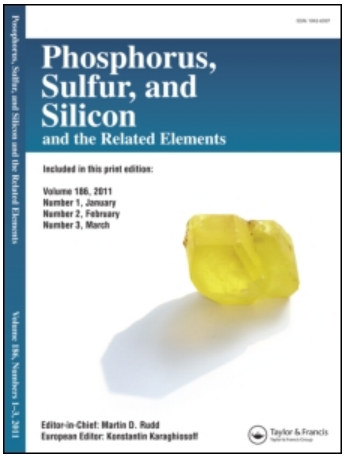

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Novel Synthesis of Oxygenated Coumarins from Substituted Phenols Mediated by Vinyl Triphenylphosphonium Salt Under Microwave Irradiation

Rahim Hekmatshoar[a]; Sanaz Souri[a]; Mahshid Rahimifard[a]; Farnoosh Faridbod[a]
[a] Azzahra University, Tehran, Iran

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NOVEL SYNTHESIS OF OXYGENATED COUMARINS FROM SUBSTITUTED PHENOLS MEDIATED BY VINYL TRIPHENYLPHOSPHONIUM SALT UNDER MICROWAVE IRRADIATION

Rahim Hekmatshoar, Sanaz Souri, Mahshid Rahimifard, and Farnoosh Faridbod
Azzahra University, Vanak, Tehran, Iran

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Protonation of the highly reactive 1:1 intermediates produced in the reaction between triphenylphosphine and dimethyl acetylenedicarboxylate(DMAD) by substituted phenols lead to vinyl triphenylphosphonium salts, which undergo aromatic electrophilic substitution reaction with a phenolate conjugate base to produce 4-carboxymethyl coumarins in fairly highly yields.

Keywords: 4-Carboxymethyl coumarins; dimethyl acetylenedicarboxylate(DMAD); phenols; triphenylphosphine; vinyl triphenyl phosphonium salts

The coumarin moiety is distributed widely in nature. Many natural products that contain this subunit exhibit such useful and diverse biological activity as antifungal,[1] anticoagulant,[2] antispasmotic,[3] anticholerostatic,[4] and molluscacide[5] activity. In addition, other coumarins are of much interest as a result of their toxicity,[6] carcinogenicity,[7] and photodynamic effect.[8,9]

Coumarins prevent disease, modulate growth and maturation and defense systems, and have antioxidant properties.

Muray, Mendez, and Brown[10] in their book detailed their occurrence, chemistry, and biology.

Egan et al.[11] gave a good review of the history of coumarins including a time table that begins with the first isolation of the compound from Tonka beans (Dipterex oduratus L) in 1822, to its manifold

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Address correspondence to Rahim Hekmatshoar, Department of Chemistry, School of Sciences, Azzahra University, Vanak, Tehran, Iran. E-mail: rhekmat@alzahra.ac.ir

use in medicine, industry, and laboratory applications. Coumarins also may be found in nature in combination with sugars, as glycosides. The coumarins can be categorized roughly as follows. The synthetic compound warfarin is used widely both as a rodenticide and an oral anticoagulant.

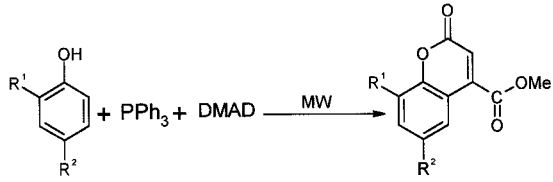
Another coumarin containing a 4-hydroxy group, phenprocoumon, has been found to possess antiviral activity and significantly inhibit the HIV-1 protease responsible for the moturation of the causative virus of acquired immunodeficiency syndrome (AIDS).[12] Members of this group of coumarins also have been used widely as fluorophores. The 4-methylumbelliferones commonly are employed to generate a fluorescent signal in assays for the detection of bacterial contamination of water supplies.[13] Peptide derivatives of 7-amino-4-methyl coumarin (AMC) have been utilized extensively for the investigation of protease activity.[14] Coumestrol is one important member of coumarins that has shown to display an oestrogenic activity. Therefore coumarins are documented widely in the literature and their preparation has received much attention due to a wide variety of biological activities they possess.[15] In this article a direct, efficient, and operationally convenient approach to the synthesis of oxygented coumarins is presented.

However, most of the processes mentioned above suffer from drawbacks such as extended reaction times, tedious purification, and undesirable side products.

Microwave-assisted organic synthesis recently has received considerable attention by synthetic chemists,[16–21] because of its short reaction times, high efficiency, enhanced selectivity, milder reaction conditions, operational simplicity, convenient work-up conditions, and associated ease of manipulation.

In continuation of our ongoing efforts for the synthesis of coumarin derivatives,[22] herein we report for the first time the synthesis of coumarin derivatives under microwave irradiation by reaction of substituted phenols with reactive intermediates produced in the reaction between triphenylphosphine and dimethyl acetylendicarboxylate (Scheme 1). Coumarin derivatives (**b.1–b.10**) apparently result from initial addition of triphenylphosphine to the acetylenic ester and concomitant protonation of the reactive 1:1 adduct, followed by electrophilic attack of the vinyltriphenylphosphonium cation to the aromatic ring at the *ortho* position relative to the strong activating group. The coumarin derivatives (**b.1–b.10**) are produced by intermolecular lactonization (Scheme 2).

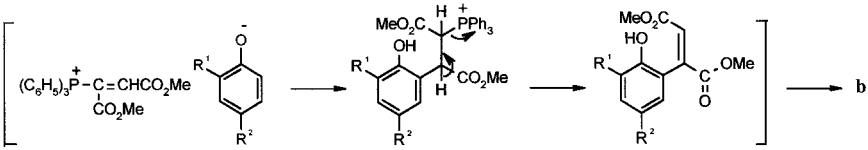
Structures (**b.1–b.10**) were assigned to the isolated products on the basis of their elemental analyses and IR, ^{1}H, and ^{13}CNMR spectra. The mass spectra of products confirm their molecular weights.



a **b**

1: R^1= H; R^2= NO_2
2: R^1= NO_2; R^2= NO_2
3: R^1= H; R^2= CH_3
4: R^1= CH_3; R^2= H
5: R^1= CH_3; R^2= Cl
6: R^1= Cl; R^2= Cl
7: R^1= H; R^2= OCH_3
8: R^1= H; R^2= t-But
9: R^1= OCH_3; R^2= $-CH_2CH=CH_2$
10: R^1= OCH_3; R^2= -CHO

SCHEME 1



SCHEME 2

EXPERIMENTAL

Melting points were determined with an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. The infrared spectra were obtained on a philips PU9800 FT-IR spectrometer; ^{1}H and ^{13}CNMR spectra were measured with JEOL EX-90A spectrometer at 90 and 22.6 MHz respectively. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 ev. Dimethyl acetylenedicarboxylate, substituted phenols, and triphenylphosphine were obtained from Fluka (Buchs, Switzerland) and were used without further purification.

Methyl-6-nitro-2-oxo-2H-chromene-4-carboxylate (b.1)

Yield 75%; m.p.: 129–130°C; ^{1}H NMR (90 MHz, δ, $CDCl_3$): 4.05 (3H, s, OCH_3), 7.15 (1H, s, CH), 7.52 (1H, d, J = 9.5 Hz, CH), 8.44 (1H, dd, J = 9.5 and 2.7 Hz, CH), 9.32 (1H, d, J = 2.7 Hz, CH) ppm; ^{13}C NMR (22.6 MHz, δ, $CDCl_3$): 53.67 (OCH_3), 116.10 (C-2 ring), 118.33 (CH), 121.80 (CH), 123.55 (CH), 127.09 (CH), 14.77 (C), 144.40 (C), 157.59 (C), 158.24 ($CO_{lactone}$), 163.25 (CO_{ester}) ppm; ($C_{11}H_7O_6N$, 249.2). Elemental analysis calculated for $C_{11}H_7O_6N$: C, 53.02; H, 2.83; N, 5.62; O, 38.53 and found

C, 53.10; H, 2.80; N, 5.58; O, 38.49. MS (70 eV) m/z (%): 249.3 (55, M^+), 221.3 (22), 190.2 (100), 144.1 (14); IR (KBr) (cm^{-1}): 1732, 1614, 1240 and 1278 (C—O), 1346 and 1523 (NO_2).

Methyl-6,8-dinitro-2-oxo-2H-chromene-4-carboxylate (b.2)

Yield 50%; m.p.: 130–131°C; ^{1}H NMR (90 MHz, δ, $CDCl_3$): 4.10 (3H, s, OCH_3), 7.32 (1H, s, CH), 8.97 (1H, d, J = 2.7 Hz, 1H), 9.65 (1H, d, J = 2.7 Hz, 1H) ppm; ^{13}C NMR (22.6 MHz, δ, $CDCl_3$): 54.12 (OCH_3), 118.50 (C), 122.57 (CH), 122.98 (CH), 126.89 (CH), 138.17 (C), 139.92 (C), 155.43 (C), 158 85 (C), 160.08 ($CO_{lactone}$), 162.64 (CO_{ester}) ppm; ($C_{11}H_6O_8N_2$, 294.21). Elemental analysis calculated for $C_{11}H_6O_8N_2$: C, 44.91; H, 2.06; N, 9.52; O, 43.51 and found C, 44.80; H, 2.10; N, 9.58; O, 43.49. MS (70 eV) m/z (%): 294.4 (42, M^+), 266.3 (21), 235 (100), 201.2 (5), 189.1 (22), 143.2 (6), 103.1 (12), 87.1 (15); IR (KBr) (cm^{-1}): 1764, 17.26, 1620, 1541 and 1346 (NO_2), 1265, 1211, 1176.

Methyl-6-methyl-2-oxo-2H-chromene-4-carboxylate (b.3)

Yield 73%; m.p.: 85–86°C; ^{1}H NMR (90 MHz, δ, $CDCl_3$): 2.42 (3H, s, CH_3), 4.04 (1H, s, OCH_3), 6.97 (1H, s, CH), 7.24 (1H, d, J = 9 Hz, CH), 7.40 (1H, dd, J = 9 and 2.2 Hz, CH), 8.02 (1H, d, J = 2.2 Hz, CH) ppm; ^{13}C NMR (22.6 MHz, δ, $CDCl_3$): 21.05 (CH_3), 53.11 (OCH_3), 115.53 (C), 116.87 (CH), 119.19 (CH), 126.56 (CH), 133.40 (CH), 134.54 (C), 142.36 (C), 152.46 (C—O), 160.11 ($CO_{lactone}$), 164.35 (CO_{ester}) ppm; ($C_{12}H_{10}O_4$, 218.25). Elemental analysis calculated for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62; O, 29.33 and found C, 66.10; H, 4.60; O, 30.01. MS (70 eV) m/z (%): 219.3 (18, M^+), 218.4 (80), 190.3 (12), 187.3 (15), 159.3 (100), 131.2 (6), 102.2 (5), 77.2 (5); IR (KBr) (cm^{-1}): 1730, 1608, 1562, 1437, 1240, 1270, 1140.

Methyl-8-methyl-2-oxo-2H-chromene-4-carboxylate (b.4)

Yield 70%; m.p.: 109–110°C; ^{1}H NMR (90 MHz, δ, $CDCl_3$): 2.47 (3H, s, CH_3), 4.00 (1H, s, OCH_3), 6.92 (1H, s, CH), 7.22 (1H, t, J = 8 Hz, CH), 7.44 (1H, dd, J = 8 and 2 Hz, CH), 8.07 (1H, dd, J = 8 and 2 Hz, CH) ppm; ^{13}C NMR (22.6 MHz, δ, $CDCl_3$): 15.72 (CH_3), 53.10 (OCH_3), 115.61 (C), 118.86 (CH), 124.24 (CH), 124.52 (CH), 126.60 (C), 133.77 (CH), 143.01 (C), 152.66 (C—O), 160.07 ($CO_{lactone}$), 164.51 (CO_{ester}) ppm; ($C_{12}H_{10}O_4$, 218.25). Elemental analysis calculated for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62; O, 29.33 and found C, 66.10; H, 4.59; O, 30.01. MS (70 eV) m/z (%): 219 (32, M^+), 218 (75), 190 (18), 159 (100), 115 (18), 102 (22), 77 (17); IR (KBr) (cm^{-1}): 1732, 1593, 1271, 1242, 1163.

Methyl-6-chloro-8-methyl-2-oxo-2H-chromene-4-carboxylate (b.5)

Yield 84%; m.p.: 106–107°C; ^{1}H NMR (90 MHz, δ, $CDCl_3$): 2.45 (3H, s, CH_3), 4.02 (1H, s, OCH_3), 7.00 (1H, s, CH), 7.42 (1H, d, J = 2.5 Hz, CH), 8.13 (1H, d, J = 2.5 Hz, CH), ppm; ^{13}C NMR (22.6 MHz, δ, $CDCl_3$): 16.00 (CH_3), 53.25 (OCH_3), 116.50 (C), 120.20 (CH), 123.85 (CH), 128.49 (C), 129.85 (C), 133.48 (CH), 141.2 (C), 151.0 (C), 159.34 ($CO_{lactone}$), 163.90 (CO_{ester}) ppm; ($C_{12}H_9O_4$ Cl, 252.60). Elemental analysis calculated for $C_{12}H_9O_4Cl$: C, 57.05; H, 3.59; Cl, 14.03; O, 25.33 and found C, 57.15; H, 3.70; Cl, 14.25; O, 25.39. MS (70 eV) m/z(%): 252.3 (30, M^+), 224.3 (12), 193.2 (70), 165.2 (6), 102.2 (25), 75.1 (21); IR (KBr) (cm^{-1}): 1739, 1608, 1569, 1236, 1205, 1164.

Methyl-6,8-dichloro-2-oxo-2H-chromene-4-carboxylate (b.6)

Yield 90%; m.p.: 120°C; ^{1}H NMR (90 MHz, δ, $CDCl_3$): 4.02 (3H, s, OCH_3), 7.07 (1H, s, vinylic CH), 7.60 (1H, d, J = 2.3 Hz, C3-H), 8.20 (1H, d, J = 2.3 Hz, C5-H) ppm; ^{13}C NMR (22.6 MHz, δ, $CDCl_3$): 53.55 (OCH_3), 117.76 (C), 121.43 (CH), 122.85 (C), 125.14 (CH), 129.98 (C), 132.30 (CH), 140.57 (C), 148.55 (C ispo-C-O), 157.83 ($CO_{lactone}$), 163.33 (CO_{ester}) ppm; ($C_{11}H_6O_4Cl_2$, 273.10). Elemental analysis calculated for $C_{11}H_6O_4Cl_2$: C, 48.38; H, 2.21; Cl, 25.97; O, 23.44 and found C, 48.10; H, 2.30; Cl, 25.88; O, 23.49. MS (70 eV) m/z = 273.1.

Methyl-6-methoxy-2-oxo-2H-chromene-4-carboxylate (b.7)

Yield 88%; m.p.: 129°C; ^{1}H NMR (90 MHz, δ, $CDCl_3$): 3.86–4.00 (6H, 2s, $2OCH_3$), 6.97 (1H, s, CH), 7.11 (1H, dd, J = 8.6 and 2.6 Hz), 7.29 (1H, d, J = 8.6 Hz), 7.79 (1H, d, J = 2.6 Hz) ppm; ^{13}C NMR (22.6 MHz, δ, $CDCl_3$): 53.14 ($OCH_{3\,ester}$), 55.79 ($OCH_{3\,ar}$), 109.09 (CH), 116.18 (C), 118.01 (CH), 120.00 (CH), 120.29 (CH), 141.59 (C), 156.25 (C), 160.07 ($CO_{lactone}$), 164.27 (CO_{ester}) ppm; ($C_{12}H_{10}O_5$, 234.10). Elemental analysis calculated for $C_{11}H_7O_6N$: C, 61.54; H, 4.30; O, 34.16 and found C, 61.40; H, 4.23; O, 34.5. MS (70 eV) m/z = 234.07.

Methyl-6-*t*-butyl-2-oxo-2H-chromene-4-carboxylate (b.8)

Yield 75%; m.p.: 119°C; ^{1}H NMR (90 MHz, δ, $CDCl_3$): 1.37 (9H, s, $3CH_3$), 4.01 (3H, s, OCH_3), 6.93 (1H, s, CH), 7.29 (1H, d, J = 9 Hz), 7.61 (1H, dd, J = 9 and 2.4 Hz), 8.27 (1H, d, J = 2.4 Hz) ppm; ^{13}C NMR

(22.6 MHz, δ, $CDCl_3$): 31.27 (C $3CH_3$), 34.69 (^{13}C $3CH_3$), 52.98 (OCH_3), 115.24 (C), 116.62 (CH), 119.19 (CH), 123.10 (CH), 129.98 (CH), 142.48 (C), 147.81 (C), 152.29 (C ipso-C-O), 160.19 ($CO_{lactone}$), 164.35 (CO_{ester}) ppm; ($C_{15}H_{16}O_4$, 260.13). Elemental analysis calculated for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20; O, 24.59 and found C, 69.80; H, 6.31; O, 24.45. MS (70 eV) m/z = 260.1.

Methyl-6-alyl(propenyl)-8-methoxy-2-oxo-2H-chromene-4-carboxylate (b.9)

Yield 70%; m.p.: 128°C; ^{1}H NMR (90 MHz, δ, $CDCl_3$): 3.44 (CH_2, m), 3.95 (OCH_3), 3.99 (OCH_3), 5.12 (=CH_2, m), 5.83 (CH=, m), 6.91 (1H, s, CH), 6.95 (1H, d, J = 2.3 Hz), 7.59 (1H, d, J = 2.3 Hz) ppm; ^{13}C NMR (22.6 MHz, δ, $CDCl_3$): 40.07 (CH_2), 53.10 (OCH_3), 56.32 (OCH_3), 114.91 (CH), 116.18 (C), 116.67 (CH), 117.36 (CH), 119.39 (CH), 136.50 (CH_2), 136.58 (C), 136.66 (C), 142.65 (C), 147.25 (C), 159.42 ($CO_{lactone}$), 164.31 (CO_{ester}) ppm; ($C_{15}H_{14}O_5$, 274.18). Elemental analysis calculated for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15; O, 29.17 and found C, 65.50; H, 5.20; N, O, 30.01. MS (70 eV) m/z = 274.1.

Methyl-6-formyl-8-methoxy-2-oxo-2H-chromene-4-carboxylate (b.10)

Yield 65%; m.p.: 196–197°C; ^{1}H NMR (90 MHz, δ, $CDCl_3$): 4.04 (3H, s, OCH_3), 7.08 (1H, s, CH), 7.27 (1H, d, J = 2.4 Hz), 8.54 (1H, d, J = 2.4 Hz), 10.00 (1H, s, CHO) ppm; ^{13}C NMR (22.6 MHz, δ, $CDCl_3$): 53.43 ($OCH_{3\,ester}$), 56.56 ($OCH_{3\,ar}$), 110.92 (CH), 116.58 (C), 120.78 (CH), 123.51 (CH), 132.87 (CH), 141.75 (C), 148.28 (C), 148.51 (C), 158.44 ($CO_{lactone}$), 163.82 (CO_{ester}), 190.41 (C=$O_{aldehyde}$) ppm; ($C_{13}H_{10}O_6$, 262.2). Elemental analysis calculated for $C_{13}H_{10}O_6$: C, 59.55; H, 3.84; O, 36.61 and found C, 59.20; H, 3.80; O, 37.04. MS (70 eV) m/z = 260.05.

GENERAL PROCEDURE

To a magnetically stirred solution of triphenylphosphine (0.524 g, 2 mmol), and phenol (2 mmol) in CH_3CN (3 mmol) was added dropwise a mixture of dimethyl acetylendicarboxylate (0.284 g, 2 mmol) in CH_3CN (2 ml) at −10°C over 10 min. After 10 min stirring at room temperature, the mixture was irradiated in a microwave oven for 1–4 min. When the reaction was complete, the mixture was cooled to room temperature and was placed over a column of silicagel (10 g) and elution was first made with hexane and was continued by gradually increasing

the polarity of the solvent mixture n-hexane:dimethyl ether. After removal of the solvent under reduced pressure, the product was obtained by recrystallization from ethanol.

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