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Article

An Efficient and Green Synthesis of Pyrazole Containing Flavones Using Polyethylene Glycol-400 as Reaction Solvent

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ABSTRACT

Green and an efficient procedure for the synthesis of 2-(5-chloro-3-methyl-1-phenyl-pyrazol-4-yl)-chromen-4-one derivatives from substituted chalcones in polyethylene glycol-400 as a green solvent using iodine as a catalyst is reported. The reported procedure is very practical, short reaction time, and high yielded over an expensive catalyst.

Key words: Polyethylene glycol-400, Pyrazole chalcones, Pyrazole flavones.

1. INTRODUCTION

Flavonoids are substances endowed with a wide number of pharmacological activities. Among the naturally occurring oxygen heterocycles, 2-phenyl-4*H*-1-benzopyran-4-ones (flavones) are an important and abundant group of flavonoids. They possess unique importance, as about 300 different compounds of this class have so far been isolated from natural sources and thousands of their derivatives have been synthesized. Synthesized flavones and their derivatives have attracted considerable attention due to their significant biological activities such as antiviral [1], anti-inflammatory [2], and retardness of lipoxygenation [3,4], depending on their pattern of oxygenation. Baicalcin, 6-hydroxy apigenin, 6-hydroxy galangin, and 6-hydroxy-kaemferol, which are naturally occurring flavonoids from a set of 14-hydroxy flavones tested, exhibited high inhibition effects on tyrosinase with respect to L-DOPA were studied [5]. Goto *et al.* [6,7] were synthesized novel flavonoids and evaluated as *in vitro* inhibitors of human cancer cell growth [8,9] reported that in recent years telomerase has been identified as a new promising target in oncology and consequently new telomerase inhibitors have been intensely explored as anticancer agents. Nelly *et al.* [10] have prepared novel flavonoid derivatives. Substituted flavones as potential HIV integrase inhibitors were synthesized from phloroglucinol. Daskiewicz *et al.* [11] natural and synthetic flavonoids have been screened for their effect of cell proliferation and apoptosis in a human colonic cell line (HT-29). Flavones and flavonols possess greater antiproliferative activity than chalcones and flavanones. Lin *et al*. [12,13] evaluated, synthesized flavonoids showed inhibitory activity against *Mycobacterium tuberculosis* H_{37} Rv. Lebeau *et al*. [14] reported newly synthesized flavonoids where one or two di-tert-butyl hydroxyphenyl groups replaced catechol moiety at position-2 of the benzopyrane heterocycle, investigated that antioxidant properties of these flavonoids. One of the key areas of green chemistry is the replacement of the hazardous solvent as with environmentally benign solvents like polyethylene glycol (PEG-400). In recent years PEG-400 attracted much more attention recently, liquid polymers or low melting polymers have emerged as alternative green reaction media with unique properties such as thermal stability, commercial availability, non-volatility, and immiscibility with a number of organic solvents and recyclability. PEGs are preferred over other polymers because they are inexpensive, completely non-halogenated, easily degradable, and of low toxicity [15]. Many organic reactions have been carried out using PEGs as solvent or co-solvent such as Heck reaction [16], asymmetric dihydroxylation [17], Suzuki cross-coupling reaction [18], oxydehydrogenation of alcohols and cyclic dienes, oxidation of sulfides and the Wacker reaction [19], and partial reduction reaction of alkynes [20]. The use of PEG as a recyclable solvent system for the metal-mediated radical polymerization of methyl methacrylate and styrene has also been reported [21].

2. RESULTS AND DISCUSSION

In continuation of our work on the synthesis of some new bioactive heterocyclic compounds [22-24], herein, we report new series of pyrazole containing flavones by the ring closure reaction of chalcones with I_2 catalyst in PEG-400 as a reaction solvent (Scheme 1). The starting chalcones were prepared by the previous reported method [25]. Initially, we attempted the condensation of in PEG-400 as reaction solvent using I_2 as a catalyst. The reaction was completed within 40 min and corresponding product **(2a)** was obtained in 92% yield. To optimize the reaction conditions, we carried out the above reaction in different solvents such as ethanol, tetrahydrofuran, dioxane, acetonitrile, and PEG-400 (Table 1). On comparative study, we found that PEG-400 as an efficient reaction medium, in terms of reaction time as well as yield (92%). Encouraged by the results, we turned our attention to a variety of substituted chalcones. In all cases, the reaction proceeded efficiently in high yields at 60°C using PEG-400 as an alternative reaction solvent (Table 2).

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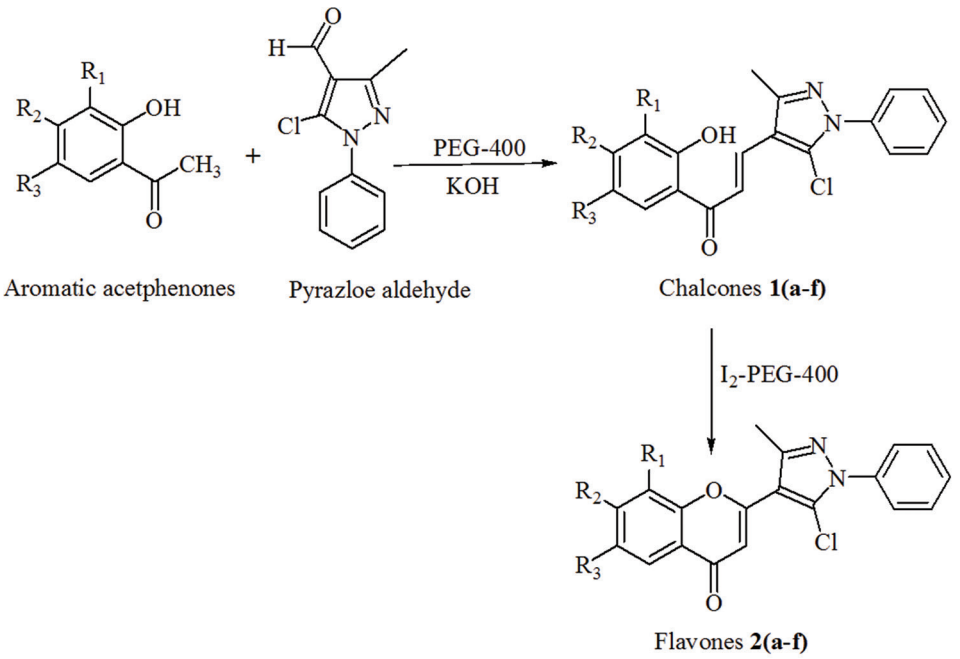

Scheme 1: Synthesis of flavones using I_2 in PEG-400 as a green reaction solvent.

Table 1: Effect of solvent on the reaction on the synthesis of pyrazole containing flavones.

Entry	Solvent	Time (h)	Yield (%)
1	EtOH	2	58
2	THF	1.5	55
3	Dioxane	2	52
4	Acetonitrile	2.5	60
5	PEG-400	40 (min)	92

THF: Tetrahydrofuran, PEG: Polyethylene glycol

Table 2: Physical-chemical data pyrazole containing flavones derivatives **2(a-f)**.

Entry	Product	R_1	R_2	R_3	M.P. (°C)	Yield (%)	Time (min)
1	2a	H	H	Cl	168	92	45
2	2b	I	H	Cl	174	90	52
3	2c	Br	H	Cl	152	86	55
4	2d	Cl	H	Cl	141	88	44
5	2e	H	H	CH_3	162	85	45
6	2f	Br	H	CH_3	172	90	50

The IR spectra of synthesized flavones showed absorption at 1660–1670 cm^{-1} due to C=O stretching and 1585–1600 cm^{-1} due to aromatic C=C- stretching. The characteristic stretching frequency between 1610 and 1620 cm^{-1} referred to C=N double band of pyrazole ring. The nuclear magnetic resonance (^{1}H NMR) spectra of some representative flavones showed a singlet near at δ 6.60–6.91 is due to 1H of 3-H, that is, pyrone ring (flavone). The peak nears at δ 6.60–6.91 is the characteristic singlet for flavones. The multiplet at δ 7.20–8.50 is due to aromatic protons and disappearance of a peak near at δ 11.50–12.50 due to *o*-hydroxy (phenolic) proton which confirmed the formation of flavones that proved their structures. Other aliphatic protons were observed at excepted regions.

3. EXPERIMENTAL

Melting points were uncorrected and determined in an open capillary tube method. IR spectra were recorded on the Fourier-transform infrared Shimadzu spectrometer. Proton ^{1}H NMR spectra were recorded in dimethyl sulfoxide (DMSO)-d_6 on Avance 300 MHz spectrometer using TMS as an internal standard. The mass spectra were recorded on the EI-Shimadzu-GC-MS spectrometer. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

3.1. General Procedure for the Synthesis of Flavones 2(a-f)

To a solution of substituted 2'-hydroxychalcones (1 mMol) in PEG-400 (15 mL), catalytic amount of iodine (10 mol%) was added and stirred for a given time (mentioned in Table 2) under mild (60°C) temperature condition. After completion of the reaction (monitored by thin-layer chromatography [TLC]), the reaction mixture was cooled at room temperature and poured into ice-cold water (100 mL). The separated solid was filtered, washed by dilute sodium thiosulfate solution (10%), followed by ice-cold water. The isolated crude product was recrystallized from acetic acid. The purity of synthesized products was checked by TLC. Their structures were confirmed by spectral analysis.

3.2. Characteristic Test

These compounds (without –OH group) did not give violet coloration with $FeCl_3$ solution and pink or dark red coloration with Conc. H_2SO_4 and Wilson's test was negative.

3.3. Spectroscopic Data of Synthesized Compounds

3.3.1. 6-Chloro-2-(5-chloro-3-methyl-1-phenyl-pyrazol-4-yl) chromen-4-one (2a)

IR (KBr): 1615, 1662, 3168; ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, CH_3), δ 6.65 (s, 1H, pyrone), δ 7.11–8.16 (m, 8H, Ar-H) ppm; M.S. (m/z): 370 (M^+), 372 (M+2), 374 (M+4); Anal. Calcd for $C_{19}H_{12}N_2O_2Cl_2$: C, 61.47; H, 3.26; N, 7.55%. Found: C, 61.55; H, 3.15; N, 7.49%.

3.3.2. 6-Chloro-2-(5-chloro-3-methyl-1-phenyl-pyrazol-4-yl)-8-iodo-7-methyl-chromen-4-one (2b)

IR (KBr): 1612, 1660, 3174; ^{1}H NMR (DMSO-d_6): δ 2.23 (s, 3H, CH_3), δ 6.71 (s, 1H, pyrone), δ 7.15–8.12 (m, 7H, Ar-H) ppm; M.S. (m/z): 496 (M^+), 498 (M+2), 500 (M+4); Anal. Calcd for $C_{19}H_{11}N_2O_2Cl_2I$: C, 45.91; H, 2.23; N, 5.64%. Found: C, 45.98; H, 2.32; N, 5.76%.

3.3.3. 8-Bromo-6-chloro-2-(5-chloro-3-methyl-1-phenyl-pyrazol-4-yl)chromen-4-one (2c)

IR (KBr): 1615, 1665, 3160; ^{1}H NMR (DMSO-d_6): δ 2.26 (s, 3H, CH_3), δ 6.75 (s, 1H, pyrone), δ 7.09–8.11 (m, 7H, Ar-H) ppm; M.S. (m/z): 448 (M^+), 450 (M+2), 452 (M+4); Anal. Calcd for $C_{19}H_{11}N_2O_2Cl_2Br$: C, 50.71; H, 2.46; N, 6.22%. Found: C, 50.82; H, 2.34; N, 6.15%.

3.3.4. 6,8-Dichloro-2-(5-chloro-3-methyl-1-phenyl-pyrazol-4-yl)chromen-4-one (2d)

IR (KBr): 1610, 1666, 3181; ^{1}H NMR (DMSO-d_6): δ 2.18 (s, 3H, CH_3), δ 6.78 (s, 1H, pyrone), δ 7.05–8.16 (m, 7H, Ar-H) ppm; M.S. (m/z): 404 (M^+), 406 (M+2), 408 (M+4); Anal. Calcd for $C_{19}H_{11}N_2O_2Cl_3$: C, 56.25; H, 2.73; N, 6.91%. Found: C, 56.19; H, 2.81; N, 6.81%.

3.3.5. 2-(5-Chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-6-methyl-4H-chromen-4-one (2e)

IR (KBr): 1616, 1662, 3179; ^{1}H NMR (DMSO-d_6): δ 2.12 (s, 3H, CH_3), δ 2.32 (s, 3H, CH_3), δ 6.68 (s, 1H, pyrone), δ 7.11–8.06 (m, 8H, Ar-H) ppm; M.S. (m/z): 350 (M^+), 352 (M+2); Anal. Calcd for $C_{20}H_{15}N_2O_2Cl$: C, 68.48; H, 4.31; N, 7.99%. Found: C, 68.56; H, 4.39; N, 7.86%.

3.3.6. 8-Bromo-2-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-6-methyl-4H-chromen-4-one (2f)

IR (KBr): 1610, 1668, 3172; ^{1}H NMR (DMSO-d_6): δ 2.18 (s, 3H, CH_3), δ 2.35 (s, 3H, CH_3), δ 6.61 (s, 1H, pyrone), δ 7.08–8.12 (m, 7H, Ar-H) ppm; M.S. (m/z): 428 (M^+), 430 (M+2); Anal. Calcd for $C_{20}H_{14}N_2O_2ClBr$: C,55.90; H, 3.28; N, 6.52%. Found: C, 55.81; H, 3.36; N, 6.63%.

4. CONCLUSION

In summary, we have designed and developed an efficient method for the synthesis of some new pyrazole containing 2-(5-chloro-3-methyl-1-phenyl-pyrazol-4-yl) chromen-4-one by an alternative method. The molecular iodine (10 mol%) is used as a catalyst in PEG-400 as a green reaction solvent. In addition to this, the present methodology has significant features such as simple and practically proved, shorter reaction time, high yields of the products with an inexpensive catalyst such as iodine in PEG-400 as an alternative reaction solvent.

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Bibliographical Sketch

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