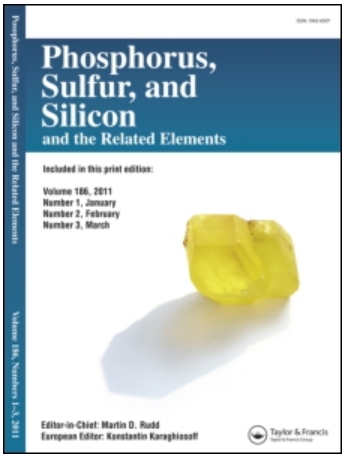

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Issa Yavari[a]; Rahebeh Amiri[a]; Mina Haghdadi[a]
[a] Department of Chemistry, Islamic Azad University, Ponak, Tehran, Iran

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TRIPHENYPHOSPHINE-MEDIATED EFFICIENT SYNTHESIS OF FUNCTIONALIZED 2-OXO-2*H*-CHROMENES

Issa Yavari, Rahebeh Amiri, and Mina Haghdadi
Department of Chemistry, Islamic Azad University, Science & Research Campus, Ponak, Tehran, Iran; and Department of Chemistry, University of Tarbiat Modarres, Tehran, Iran

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*Dimethyl acetylenedicarboxylate reacts smoothly with phenol derivatives, such as 4-chloro-3,5-dimethylphenol, 2-chloro-5-methylphenol, 4-chloro-2-methylphenol, 2,4-dichlorophenol, or 2-bromophenol in the presence of triphenylphosphine to produce highly functionalized 2-oxo-2*H*-chromenes (coumarins) in moderate yields.*

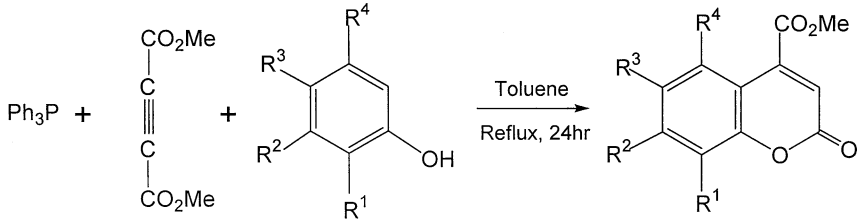
Keywords: 2-Oxo-2*H*-chromenes; acetylenic ester; aromatic substitution; triphenylphosphine

INTRODUCTION

The development of simple synthetic routs for widely used organic compounds from readily available reagents is one of the major tasks in organic synthesis.[1] 2-Oxo-2*H*-chromenes (coumarins) and their derivatives have stimulated interesting research in biology, organic chemistry, and medicine due to their antibiotic,[2] anticoagulant,[3,4] anticancer,[5] anti-inflamatory,[6] and anti-HIV[7] properties. Also, a considerable number of natural or synthetic derivatives of coumarin have found pharmaceutical applications.[8,9] Thus, the synthesis of this heterocyclic nucleus is of current interest. Coumarins have been synthesized by several methods including von Pechman,[10] Knovenagel,[11] and Reformatsky[12] reactions. Recently, we reported a new and operationally convenient approach to the synthesis of coumarin derivatives based on the aromatic electrophilic substitution reaction between the conjugate base of substituted phenols and a vinyltriphenylphosphonium salt.[13]

Address correspondence to Issa Yavari, Department of Chemistry, University of Tarbiat Modarres, P.O. Box 14115-175, Tehran, Iran. E-mail: isayavar@yahoo.com

As part of our current studies on the development of new routes to heterocyclic and carbocyclic systems, we now report the reaction between phenols and dimethyl acetylendicarboxylate (DMAD) in the presence of triphenylphosphine. This reaction leads to functionalized 2-oxo-2*H*-chromenes (coumarins) in moderate yields (see Scheme 1). The reactions of tertiary phosphorus compounds with DMAD and phenol have been discussed with emphasis upon the synthesis of phosphorous hetrocycles.[14]



1 **2**

1, 2	R 1	R 2	R 3	R 4	%Yield of **2**
a	H	Me	Cl	Me	81
b	Cl	H	H	Me	48
c	Me	H	Cl	H	84
d	Cl	H	Cl	H	71
e	Br	H	H	H	62

SCHEME 1

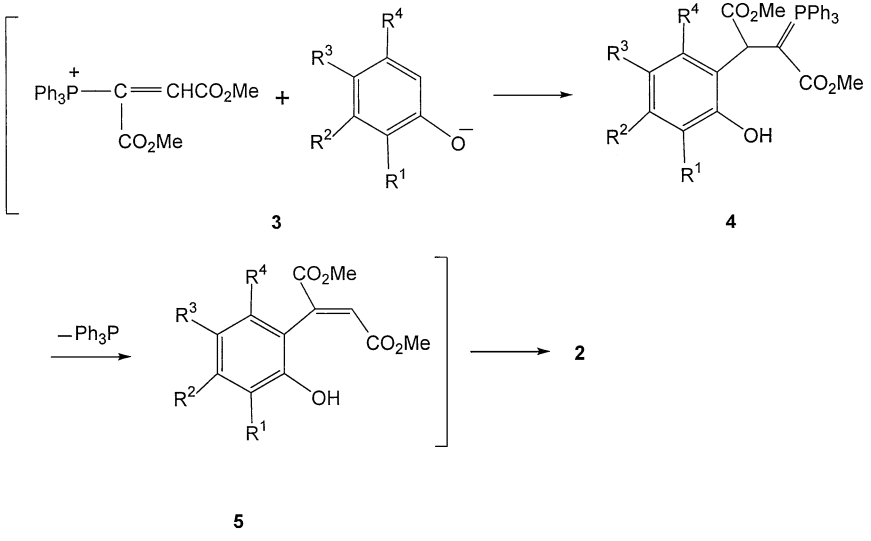
RESULTS AND DISCUSSION

The reaction of DMAD with 4-chloro-3,5-dimethylphenol in the presence of triphenylphosphine was carried out in toluene at reflux temperature. The light-yellow powder that separated from this reaction mixture was identified as methyl 6-choro-5,7-dimethyl-2-oxo-2-*H*-chromene-4-carboxylate (**2a**). Any product other than **2a** could not be detected by NMR spectroscopy. The structures of compounds **2a–e** were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}C NMR spectral data. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m/z* values. Any initial fragmentation involved the loss of ester moieties.

The ^{1}H NMR spectrum of **2a** exhibited five signals identified as methyl ($\delta = 2.39$ and 2.47 ppm), methoxy ($\delta = 4.00$ ppm), and methine ($\delta = 6.47$ and 7.17 ppm) protons. The ^{13}C NMR spectrum of **2a** showed 13 distinct resonances in agreement with the proposed structure. Partial assignments of these resonances are given in the Experimental section. The ^{1}H and ^{13}C NMR spectra of **2b–e** are similar to those of **2a** except for the aromatic residue, which exhibits characteristic signals with appropriate chemical shifts (see Experimental section below).

The structural assignment of compounds **2a–e** made on the basis of the ^{1}H and ^{13}C NMR spectra was supported by their IR spectra, the carbonyl region of which displayed two distinct adsorbtion bands for each compound (see Experimental section below).

A plausible mechanism for the formation of coumarin derivative **2a** is shown in Scheme 2. On the basis of the well-established chemistry of trivalent phosphorus nucleophiles,[15–17] it is reasonable to assume that compound **2a** results from the initial addition of triphenylphosphine to DMAD and subsequent protonation of the reactive 1:1 adduct by 4-chloro-3,5-dimethylphenol. Then, the positively charged ion is attacked by the conjugate base of the phenol. The product is presumably produced by intramolecular lactonization of the unsaturated diester **5**.



SCHEME 2

In conclusion, we have found a simple and efficient reaction for the synthesis of highly functionalized coumarins of potential synthetic interest. The one-pot nature of the present procedure makes it an

acceptable method for preparation of substituted coumarins with variable functionalities.

EXPERIMENTAL

Triphenylphosphine, DMAD, and compounds **1a–e** were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on Electrothermal 9100 apparatus. Elemental analyses for C and H were performed using a Leco 600 instrument. ^{1}H NMR and ^{13}C NMR spectra measured with Bruker spectrospin at 300.75 and 121.4 MHz, respectively. IR spectra were recorded on a Bomem MB-100 IR spectrometer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV.

Preparation of Methyl 6-Chloro-5,7-dimethyl-2-oxo-2*H*-chromene-4-carboxylate (2a): General Procedure

A mixture of DMAD (0.28 g, 2 mmol) in toluene (3 ml) was added dropwise to a magnetically stirred solution of triphenylphosphine (0.53 g, 2 mmol) and 4-chloro-3,5-methylphenol (0.31 g, 2 mmol) in toluene (17 ml) at −5°C for 10 min. The reaction mixture was then allowed to warm up to room temperature and refluxed for 24 h. The solvent was removed under reduced pressure, and the residue was purified by thin layer chromatography using *n*-hexan-EtoAc (3:1) as elutent. The solvent was removed under reduced pressure and the product was obtained as light-yellow powder. Yield, 0.43 g (81%); m.p. 109–111°C.

IR (KBr): 1731, 1724 (2 C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.39, 2.47$ (s, 6 H, 2 CH_3), 4.01 (s, 3 H, OCH_3), 6.47 (s, 1H, CH), 7.17 (s, 1H, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.78$ and 22.19 (2 CH_3), 53.84 (OCH_3), 114.91 (C), 116.7 and 117.55 (2 CH), 132.63 and 133.80 (2 C) 142.19 and 146.36 (2 C), 153.27 (C—O), 159.45 and 167.49 (2 C=O) ppm. MS (EI, 70 eV): m/z (%) = 266 (M^+, 90), 234 (M^+ – OMe, 55), 207 ($M^+ - CO_2Me$, 50), 178 ($M^+ - CO_2Me$ and CO, 30), 150 (20), 115 (90), 89 ($M^+ - CO_2Me$ and 2CH3, 30), 59 (CO_2Me^+, 55), 39 (60). Anal. Calcd for $C_{13}H_{11}O_4Cl$ (266.5): C, 58.54; H, 4.13. Found: C, 58.5 ; H, 4.1.

Methyl 8-Chloro-5-methyl-2-oxo-2*H*-chromene-4-carboxylate (2b)

White powder. Yield, 0.24 g (48%); m.p. 116–118°C. IR (KBr): 1733, 1715 (2 C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.40$ (s, 3 H,

CH_3), 4.01 (s, 3 H, OCH_3), 6.48 (s, 1 H, CH), 7.07 (d, 1 H, $^3J_{HH} = 8$ Hz, CH), 7.53 (d, 1 H, $^3J_{HH} = 8$ Hz, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 20.69$ (CH_3), 53.89 (OCH_3), 116.27 (C), 116.86 (CH), 120.74 (C), 128.07 and 132.78 (2 CH), 134.95 (C), 146.59 (C), 150.86 (C—O), 158.51, and 167.21 (2 C=O) ppm. MS (EI, 70 eV): *m/z* (%) = 252 (M^+, 90), 220 (M^+– OMe, 20), 193 (M^+– CO_2Me, 45), 165 (M^+–CO_2Me and CO, 15), 136 (15), 102 (M^+– C_8H_6, 35), 63 (15), 39 (10). Anal. Calcd for $C_{12}H_9O_4Cl$ (252.5): C, 57.03; H, 3.56. Found: C, 57.1 ; H, 3.6.

Methyl 6-Chloro-8-methyl-2-oxo-2*H*-chromene-4-carboxylate (2c)

Yellow powder. Yield, 0.42 g (84%); m.p. 92–94°C. IR (KBr): 1739, 1728 (2 C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.46$ (s, 3 H, CH_3), 4.04 (s, 3 H, OCH_3), 6.99 (s, 1 H, CH), 7.42 (d, 1 H, $^4J_{HH} = 2$ Hz, CH), 8.16 (d, 1H, $^4J_{HH} = 2$ Hz, CH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.15$ (CH_3), 53.73 (OCH_3), 116.87 (C), 120.58 and 124.35 (2 CH), 128.83 and 130.10 (2 C), 133.89 (CH), 142.01 (C), 151.47 (C—O), 159.87 and 164.34 (2 C=O) ppm. MS (EI, 70 eV): *m/z* (%) = 252 (M^+, 90), 224 (M^+– CO, 20), 193 (M^+– CO_2Me , 80), 165 (M^+ – CO_2Me and CO, 15), 102 (M^+– C_8H_6, 30), 75 (15), 51 ($C_4H_3^+$, 15). Anal. Calcd for $C_{12}H_9O_4Cl$ (252.5): C, 57.03; H, 3.56. Found: C, 57.0 ; H, 3.6.

Methyl 6,8-Dichloro-2-oxo-2*H*-chromene-4-carboxylate (2d)

Light-yellow powder. Yield, 0.39 g (71%); m.p. 102–104°C. IR (KBr): 1740, 1726 (2 C=O) cm^{-1}. ^{1}H NMR (300.1 MHz, $CDCl_3$): $\delta = 4.04$ (s, 3 H, OCH_3), 7.08 (s, 1 H, CH), 7.66 (d, 1 H, $^4J_{HH} = 2$ Hz, CH), 8.31 (d, 1 H, $^4J_{HH} = 2$ Hz, CH) ppm. ^{13}C NMR (121.4 MHz, $CDCl_3$): $\delta = 53.96$ (OCH_3), 118.16 (C), 121.78 (CH), 123.41 (C), 125.58 (CH), 130.51 (C), 132.9 (CH), 141.18 (C), 148.99 (C—O), 158.50 and 163.81 (2 C=O) ppm. MS (EI, 70 eV): *m/z* (%) = 274 (M^++2, 60), 272 (M^+, 90), 244 (M^+– CO, 15), 213 (M^+– CO_2Me, 90), 185 (M^+–CO_2Me and CO, 20), 157 (35), 107 (10), 87 (30), 59 (CO_2Me^+, 15). Anal. Calcd for $C_{11}H_6O_4Cl_2$ (273.0): C, 48.35; H, 2.19. Found: C, 48.4 ; H, 2.2.

Methyl 8-Bromo-2-oxo-2*H*-chromene-4-carboxylate (2e)

White powder. Yield, 0.35 g (62%); m.p. 112–114°C. IR (KBr): 1747 and 1730 (2 C=O) cm^{-1}. ^{1}H NMR (300.1 MHz, $CDCl_3$): $\delta = 4.01$ (s, 3 H, OCH_3), 6.98 (s, 1 H, CH), 7.23 (t, 1 H, $^3J_{HH} = 8$ Hz, CH), 7.84 (dd, 1 H, $^3J_{HH} = 8$ Hz and $^4J_{HH} = 2$ Hz, CH), 8.27 (dd, 1 H, $^3J_{HH} = 8$ Hz, CH

and $^4J_{HH} = 2$ Hz, CH) ppm. ^{13}C NMR (121.4 MHz, $CDCl_3$): $\delta = 53.76$ (OCH_3), 111.18 and117.65 (2 C) , 120.52, 125.75, 126.62 and 136.45(4 CH), 142.48 (C), 151.27 (C—O), 159.24 and 164.25 (2 C=O) ppm. MS (EI, 70 eV): m/z (%) = 284 ($M^+ + 2$, 90), 282 (M^+, 90), 254 ($M^+ - CO$, 25), 223 ($M^+ - CO_2Me$, 90), 167 (20), 116 (20), 88 (30), 62 (35). Anal. Calcd for $C_{11}H_7O_4Br$ (283.0): C, 46.64; H, 2.47. Found: C, 46.5; H, 2.5.

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