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One-pot, solvent-free synthesis of 2,5-disubstituted indolyl imidazoles by microwave irradiation

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ABSTRACT

A series of 2,5-disubstituted indolyl imidazole analogues are synthesized by one-pot, solvent-free and under microwave conditions. The method is rapid, efficient and environmental benign. The compounds obtained are in excellent yields with high purity by easy work up.

Key Words: 2,5-Disubstituted indole-3-carboxaldehydes, 1,2-diketones, Microwave irradiation, Green chemistry.

INTRODUCTION

Indoles, an important class of fused heterocyclic compounds have attracted much synthetic attention because of their wide range of pharmacological and therapeutic activities such as anticancer [1], antioxidant [2], anti-HIV [3], anti-inflammatory, analgesic and CNS-depressants [4]. Alongside, the importance of imidazoles in biological systems has attracted much interest due to their chemical and biochemical properties. Many of the substituted imidazoles are known for inhibitory of P38 MAP kinase [5], antihypertensive [6], anti-inflammatory [7], fungicidal, herbicidal, plant growth regulatory & therapeutic agents [8]. Certain imidazole derivatives, like cimetidine are clinically useful as H_2 antagonist in the treatment of peptic ulcers [9].

There is an immense aspiration in preparative chemistry to avoid waste. The replacements of benign chemicals for toxic ones and to employ solvent-less reactions are also major objectives of synthetic chemists. Hence, organic reactions under solvent-free [10] environment have increasingly attracted chemist's interest, particularly from the viewpoint of green chemistry [11]. On the other hand, solvent-free reactions are more suitable and successful under microwave activation and several advantages are manifested in this approach [12].

In continuation of our enduring interest in green chemistry of "Bio-Active" indole analogues [1c, 13], herein we report, improved synthesis of 2,5-disubstituted indolyl imidazoles by one-pot, solvent free microwave assisted synthesis **(Scheme 1)**.

MATERIALS AND METHODS

Experimental

All the chemicals and reagents were purchased from MERCK and Himedia fine chemical companies and are used without further purification. Melting points of the synthesized compounds are determined in open capillaries and are uncorrected. Reactions are monitored by thin-layer chromatography (TLC) on silica gel 60 F_{254} aluminium sheets (MERCK). The mobile phase was chloroform and benzene and detection was made using UV light and iodine. IR spectra are recorded in KBr on Perkin-Elmer and FTIR Spectrophotometer (ν_{max} in cm $^{-1}$) and ^{1}H NMR spectra on BRUKER AVENE II 400 MHz NMR Spectrometer (Chemical shift in δ ppm down field from TMS as an internal reference). The Mass spectra were recorded on LC-MSD-Trap-SL instruments.

General procedure for the synthesis of 2,5-Disubstituted indolyl imidazoles:

Mixture of 2,5- disubstituted indole-3-carboxaldehydes **(1a-e)** (1 mmol), 1,2-diketones **(**1 mmol) and ammonium acetate (5 mmol) in acetic acid (2 ml) were made to paste and introduced in to open borosil glass tube. This was subjected to microwave irradiation for 9 minutes with 70% microwave power. After completion (TLC) the reaction mixture was brought to room temperature, washed with aqueous ethanol and dried. The crude products were recrystallised to get the title compounds which are found to be in good purity (TLC) and yield **(Table 1)**.

Representative examples for the Spectral analysis of Indolyl imidazole analogues:

3-(4,5-diphenyl-1H-imidazol-2-yl)-1H-indole (2a)

IR (KBr) ν_{max} (cm^{-1}): 3240, 3117, 3012, 1597. ^{1}H NMR (DMSOd_6+CDCl_3) δ (ppm): 12.00 (s, 1H, indole NH), 10.90 (s, 1H, imidazole NH), 7.00-8.20 (m, 15H, Ar-H); ^{13}CNMR (DMSO-d_6) δ (ppm): 112, 116, 120, 121, 122, 123, 124, 126, 127, 128, 129, 133, 134, 135, 159; MS: m/z= 336 [m+1]$^{+\cdot}$.

3-(4,5-dip-tolyl-1H-imidazol-2-yl)-1H-indole (3a)

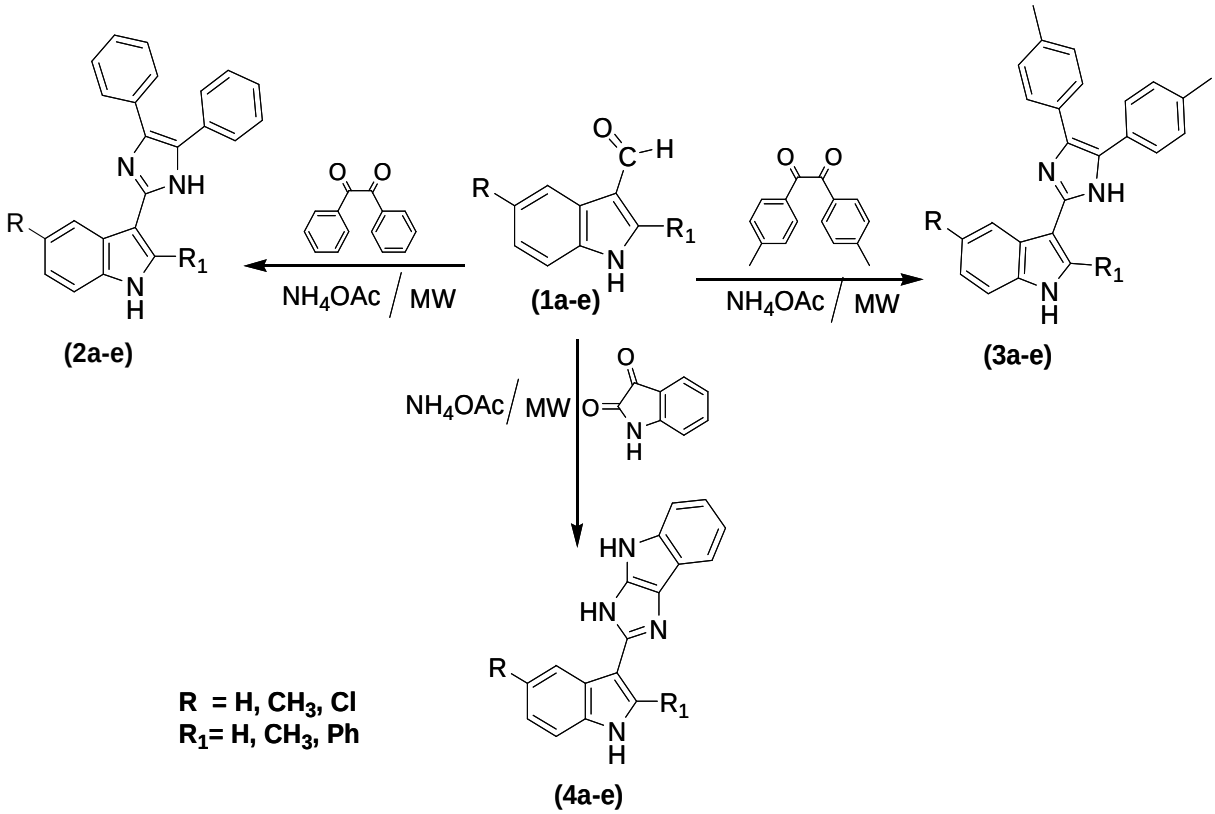
IR (KBr) ν_{max} (cm^{-1}): 3262, 3126, 2972, 1576. ^{1}H NMR (DMSOd_6+CDCl_3) δ (ppm): 12.40 (s, 1H, indole NH), 10.70 (s, 1H, imidazole NH), 7.20-8.20 (m, 13H, Ar-H), 2.5 (s, 6H, CH_3); ^{13}CNMR (DMSO-d_6) δ (ppm): 27, 110, 112, 118, 119, 122, 123, 124, 126, 127, 128, 129, 133, 135, 136, 153; MS: m/z= 364 [m+1]$^{+\cdot}$.

3,4-dihydro-2-(1H-indol-3-yl)imidazo[4,5-b]indole (4a)

IR (KBr) ν_{max} (cm^{-1}): 3427, 3249, 3213, 2978, 1597. ^{1}H NMR (DMSOd_6+CDCl_3) δ (ppm): 11.70 (s,1H, indole NH), 11.20 (s,1H, indole NH) 10.70 (s, 1H, imidazole NH), 7.20-8.10 (m, 9H, Ar-H); ^{13}CNMR (DMSO-d_6) δ (ppm): 114, 119, 121, 122, 123, 126, 127, 128, 129, 133, 135, 153; MS: m/z= 273 [m+1]$^{+\cdot}$.

RESULTS AND DISCUSSION

Avoiding organic solvents during the reactions in organic synthesis leads to a clean, efficient and economical technology (green chemistry). There is an increasing interest in the use



Scheme 1. Schematic representation for the synthesis of indolyl imidazoles

of environmentally benign reagents and methods. In the present investigation, the cyclocondensation was carried out under micro wave irradiation. First the cyclocondensation was optimized at different power levels, from 50% to 90% for both neat and by utilizing acetic acid as an energy-transfer medium and homogenizer [1c, 13]. After the brief examination, yield and purity of the compounds assessed 70% power as the most suitable condition **(Table 1)**. Having established an effective method for the synthesis of indolyl imidazole analogues **(2a-e) (3a-e)** and **(4a-e)**, we then examined the reaction for a variety of 2,5-disubstituted indole-3-carboxaldehydes with substituted 1,2-diketones and ammonium acetate to explore the scope of the cascade reaction under the optimized conditions. The products obtained in good yields with high purity with out using any solvent. Conventional synthesis suffers from many disadvantages such as use of solvent, long reaction periods, lengthy work up process and low yields with moderate purity **(Table 1)** [14].

Table 1: Comparative data of conventional and MW methods for the synthesis of indolyl Imidazole analogues

Entry	Substituents		Conventional Method [14]		Microwave Method			Mp (^oC)	Mp (^oC) [b]
	R	R_1	Time (min)	Yield (%)	Time (min)	Power (%)	Yield (%)[a]		
2a	H	H	240-300	76	9	70	90	157-59	158-60
2b	H	CH_3	240-300	65	9	70	86	175-76	174-75
2c	H	Ph	240-300	69	9	70	86	203-05	205-06
2d	CH_3	Ph	240-300	71	9	70	91	224-26	224-25
2e	Cl	Ph	240-300	80	9	70	90	240-42	242-43
3a	H	H	240-300	70	9	70	92	180-82	181-82
3b	H	CH_3	240-300	68	9	70	87	160-61	159-60
3c	H	Ph	240-300	62	9	70	88	221-23	221-23
3d	CH_3	Ph	240-300	76	9	70	93	216-18	217-18
3e	Cl	Ph	240-300	85	9	70	90	260-61	262-63
4a	H	H	240-300	72	9	70	93	217-19	219-20
4b	H	CH_3	240-300	72	9	70	90	176-78	179-80
4c	H	Ph	240-300	62	9	70	85	164-66	164-66
4d	CH_3	Ph	240-300	60	9	70	88	236-38	239-40
4e	Cl	Ph	240-300	82	9	70	93	228-30	230-31

[a] *Yields are isolated.*

[b] *Melting points are uncorrected and compared with literature reports [14].*

[c] *All products are known compounds and were characterized by their mp, IR, NMR, Mass spectral data and elemental analysis.*

CONCLUSION

In summary, we have developed a rapid, expedient and environmentally benign microwave assisted cyclocondensation to produce novel indolyl imidazole analogues. Consequently, our approach can be applied to the preparation of a wide range of indoles and its bioactive analogues for structure-activity studies. Investigations in this direction are ongoing.

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