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An Efficient Synthesis of 4h-Chromene-4-One Derivatives under Microwave Irradiation

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Abstract

Chromenes are heterocyclic molecules of considerable interest because of the diverse range of their biological properties. A series of 3-hydroxy-2-(substituted) phenyl-4H-chromene-4-one were synthesized in microwave oven and by conventional method. Derivatives of 3-hydroxy-2-(substituted)phenyl-4H-chromene-4-one were synthesized from 2'-hydroxychalcones using hydrogen peroxide and sodium hydroxide. Their chemical transformations by conventional method took hours for reaction completion whereas reactions under microwave irradiation resulted in drastic reduction of time along with improved yield of the product.

Keywords: chromene, microwave irradiation, hydrogen peroxide.

Introduction

Heterocyclic compounds are of immense importance owing to various biological activities associated with them. Heterocyclic compounds constitute the core structure of a number of pharmacologically and biologically active compounds[1]. Chromones are oxygen-containing heterocyclic compounds with a benzoannelated γ-pyrone ring, with the parent compound being chromone (4H-chromene-4-one, 4H-1-benzopyran-4-one)[2]. Chromones constitute one of the major class of naturally occurring compounds and interest in their chemistry continues unabated because of their diverse biological activities such as cytotoxic (anticancer)[3], neuroprotective[4], HIV-inhibitory[5], antimicrobial[6], antifungal[7] and antioxidant activity[8]. Due to their abundance in plants and their low mammalian toxicity, chromone derivatives are present in large amounts in the human diet.

The widespread use of chromone as a scaffold in medicinal chemistry establishes this moiety as an important bioactive class of heterocyclic compounds. These molecules are also used as pharmacophores due to their favorable metabolic profiles and ability to engage in hydrogen bonding[9].

Among the various methods towards synthesis of chromenes the most widely used method is via synthesis of chalcone by Claisen-Schmidt condensation. Chalcone on cyclization yields chromene. Cyclization is usally done in presence hydrogen peroxide & sodium hydroxide in ethanol. However this reaction under conventional condition takes longer time for completion. Microwave irradiation as a source of energy has been used effectively for various chemical transformation[10-12]. In order to develop a more efficient process towards cyclization of chalcone, we have attempted cyclization reaction under microwave irradiation and the results are reported herein.

Materials and Methods

All the chemicals and solvents used were from Merck and Sigma Aldrich India. ^{1}H NMR was recorded in $CDCl_3$, on Bruker advance II 400 NMR spectrometer with TMS as internal standard. Mass analysis was carried out using Waters Q-T Micro Mass spectrometer. IR spectrum was obtained on a Perkin Elmer FT-IR spectrometer. Kenstar Microwave oven 300 W (Model MO9621, 2450 MHz, 900W) was used for microwave irradiation. Purity of the compounds was checked on Merck TLC silica gel plates using UV cabinet and iodine vapors as a visualizing agent. Melting points measured in open capillary tubes were uncorrected.

Experimental

General procedure for synthesis of chromene derivatives

Conventional method: In 150 ml beaker 13.6 g of 1-(2-hydroxyphenyl)-3-phenyl-2-propen-1-one (chalcone) (0.01 mole), ethanol (50 ml) and 20% aqueous sodium hydroxide (9.5 ml) was added with stirring, followed by careful addition of 20% hydrogen peroxide (18 ml)over a period of 1 hr. The reaction mixture was stirred for 3 hrs. at 30^{0}C and poured onto crushed ice containing 5N HCl[13]. The precipitate was filtered, washed, dried and crystallized from alcohol and passed through column using chloroform as a solvent.

Under microwave: 1-(2-hydroxyphenyl)-3-phenyl-2-propen-1-one (0.01 mole) was dissolved in ethanol (20 ml), to this 20% sodium hydroxide (10 ml) and 20% hydrogen peroxide (18 ml) was added and this mixture was subjected to microwave irradiation at 300 W. The reaction mixture was monitored by TLC. It was poured into crushed ice containing 5N hydrochloric acid[14] and allowed to precipitate. The product was filtered, washed with water, dried and recrystalized using alcohol and passed through column using chloroform as solvent.

Synthesis of 3-hydroxy-2-phenyl-4H-chromene-4-one (S1): Yield 69%; mp 170 °C; FT-IR (KBr): 3222 (Ar-OH), 3033, 3075 (aromatic str.), 1611 (C=O pyrone ring) cm^{-1}; 1H NMR (400 MHz, CDCl3): δ 9.92 (s, 1H, OH), 7.26-8.27 (m, 9H, Ar-H) ppm; MS-EI, m/z = (M)+ = 238.

Synthesis of 3-hydroxy-2-p-tolyl-4H-chromene-4-one (S2): Yield 73%; mp 112 °C; FT-IR (KBr): 3218 (Ar-OH), 1615 (C=O pyrone ring) cm^{-1}; 1H NMR (400 MHz, CDCl3): δ 2.35 (s, 3H, CH3), 10.02 (s, 1H, OH), 7.26-8.27 (m, 8H, Ar-H) ppm; MS-EI, m/z = (M)+ = 252.

Synthesis of 2-(4-chlorophenyl)-3-hydroxy-4H-chromene-4-one (S3): Yield 71%; mp 190 °C; FT-IR (KBr): 3202 (Ar-OH), 1619 (C=O pyrone ring) cm^{-1}; 1H NMR (400 MHz, CDCl3): δ 10.56 (s, 1H, OH), 7.26-8.27 (m, 8H, Ar-H) ppm; MS-EI, m/z = (M)+ = 272.

Synthesis of 3-Hydroxy-2-(3-methoxyphenyl)-4H-chromene-4-one (S4): Yield 70%, mp 140 °C; FT-IR (KBr): 3212 (Ar-OH), 1631 (C=O pyrone ring) cm^{-1}; ^{1}H NMR (400 MHz, CDCl3) : δ 3.83(s, 3H),7.08(m, 1H),7.46(m, 2H), 7.80 (m, 4H), 8.12 (dd, 1H), 9.63 (s, 1H OH) ppm; MS-EI, m/z=(M)+ = 269.

Synthesis of 2-(4-fluorophenyl)-3-hydroxy-4H-chromene-4-one (S5): Yield 72%; mp 162 °C; FT-IR (KBr): 3323 (Ar-OH), 1512 cm-1(C=C str.), 1693 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, CDCl3): δ 6.92-7.64 (m, 8H, Ar-H), 10.22 (s, 1H, OH) ppm; MS-EI, m/z= (M)+ =256.

Synthesis of 3-hydroxy-2-(3-nitrophenyl)-4H-chromene-4-one (S6): Yield 75%; mp 126 °C; FT-IR (KBr): 3264 (Ar-OH), 1602 (C=C str.), (C=O pyrone ring), 1529 (-O-N=O) cm^{-1}; ^1H NMR (400 MHz, CDCl3) : δ 6.92-8.23 (m, 8H, Ar-H), 10.08 (s, 1H, OH) ppm; MS-EI, m/z=(M)+ = 283.

Synthesis of 3-hydroxy-2-(3,4-dimethoxyphenyl)-4H-chromene-4-one (S7): Yield 74%; mp 210 °C; FT-IR (KBr): 3212 (Ar-OH), 1622 (C=O pyrone ring) cm^{-1}; ^1H NMR (400 MHz, CDCl3): δ 3.95 (s, 3H, OCH3), 3.97 (s, 3H, OCH3), 9.82 (s, 1H, OH), 7.00-8.25 (m, 7H, Ar -H) ppm; MS-EI, m/z = (M)+ = 298.

Synthesis of 3-hydroxy-2-(4-nitrophenyl)-4H-chromene-4-one (S8): Yield 64%; mp 158 °C; FT-IR (KBr): 3246 (Ar-OH), 1515 (C=C str.), 1699 (C=O pyrone ring), 1108 (C-O-C), 1558 (-O-N=O) cm^{-1}; ^1H NMR (400 MHz, CDCl3) : δ 6.92-8.14 (m, 8H, Ar-H), 9.89 (s, 1H, OH), ppm; MS-EI, m/z = (M)+ = 283.

Synthesis of 3-Hydroxy-2-(4-methoxyphenyl)-4H-chromene-4-one (S9): Yield 79%; mp 224 °C; FT-IR (KBr): 3280 (Ar-OH), 1715 (C=O pyrone ring), 1620 (C=C), 1345 (C-O-C), cm^{-1}; ^{1}NMR (400 MHz, CDCl3) : δ 7.70 (t, 1H), 7.41(t, 1H), 7.30 (d, 1H), 7.05 (d, 1H), 9.80 (s, 1H, OH), 7.57 (d, 2H), 8.20 (d, 2H), 3.89 (s, 3H, OCH3) ppm; MS-EI, m/z = (M)+ = 268.

Results and Discussion:

In the present investigation 2'-Hydroxychalcones were cyclized to their corresponding 3-Hydroxychromenes derivatives under microwave irradiation (Scheme-I). The reaction was attempted with variously substituted 2'-Hydroxychalcones (Table 1). The reaction is also studied under conventional conditions. Conventional heating took hours for completion, whereas under microwave irradiation reaction was completed in minutes (Table 2).

Scheme-I

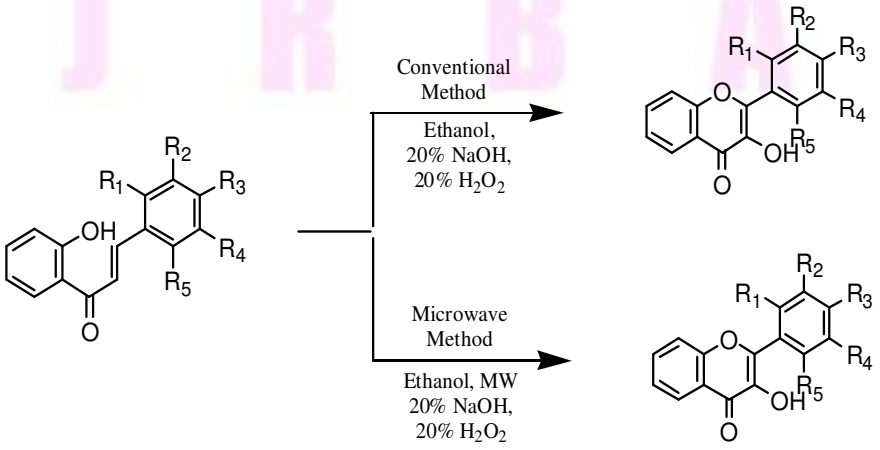

Table 1: Substitution table

Sr. No.	Compound code	Substitution				
		R1	R2	R3	R4	R5
1	S1	H	H	H	H	H
2	S2	H	H	CH_3	H	H
3	S3	H	H	Cl	H	H
4	S4	H	OCH_3	H	H	H
5	S5	H	H	F	H	H
6	S6	H	NO_2	H	H	H
7	S7	H	OCH_3	OCH_3	H	H
8	S8	H	H	NO_2	H	H
9	S9	H	H	OCH_3	H	H
10	S10	Cl	H	H	H	H

Table 2: Comparison between conventional and microwave method in synthesis of chromene-4-ones derivatives

Sr. No.	Compound code	Reaction Time		Yield		Melting Point(^{0}C)
		A (hrs)	B (min)	A (%)	B (%)	
1	S1	3	5	64	69	170
2	S2	3	4	62	68	112
3	S3	3	3.5	63	71	190
4	S4	3	6	65	70	140
5	S5	3	7	59	67	162
6	S6	3	8	61	69	126
7	S7	3	3	65	74	210
8	S8	3	9.5	56	64	158
9	S9	3	3.5	68	73	224
10	S10	3	4.5	63	68	156

Conclusion:

Chromene-4-ones were synthesized using both conventional and microwave method. Substituted 2'-hydroxychalcones on treatment with sodium hydroxide and hydrogen peroxide in ethanol yielded Chromene-4-ones. By conventional method this reaction requires about 3 hours whereas in microwave method they have been optimally synthesized within 10 minutes with appropriate power setting. Thus, this microwave synthesis of 3-hydroxychromenes is found to be undoubtedly more economic, efficient, ecofriendly and convenient than other reported methods.

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