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Microwave assisted efficient synthesis of diphenyl substituted pyrazoles using PEG-600 as solvent – A green approach

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ABSTRACT

A conventional and microwave assisted efficient synthesis of diphenyl substituted pyrazole using PEG 600 as green solvent has been described. A relatively shorter reaction time with excellent yield of the piperidine mediated protocol has been attracted economically attractive and eco-friendly. All newly synthesized compounds were characterized by standard spectroscopic techniques viz., UV–visible, FT-IR, ^{1}H-NMR and Mass spectra. The anti-microbial activities of compounds have also been tested using Minimum Inhibitory Concentration (MIC) method with two different microorganisms *Staphylococcus aureus* (MTCC3381) and *Escherichia coli* (MTCC739). The results of the antimicrobial activity revealed that the diphenyl substituted pyrazole derivatives have nice inhibiting nature against both types of bacteria of present investigation than corresponding chalcones. Since, the work has been focused on green chemical approach towards the synthesis, this protocol may be recommended for eco-friendly applications.

1. Introduction

Chalcones comprise a class of compounds with important therapeutic potential. The ease of preparation, the potential of oral administration, and safety protocol enable chalcone-based compounds as therapeutic agents. Chalcones (α, β-unsaturated ketones) possess a wide range of pharmacological activities such as anti-inflammatory (Hsieh et al., 1998), anticancer (Shibata, 1994), analgesic (Viana et al., 2003), antiulcerative (Murakami et al., 1991), antiviral (Wu et al., 2003), antimalarial (Liu et al., 2001) and antibacterial (Bekhit et al., 2001). The presence of a reactive α, β-unsaturated keto group in chalcones is found to be responsible for their pharmacological activities. Pyrazole derivatives have been reported to possess diverse biological activities such as antibacterial (Abdel-Hafez et al., 2009) antifungal (Ali, 2009) herbicidal (Witschel, 2009), insecticidal (Lahm et al., 2007) anti-inflammatory (Youssef et al., 2010), anticonvulsant (Abdel-Aziz et al., 2009) anti-oxidant (Oliver and Dallinger, 2006) and so on. Considerable interest has been focused on the pyrazole structure which has been known to possess a broad spectrum of biological activities.

Designing of safer chemicals which prevents the environmental pollution found to be a greater environmental impact in minimizing the use and disposal of organic solvents into the environment. In view of this, polyethylene glycol (PEG) has found to be an interesting solvent system. PEG is an environmentally benign reaction solvent, it is inexpensive, potentially recyclable and water soluble, which facilitates its removal from there action product.

Microwave-assisted synthesis is an eco-friendly and efficient method of synthesis of organic compounds as compared to the conventional method of synthesis. In this method, reaction occurs more rapidly, safely and with higher chemical yields due to which this method becomes superior to the conventional method. The conventional method, requiring a longer reaction time and larger quantities of solvents and reagents, causes environmental pollution and contributes to the health hazards (Oliver and Dallinger, 2006). Based on the careful analysis of the literature, present investigation was aimed to focus on the PEG-600 solvent system. The series of chalcones and diphenyl substituted pyrazoles compounds were synthesized by both conventional and microwave irradiation methods. The synthesized compounds were characterized on the basis of UV–visible, FTIR, ^{1}HNMR and mass spectral data. Further, the present investigation have also been recommended for the antibacterial activities of the synthesized

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compound with some selected gram positive and gram negative bacteria viz., *Staphylococcus aureus,* and *Escherichia coli respectively.*

2. Experimental

2.1. Methods and materials

The chemicals acetophenone **(1)**, 4-chloroacetophenone **(2)**, 4-nitroacetophenone **(3)**, 4-hydroxybenzaledehyde **(4)**, PEG-600 **(5)**, hydrazine hydrate **(6)**, sodium hydroxide and piperidine were obtained from Avra chemicals, Hyderabad and were used as such without further purification. Silica gel (TLC and Column grade) were purchased from Merck. The solvents were purified as per the standard procedure reported elsewhere.

FTIR spectra (KBr pellets) were measured using Alpha Bruker FTIR instrument scanning with the entire region of 4000–400 cm^{-1} with typical resolution of 1.0 cm^{-1}. UV–visible spectra were also recorder using Alpha Bruker UV spectrophotometer. The NMR spectra of the compounds have been recorded on Bruker AV400 spectrometer operating at 400 MHz for recording ^1H spectra in DMSO solvent using TMS as internal standard. Mass spectra have been recorded on SHIMADZU spectrometer using chemical ionization technique. Melting points of all synthesised compounds have been determined in open glass capillaries on Mettler FP51 melting point apparatus and are uncorrected. Microwave reactions are carried out commercially available IFB domestic microwave oven having a maximum power output of 110 W operating at 450 Hz.

2.2. Synthesis of 3-(4-hydroxyphenyl)-1-phenylprop-2-en-1-one (7)

2.2.1. Method-A (conventional method)

A mixture of acetophenone (0.01 mol) and 4-hydroxy benzaldehyde (0.01 mol) and NaOH (0.02 mol) were stirred in PEG-600 (20 mL) as solvent at 65 °C for 1 h. The completion of the reaction was monitored by TLC and the crude mixture was worked up in ice-cold water (100 mL). The product was separated out and filtered. The filtrate was evaporated to dryness to remove water leaving behind PEG-600. The recovered PEG-600 has been utilized for the synthesis of chalcones. Synthesised compounds were recrystallised from ethanol to afford pure compound (5). (Yield – 80% and melting point: 100–102 °C).

2.2.2. Method-B (microwave irradiation method)

A mixture compounds 1 (0.01 mol) and 4 (0.01 mol) and NaOH (0.02 mol) were grinded in to the mortar. Then it was mixed with 20 mL of PEG-600. The mixed compounds were taken in a 100 mL beaker and it was irradiated in a microwave oven for the 3–5 min at 110 W operating at 2450 Hz at 30 s of intervals. After completion of reaction as followed by T.L.C examination, chilled water was added to the reaction mixture and neutralized by an acid. The solid product was obtained, which was filtered, dried and crystallized from an ethanol. The filtrate was evaporated to dryness to remove water leaving behind PEG-600. (Yield – 98% and melting point: 101–102 °C).

2.3. Synthesis 4-(4,5-dihydro-3-phenyl-1H-pyrazol-5-yl)phenol (10)

2.3.1. Method-A (conventional method)

A mixture of compound **(5)** (0.01 mol) in ethanol (20 mL) was refluxed with hydrazine hydrate (0.01 mol) in the presence of piperidine (2–3 drops) as catalyst for an hour. The completion of reaction was monitored by TLC. The reaction mixture was quenched by poured into ice-cold water. The product was separated out and filtered. A synthesised compound **(6)** was recrystallised from ethanol. (Yield – 75% and melting point: 110–111 °C)

2.3.2. Method-B (microwave irradiation method)

A mixture of compounds **(5)** (0.01 mol), **(6)** (0.01 mol) and 2–3 drops piperidine catalyst were mixed thoroughly in mortar. Then it was dissolved into minimum amount of PEG-600. The mixed compounds were taken in a 100 mL beaker and it was irradiated in a microwave oven for the 4–5 min at 110 W operating at 2450 Hz at 30 s of intervals. The completion of the reaction was monitored by TLC and the crude mixture was worked up in ice-cold water. The filtrate was evaporated to dryness to remove water leaving behind PEG-600. Yield: 90% and 110–112 °C.

The rest of the compounds of **8**, **9** and **11**, **12** were synthesised by the above mentioned same procedures.

3. Results and discussion

3.1. Results

3.1.1. Spectral details of 3-(4-hydroxyphenyl)-1-phenylprop-2-en-1-one (7)

Melting point	: 101–102 °C	
UV–visible (λ_{max}:nm)	: 226 ($\pi \rightarrow \pi^*$ transition), 314 ($n \rightarrow \pi^*$ transition)	
FTIR (cm^{-1})	: 3203 (O–H), 3184 (Aromatic C–H str), 1271(–C–C str.), 1644 (C=O), 1554 (C=C str), 828 (C–H out plane bending	Suppl. Fig. S1
^1H NMR (ppm)	: 6.82-6.91 (2d, 2H, –CH=CH–), 7.42–8.08 (m, 9H, Ar–H), 10.41 (s, 1H, Ar–OH)	Fig. 1
Mass (*m*/*z*)	: Calculated M.W 224.25, Observed M.W 225.2	Suppl. Fig. S2

3.1.2. Spectral details of 4-(4,5-dihydro-3-phenyl-1H-pyrazol-5-yl) phenol (10)

Melting point	: 110–112 °C	
UV–visible (λ_{max}:nm)	: 204 ($\pi \rightarrow \pi^*$ transition), 314 ($n \rightarrow \pi^*$ transition)	
FTIR (cm^{-1})	: 3378(O–H), 2090(Aromatic C–H str), 1649(C=N), 1333(–C=C–str.), 1108(C–N str.), 824(N–H bending vib.)	Suppl. Fig. S3
^1H NMR (ppm)	: 2.48–3.429 (2H, m, $-CH_2$ protons–), 4.7–4.77 (q, 1HC–H Protons adjacent to N–H), 6.62–6.626 (d, 1H, N–H), 6.72 to 7.63 (m, 9H, Ar–H), 9.35(s, 1H, Ar–OH)`	Fig. 2
Mass (*m*/*z*)	: Calculated M.W 238.11, Observed M.W 239.0	

3.1.3. Spectral details of 1-(4-chlorophenyl)-3-(4-hydroxyphenyl) prop-2-en-1-one (8)

Melting point	: 90–92°C
UV–visible (λ_{max}:nm)	: 230 ($\pi \rightarrow \pi^*$ transition), 345 ($n \rightarrow \pi^*$ transition)