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Commercial Alum/PEG 400 Catalyzed Efficient Synthesis of Substituted 2-Phenyl-4*H*-chromen-4-ones by Microwave Irradiation

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Commercial alum/PEG 400 catalyzed, an alternate and efficient synthesis of appropriately substituted 2-phenyl-4*H*-chromen-4-ones by microwave irradiation has been reported here. In this one pot reaction, maximum atom economy was achieved; reaction time was highly reduced from hours to seconds and hence it is claimed that this methodology as an environmentally benign procedure.

Key Words: Commercial alum/PEG 400, 2-Phenyl-4*H*-chromen-4-one.

INTRODUCTION

Flavanoids or chromones represent an awfully important group of organic compounds. They constitute one of the major classes of naturally occurring compounds, which exhibit significant biological activity, including antiinflammatory[1,2] and pharmaco-logical effects. Some flavones have potential as radioligands for imaging the multidrug resistance associated protein (ABCC1/MRP1)[3].

In the late 1960, the Fisons Corporation in England introduced a new class of compounds referred to as *bis*-flavones. Later it was found that *bis*-flavones such as cromolyn sodium were effective in preventing but not reversing, antigen-induced bronchopasms[4-6]. Thus synthesis of flavones and their derivatives has attracted considerable attention due to their pharmacological therapeutic relevance like cyto-toxic (anticancer)[7-9], neuroprotective[10], HIV-inhibitory[11], antimicrobial[12,13], antifungal[14], antiinflammatory and antioxidant activity[15]. Adequately abundance in plants and their low mammalian toxicity, chromones are present in large amounts in the diet of humans[16].

A multi-component reaction with microwave organic reaction enhancement technique (MORE) is an efficient and environmentally benign method to activate various organic transformations, which affords products in higher yields in shorter reaction periods involving a very small amount of solvent. Thus, from a green chemistry point of view with utilization of multi-component reaction (MCR) protocol, new routes for the synthesis of these molecules have attracted considerable attention in the search of methods for rapid entry to these heterocycles. Thus, we report an alternate, attractive synthetic strategy for rapid and efficient library generation of appropriately substituted 2-phenyl-4*H*-chromen-4-ones (**4**). In addition, the products

could be obtained in a single step and diversity could be achieved simply by varying the reacting components.

The synthesis of **4** from β-diketones by conventional method[17] reported the use of strong acid like sulphuric acid in ethanol. In present methodology, we have used PEG-400 as reaction medium with catalytic amount of commercial alum for the cyclization of 2'-hydroxy-5'-methyl phenyl-3-phenylpropane-1,3-dione (**3**) by microwave irradiation to furnish differently substituted 2-phenyl-4*H*-chromen-4-ones (**4**). Isolation of products was easy, as catalyst and reaction medium used in this method are non-toxic and water-soluble. TLC and co-TLC monitored the progress of the reaction. The time required for the completion of the reaction was ranging from 50 to 66 s.

EXPERIMENTAL

Melting points were determined by open capillary method and are uncorrected. All solvents were distilled prior to use TLC was performed on silica gel G. ^{1}H NMR spectra were recorded from $CDCl_3$ or DMSO-d_6 solutions on a Brucker AC 400 (400 MHz). Chemical shifts are reported in ppm using TMS as an internal standard. IR spectra were obtained on a Perkin-Elmer 1800 spectrophotometer using KBr discs.

General procedure

Synthesis of 2'-hydroxy-5'-methyl phenyl-3-phenyl propane-1,3-dione (3): 2-Benzoyloxy-5-methyl-acetophenone (0.01 mol) was dissolved in minimum quantity of DMF. To it, pulverized KOH (0.015 mol) was added with stirring under ice-cold condition. The reaction mixture was further stirred for 2 h and left overnight. The reaction mixture was carefully acidified using dil. hydrochloric acid to get deep yellow solid. The course of the reaction was monitored by TLC using benzene: ethylacetate as eluant. The product obtained was filtered, washed with water and recrystallized from ethanol. The results obtained were compared with that of the authentic samples and they were found to be in good agreement with reported data.

Synthesis of 6-methyl-2-phenyl-4*H*-chromen-4-one (4): To a solution of the 2'-hydroxy-5'-methyl phenyl-3-phenyl propane-1,3-dione (0.01 mol) in PEG 400 (20 mL), catalytic amount of commercial alum was added with constant stirring. It was irradiated for 50-66 s in a Kenstar OM-20 ESP (800 W) unmodified domestic oven operating at 2450 MHz. The progress of reaction was monitored by TLC. The reaction mixture was poured into 100 g of crushed ice furnished **4**. The crude product was filtered off, washed well with water and dried. Further, it was recrystallized from ethanol.

6-Methyl-2-phenyl-4*H*-chromen-4-one 4(a): Yield 70 %; m.p. 125 °C; CHN (Found: C, 81.35; H, 5.06; O, 13.53. $C_{16}H_{12}O_2$ requires: C, 81.35; H, 5.08; O, 13.55 %); IR (KBr) ν_{max}/cm^{-1} 1657 (C=O), 1606, 1379, 1308, 769; ^{1}H NMR (δ_H) ($CDCl_3$, TMS) δ: 2.4 (s, 3H, CH_3), 6.7 (s, 1H, C_3H), 7.3-7.9 (m, 8H, Ar-H); MS (m/z) 236 (M^+, 100), 208 (M^+-CO), 134, 102.

6-Chloro-2-phenyl-4*H*-chromen-4-one 4(b): Yield 75 %; m.p. 175 ºC; IR (KBr) ν_{max}/cm^{-1} 1649 (C=O), 1600, 1382, 1312, 771; ^1H NMR (δ_H) ($CDCl_3$, TMS) δ: 6.4 (s, 1H, C_3H), 7.5-8.2 (m, 8H, Ar-H); MS (m/z) 256.

8-Bromo-6-methyl-2-phenyl-4*H*-chromen-4-one 4(c): Yield 55 %; m.p. 172 ºC; IR (KBr) ν_{max}/cm^{-1} 1653 (C=O), 1609, 1378, 1321, 764; ^1H NMR (δ_H) ($CDCl_3$, TMS) δ: 2.6 (s, 3H, CH_3), 6.0 (s, 1H, C_3H), 7.2-7.8 (m, 7H, Ar-H); MS (m/z) 315.

8-Bromo-6-chloro-2-phenyl-4*H*-chromen-4-one 4(d): Yield 60 %; m.p. 168 ºC; IR (KBr) ν_{max}/cm^{-1} 1655 (C=O), 1608, 1374, 1308, 769; ^1H NMR (δ_H) ($CDCl_3$, TMS) δ: 6.4 (s, 1H, C_3H), 7.2-8.2 (m, 8H, Ar-H); MS (m/z) 335.

8-Iodo-6-methyl-2-phenyl-4*H*-chromen-4-one 4(e): Yield 60 %; m.p.147 ºC; IR (KBr) ν_{max}/cm^{-1} 1655 (C=O), 1612, 1380, 772; ^1H NMR (δ_H) ($CDCl_3$, TMS) δ: 2.8 (s, 3H, CH_3), 6.6 (s, 1H, C_3H), 7.1-8.0 (m, 7H, Ar-H); MS (m/z) 361.

6-Iodo-7-methoxy-2-phenyl-4*H*-chromen-4-one 4(f): Yield 56 %; m.p. 179 ºC; IR (KBr) ν_{max}/cm^{-1} 1647 (C=O), 1604, 1512, 1382, 771; ^1H NMR (δ_H) ($CDCl_3$, TMS) δ: 3.81 (3H, s, $-OCH_3$), 5.41 (s, 1H, C_3H), 6.7-7.6 (m, 7H, Ar-H); MS (m/z) 377.

3-Chloro-6-methyl-2-phenyl-4*H*-chromen-4-one 4(g): Yield 72 %; m.p. 139 ºC; IR (KBr) ν_{max}/cm^{-1} 1654 (C=O), 1608, 1383, 1318, 765; ^1H NMR (δ_H) ($CDCl_3$, TMS) δ: 2.4 (s, 3H, CH_3), 7.3-7.9 (m, 8H, Ar-H); MS (m/z) 270.

3,6-Dichloro-2-phenyl-4*H*-chromen-4-one 4(h): Yield 70 %; m.p. 175 ºC; IR (KBr) ν_{max}/cm^{-1} 1648 (C=O), 1611, 1378, 1321, 771; ^1H NMR (δ_H) ($CDCl_3$, TMS) δ: 7.5-8.2 (m, 8H, Ar-H); MS (m/z) 290.

3-Bromo-6-methyl-2-phenyl-4*H*-chromen-4-one 4(i): Yield 60 %; m.p. 151 ºC; IR (KBr) ν_{max}/cm^{-1} 1655 (C=O), 1622, 1389, 1327, 782; ^1H NMR (δ_H) ($CDCl_3$, TMS) δ: 2.7 (s, 3H, CH_3), 7.1-7.9 (m, 8H, Ar-H); MS (m/z) 315.

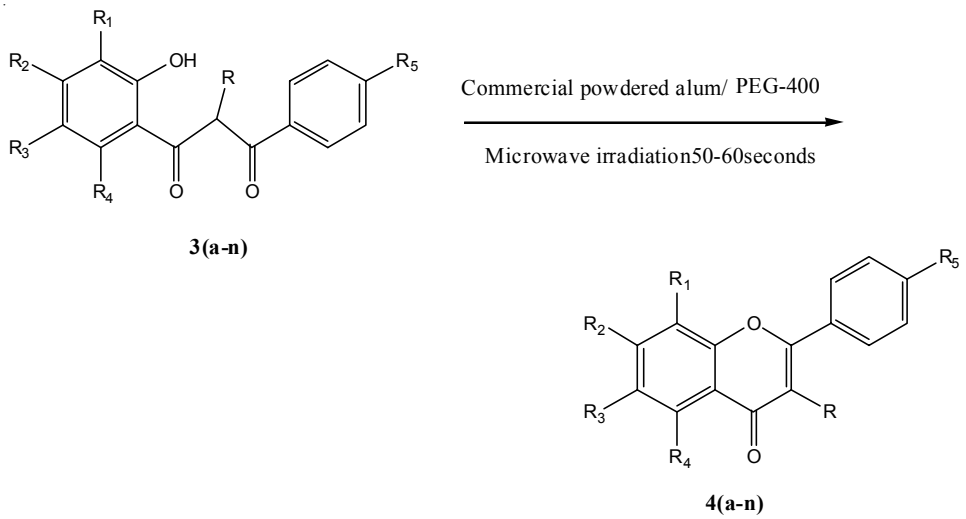
3-Bromo-6-chloro-2-phenyl-4*H*-chromen-4-one 4(j): Yield 60 %; m.p. 185 ºC; IR (KBr) ν_{max}/cm^{-1} 1647 (C=O), 1615, 1374, 1321, 766; ^1H NMR (δ_H) ($CDCl_3$, TMS) δ: 7.5-8.2 (m, 8H, Ar-H); MS (m/z) 335.

2-(4-Methoxyphenyl)-6-methyl-4*H*-chromen-4-one 4(k): Yield 70 %; m.p. 168 ºC; IR (KBr) ν_{max}/cm^{-1} 1653 (C=O), 1609, 1378, 1321, 764; ^1H NMR (δ_H) ($CDCl_3$, TMS) δ: 2.2 (s, 3H, CH_3), 6.0 (s, 1H, C_3H), 4.02 (3H, s, $-OCH_3$), 7.2-7.8 (m, 7H, Ar-H); MS (m/z) 266.

6-Chloro-2-(4-methoxyphenyl)-4*H*-chromen-4-one 4(l): Yield 75 %; m.p. 172 ºC; IR (KBr) ν_{max}/cm^{-1} 1655 (C=O), 1607, 1378, 1325, 769; ^1H NMR (δ_H) ($CDCl_3$, TMS) δ: 6.0 (s, 1H, C_3H), 4.02 (3H,s, $-OCH_3$), 7.2-7.8 (m, 7H, Ar-H); MS (m/z) 286.

6-Iodo-7-methoxy-2-(4-methoxyphenyl)-4*H*-chromen-4-one 4(m): Yield 55 %; m.p. 255 ºC; IR (KBr) ν_{max}/cm^{-1} 1656 (C=O), 1612, 1469, 1331, 756; ^1H NMR (δ_H) ($CDCl_3$, TMS) δ: 6.0 (s, 1H, C_3H), 3.78 (3H,s, C4'-OCH_3), 3.85 (3H, s, $-OCH_3$), 7.2-7.8 (m, 7H, Ar-H); MS (m/z) 282.

3-Iodo-6-methyl-2-phenyl-4*H*-chromen-4-one 4(n): Yield 55 %; m.p. 154 ºC; IR (KBr) ν_{max}/cm^{-1} 1658 (C=O), 1615, 1464, 1333, 756; ^1H NMR (δ_H) ($CDCl_3$, TMS) δ: 2.8 (3H,s, $-CH_3$), 7.2-7.8 (m, 8H, Ar-H); MS (m/z) 362.



Scheme-I

TABLE-1
PHYSICAL CHARACTERIZATION OF SYNTHESIZED ORGANIC COMPOUNDS **4a-n**

Entry	R	R^1	R^2	R^3	R^4	R^5	m.p. (ºC)	Yield (%)	Reaction time (s)	
									MW	Δ
4a	H	H	H	CH_3	H	H	125	70	50	420
4b	H	H	H	Cl	H	H	175	75	55	420
4c	H	Br	H	CH_3	H	H	172	55	65	420
4d	H	Br	H	Cl	H	H	168	60	45	420
4e	H	I	H	CH_3	H	H	147	60	66	420
4f	H	H	OCH_3	I	H	H	179	56	60	420
4g	Cl	H	H	CH_3	H	H	139	72	50	420
4h	Cl	H	H	Cl	H	H	175	70	65	420
4i	Br	H	H	CH_3	H	H	151	60	50	420
4j	Br	H	H	Cl	H	H	185	60	60	420
4k	H	H	H	CH_3	H	OCH_3	168	70	55	420
4l	H	H	H	Cl	H	OCH_3	172	75	66	420
4m	H	H	OCH_3	I	H	OCH_3	255	55	60	420
4n	I	H	H	CH_3	H	H	154	55	64	420

RESULTS AND DISCUSSION

In this communication the synthesis of substituted-2-phenyl-4*H*-chromen-4-ones **4(a-n)** *via* cyclization of differently substituted 2'-hydroxy-5'-methyl phenyl-3-phenylpropane-1,3-diones **3(a-n)** are reported. The conventional procedure[17] involved heating under reflux conditions of **3(a-n)** with H_2SO_4 in ethanol for 1 h. While in present study, **3(a-n)** were treated with catalytic amount of easily available commercial alum in PEG-400 (solvent) by microwave irradiation. The reaction

mixture was irradiated in intermittent intervals of 10 s. The domestic microwave oven of 800 watt at 2450 MHz was used for the reaction. TLC monitored the progress of reaction. Ethanol with H_2SO_4 was a solvent of choice in conventional method, which was replaced by PEG-400 in newly developed method because of its high dielectric constant, non-polar nature, water solubility, eco-friendly and non-toxic nature. Thus, this methodo-logy offers tremendous advantages: high reduction of reaction time, operational simplicity, cleaner reaction, easy work-up and better yields as compared to the conventional method.

The formation of **4(a)** has been supported by spectral data and elemental analysis. The IR absorption peaks at 1657 cm^{-1} showed the presence of a carbonyl group and the absence of a hydroxyl group band confirmed the cyclization of **3(a)** into **4(a)**. This was also supported by ^1H NMR spectral data that showed 1H singlet peak at δ 6.7, which is particularly shown by the proton of the differently substituted 2-phenyl-4*H*-chromen-4-one ring and further the mass spectral analysis finally confirmed the structure by showing the m/z peak at 236.

Conclusion

As a consequence, a novel one-pot methodology of synthesis of 6-methyl-2-phenyl-4*H*-chromen-4-ones (**4**) by using 2'-hydroxy-5'-methyl phenyl-3-phenyl-propane-1,3-diones (**3**) as precursors is employed.

Thus herein, an efficient one pot, a clean methodology is reported, which leads to a notable improvement in reaction conditions: the reaction time is highly reduced from hours to seconds, with maximum yield. Also the use of hazardous chemicals has been done away with less energy consumption protocol. Hence this methodology represents a green chemistry approach and eco friendly protocol.

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