completion of reaction, ethanol was removed and the residue was poured into crushed ice. Then it was converted into solid form by addition of acetic acid. The product was filtered, dried and recrystallised from ethanol.

Synthesis of N-Mannich bases of 2-mercaptobenzimidazole:

Conventional Method

To a solution 1 gm of 2-mercaptobenzimidazole in 10 ml of ethanol, respective secondary amine (0.11mol) and formaldehyde (0.11mol) were added with stirring for 1 hr. Then the reaction mixture was refluxed for 1hr. On cooling the product formed was filtered dried in vacuum and recrystallised.

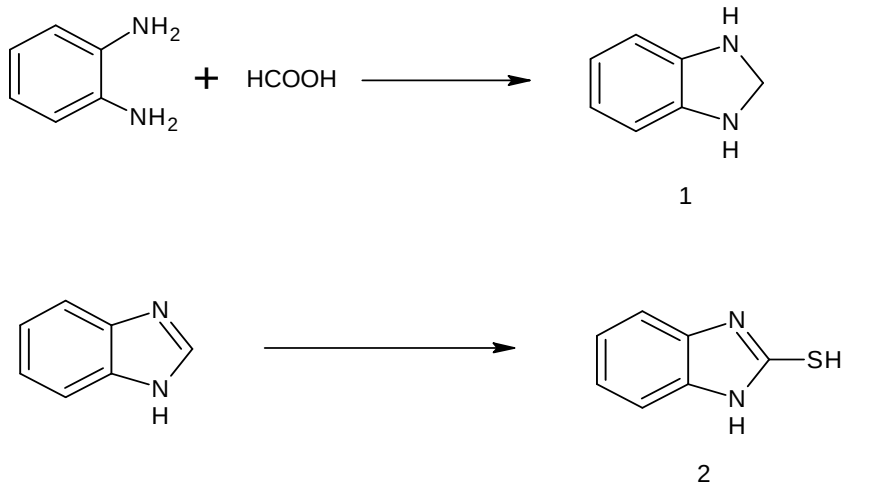
Microwave Irradiation Method

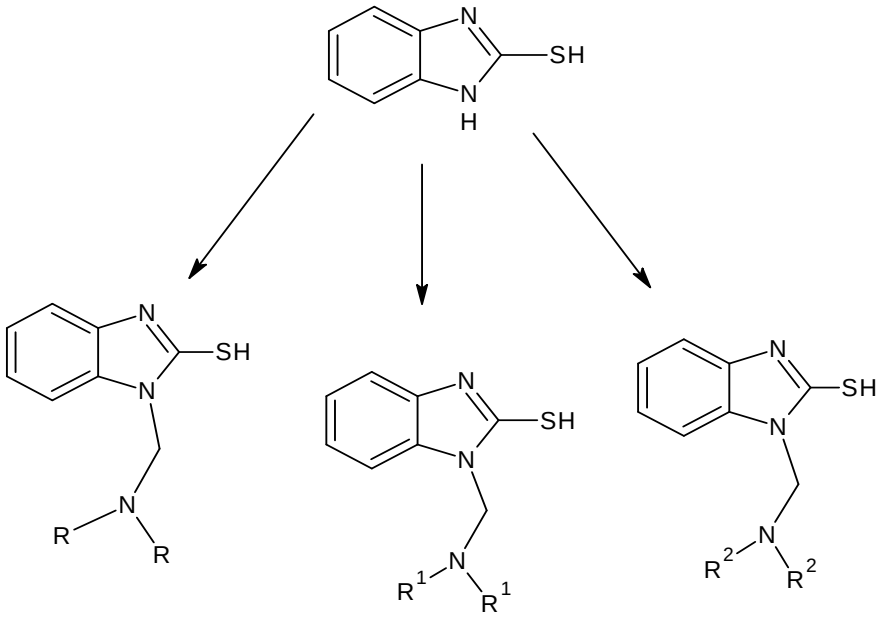
In a solution of 2-mercaptobenzimidazole (0.1mol) in ethanol (10ml), were added formaldehyde (0.11mol) and secondary amine (0.11mol). The mixture was heated in microwave at power of 350W for 10 minute. The mixture was allowed to cool in refrigeration. The product thus obtained was filtered.

Secondary amines used:

3a- Dimethyl amine, 3b- Diphenyl amine, 3c- Diethyl amine

Scheme:





(3a) $R = CH_3$
(3b) $R^1 = C_6H_5$
(3c) $R^2 = C_2H_5$

Result and Discussion

Pharmacological Evaluation (anthelmintic activity)

The synthesized compound was screened for their anthelmintic activity. Out of the entire synthesized compounds **3a, 3b, 3c** showed significant anthelmintic activity due to presence of Mannich bases derived from substituted benzimidazole then all synthesized compounds were also characterized by their physical, chemical and spectral data.

Tables:-1. Comperison of conventional and microwave assisted synthesis

Comp	Yield (%)		Reaction Time		Energy	
	Conventional	Microwave	Conventional (hr)	Microwave (min)	Conventional (Temp.°C)	Microwave (PowerWatt)
1	68	82	2	25	100-110	350
2	63	78	$3_{1/2}$	7	100-110	350
3a	58	75	1	10	100-110	350
3b	54	72	1	10	100-110	350
3c	51	69	1	11	100-110	350

Tables:-2. Characterisation data of 2-substituted benzimidazole derivatives

Comp.	M.P (°C)	^{1}H NMR ($CDCl_3$) δ ppm and IR (cm^{-1}) (KBr)
1	170-172	^{1}H NMR ($CDCl_3$) 7.14-7.78 (8H, m, Ar-H), 11.3 (1H, s, NH) IR (KBR cm^{-1}) 3120 (NH), 1650 (C=N),1475 (C-N)
2	303-304	^{1}H NMR ($CDCl_3$) 7.14-7.78 (8H, m, Ar-H), 11.3 (1H, s, NH), 3.2 (1H, s ,SH) I R (KBR cm^{-1}) 3120 (NH), 1650 (C=N), 1380 (C=S), 1475 (C-N)
3a	121-123	^{1}H NMR ($CDCl_3$) 7.14-7.78 (8H, m, Ar-H), 11.3 (1H, s, NH), 3.2 (1H, s ,SH) 4.37-4.55 (2H, m, CH_2) 2.1-2.32 (6H, m, $(CH_3)_2$) IR (KBR cm^{-1}) 3120 (NH),1650 (C=N), 1380 (C=S), 1475 (C-N)
3b	211-212	^{1}H NMR ($CDCl_3$) 7.14-7.78 (8H, m, Ar-H), 11.3 (1H, s, NH), 3.2 (1H, s ,SH) 4.37-4.55 (2H, m, CH_2) 5.41-5.57 (10H, m, $(C_6H_5)_2$) IR (KBR ^{1}) 3120 (NH), 1650 (C=N), 1380 (C=S), 1475 (C-N)
3c	134-135	^{1}H NMR ($CDCl_3$) 7.14-7.78 (8H, m, Ar-H), 11.3 (1H, s, NH), 3.2 (1H, s ,SH) 4.37-4.55 (2H, m, CH_2) 2.31-2.47 (10H, m, $(C_2H_5)_2$) IR (KBR ^{1}) 3120 (NH), 1650 (C=N), 1380 (C=S),1475 (C-N)

Tables:-3. Anthelmintic activity of substituted Benzimidazole Derivatives

S.No.	Parameters	Concentration mg/ml	3a	3b	3c	Piperazine citrate
1	Time taken for paralysis in minutes	100	3.54±0.227	3.12±0.241	2.65±0.534	
		50	5.88±0.430	25.56±0.304	8.43±0.546	
		10	15.56±0.356	13.34±0.456	12.65±0.132	
		15				43.45±0.57
2	Time taken for death in minutes	100	3.14±0.312	2.132±0.134	3.76±0.756	
		50	5.42±0.154	5.124±0.432	4.76±0.543	
		10	15.64±0.116	16.58±0.456	14.56±0.675	
		15				47.45±0.35

Conclusion

Microwave assisted organic synthesis has attracted attention in recent years due to enhanced reaction rates, higher yield. These are eco-friendly reactions compared with conventional method. However substituted benzimidazole compound with mannich bases showed excellent activity, the fact that aromatic substitution is necessary for exhibiting some biological activity.

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