Trimethyl Phosphite Mediated Simple Synthesis of Coumarins and Azacoumarins Through the Reaction of Phenols or Hydroxypyridines and Dimethyl Acetylenedicarboxylate (DMAD) or Diethyl Acetylenedicarboxylate (DEAD)

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ABSTRACT: *Protonation of the reactive intermediate produced in the reaction between trimethyl phosphite and dimethyl acetylenedicarboxylate or diethyl acetylenedicarboxylate by resorcinol, 5-methylresorcinol, 2,5-dihydroxyacetophenone, 4-chloro-2-methylphenol, 4-chloro-3,5-dimethylphenol, 4-hydroxypyridine, 2-hydroxypyridine, 3-hydroxypyridine, or 8-hydroxyquinoline leads to vinylphosphonium salts, which undergo Michael addition with the conjugate base of the OH-acid to produce highly functionalized 2-oxo-2H-chromene or azacoumarins in good yields.*

KEY WORDS: *2-Oxo-2H-chromenes, Azacoumarins, Acetylenicester, Aromatic substitution, Trimethyl phosphate.*

INTRODUCTION

2-Oxo-2H-chromenes (coumarins) and their derivatives have stimulated extensive research in biology, organic chemistry and medicine, due to their antibiotic [1], anti-coagulant [2], anticancer [3], anti-inflamatory [4], and anti-HIV [5] properties. A number of natural or synthetic derivatives of coumarin have found pharmaceutical applications [6]. The synthesis of this heterocyclic nucleus is of current interest. Coumarins have been synthesized by several methods including *Von Pechman* [7], *Knovenagel* [8], and *Reformatsky* [9] reactions. Recently, we reported a new and operationally convenient approach to the synthesis of coumarin derivatives based

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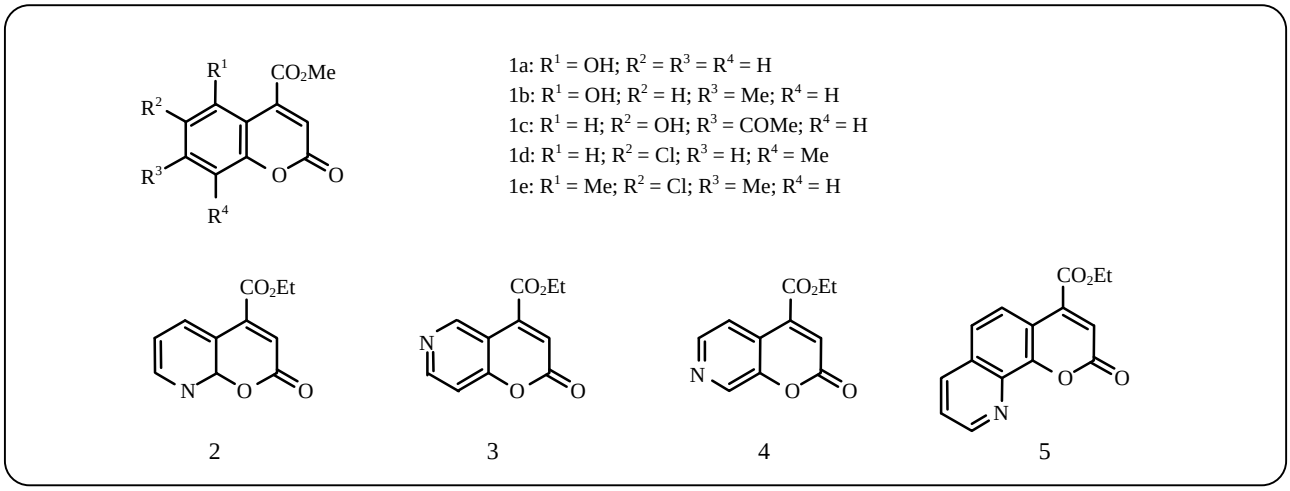
1021-9986/08/4/35 5/$/2.50



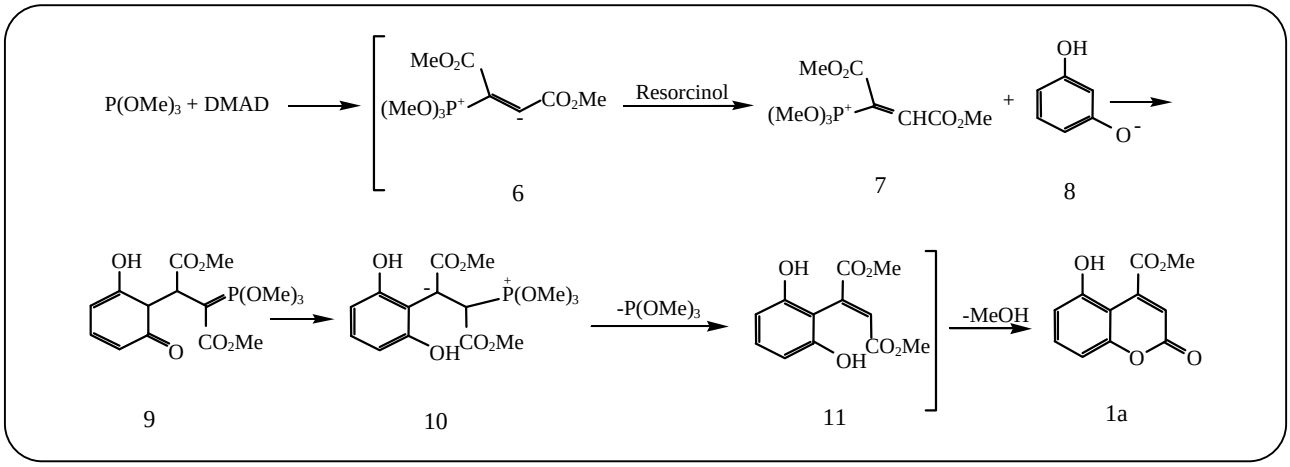
Scheme 1.

on the aromatic electrophilic substitution reaction between the conjugate base of substituted phenols and a vinyl-phosphonium salt [10]. As part of our current studies [11] on the development of new routes to heterocyclic and carbocyclic systems, we now report the reaction between substituted phenols and hydroxypyridines with dimethyl acetylenedicarboxylate (DMAD) or diethyl acetylene-dicarboxylate (DEAD) in the presence of trimethyl phosphite. This reaction leads to functionalized 2-oxo-2H-chromenes or azacoumarins. Thus, reaction of DMAD or DEAD and trimethylphosphite in the presence of resorcinol, 5-methylresorcinol, 2,5-dihydroxy-aceto-phenone, 4-chloro-2-methylphenol, 4-chloro-3,5-di-methylphenol, 4-hydroxypyridine, 2-hydroxypyridine, 3-hydroxypyridine, or 8-hydroxyquinoline leads to functionalized 4-carboxymethyl-2-oxo-2*H*-chromenes **1a-e** and azacoumarins **2-5** Scheme 1. The reactions of tertiary phosphorus (trimethyl phosphite, triethyl phosphite and triphenyl phosphine) compounds with DMAD or DEAD and, in some cases, other acetylenic systems have been discussed with emphasis upon the synthesis of phosphorus heterocycles [12].

RESULTS AND DISCUSSION

The reaction of DMAD with resorcinol in the presence of trimethyl phosphite was carried out on toluene at reflux temperature. The light-yellow crystals obtained from the reaction mixture was identified as methyl 5-hydroxy- 2-oxo- 2H-chromene- 4-carboxylate (**1a**) (Scheme 1). The structure of **1a** was deduced from its elemental analysis and its IR, ^{1}H NMR and ^{13}C NMR spectral data. The mass spectrum of this compound displayed molecular ion peak at m/z = 220. Any initial fragmentation involved the loss of ester moieties. Under similar reaction conditions, 5-methylresorcinol produced methyl 5-hydroxy- 7-methyl- 2-oxo- 2H-chromene- 4-carboxylate (**1b**). The ^{1}H NMR and ^{13}C NMR spectra of **1b** are similar to those of **1a** except for the aromatic residue, which exhibits characteristic signals with appropriate chemical shifts. A plausible explanation for the formation of **6** is proposed in Scheme 2. On the basic of the chemistry of trivalent phosphorus nucleophiles [6,7], it is reasonable to assume that compound **1a** results from an initial addition of trimethyl phosphite to the acetylenic ester. Subsequent protonation of 1:1 adduct **6** by the OH-acid leads to **7**. Then, the positively charged ion might be attacked by the conjugate base of resorcinol to produce the ylide **9**, which is converted to **10** by [1,2]-H^{+} shift. The intermediate **11**, formed by elimination of trimethyl phosphite, is then converted to compound **1a** by intramolecular lactonization (Scheme 2).

The yellow oil isolated from the reaction mixture of 2,5-dihydroxyacetophenone and DMAD in the presence of trimethyl phosphite was identified as methyl 7-acetyl- 6-hydroxy- 2-oxo- 2H-chromene- 4-carboxylate (**1c**). Structure of **1c** was assigned of this product on the basis of its ^{1}H and ^{13}C NMR spectra. Using 4-chloro-2-methylphenol as the proton source/nucleophile leads to pale yellow crystals, which was identified as methyl 6-chloro-8-methyl-2-oxo-chromene-4-carboxylate



Scheme 2.

(**1d**). The yellow crystals isolated from the reaction mixture of 4-chloro-3,5-dimethylphenol and DMAD in the presence of trimethyl phosphite was identified as methyl 6-chloro-5,7-dimethyl-2-oxo-chromene-4-carboxylate (**1e)**. Compounds **1b-1e** are formed by similar mechanism outlined in Scheme 2.

The reaction of one equivalent of 2-hydroxypyridine, 4-hydroxypyridine, 3-hydroxypyridine, or 8-hydroxy-quinoline with two equivalents of DEAD in the presence of two equivalents of trimethyl phosphite was carried out in refluxing dichloromethane. The orange oil and yellow oil separated from the reaction mixture were identified as methyl 2-oxo-2*H*-pyrano [2,3-b] pyridine-4-carboxylate (**2**), methyl 2-oxo-2H-pyrano [3,2-c] pyridine-4-carboxylate (**3**). The light-orange oil separated from the reaction mixture were identified as methyl 2-oxo-2H-pyrano [3,2-*b*] pyridine-4-carboxylate (**4**), or methyl 2-oxo-2*H*-pyrano [3,2-h] quinoline-4-carboxylate (**5**) (Scheme 1).

In conclusion, this protocol provides a simple entry into the synthesis of functionalized coumarins and azacoumarins of potential interest. The present method carries the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification. The one-pot nature of the present procedure makes it an acceptable alternative to multistep approaches [14]. The present coumarin synthesis complements the older established methods and offers significant advantages for the synthsis of coumarins having acid sensitive functional groups [12]. In contrast, the well-known von Pechmann synthesis [15,16] entails strongly acidic conditions and frequently affords low and erratic yields.

EXPERIMENTAL

Melting points were measured on Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Mass spectra were recorded on a FINNIGANMAT 8430 mass spectrometer operating at an ionization potential of 70 eV. The NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz on a Bruker Avance DPX-300 MHz NMR instrument with $CDCl_3$ as solvent. Chemical shifts (δ) are reported relative to TMS as the internal standard. The reagents and solvents used in this work were obtained from Fluka and used without further purification columns Chromatography was carried out from silicagel 100 mesh and plates chromatography were prepared from silicagel 60 mesh.

Preparation of Coumarin and Azacoumarin Derivatives Examplified on Methyl 5-hydroxy- 2-oxo-2*H*-chromene-4-carboxylate (1a); Typical Procedure

To a stirred solution of trimethyl phosphite (4 mmol) and resorcinol (2 mmol) in toluene (17 mL) was added drop wise a mixture of DMAD (4 mmol) in toluene (3 mL) at -5 ^{o}C for 10 min. The reaction mixture was then allowed to warm up to room temperature and refluxed for 20 h. The slovent was removed under reduced pressure and the residue was purified by column chromatography using n-hexane-EtOAc as eluent to produce **1a** as

Yellow crystals, yield: 0.87g (94 %), m.p.115-116 °C. IR (KBr) (ν_{max}/cm^{-1}): 3421 (OH), 1724 (C=O), 1578 (C=C), 1232 and 1247 (C-O). ^{1}H NMR: δ = 3.80 (s, 3H, OMe), 5.03 (s, br, OH), 6.43 (s, CH), 6.46 (dd, CH, $^3J_{HH}$ = 6 Hz, $^4J_{HH}$ = 3 Hz), 6.52 (dd, CH, $^3J_{HH}$ = 6 Hz, $^4J_{HH}$ = 3 Hz), 7.14 (t, CH, $^3J_{HH}$ = 6 Hz, $^3J_{HH}$ = 6 Hz) ppm. ^{13}C NMR: δ = 55.6 (OMe), 101.9 (CH), 106.7 (2CH), 108.1 (CH), 130.5 (2C), 157.2 (2C), 161.3 (2C) ppm. MS: m/z (%) = 220.04 (100). Anal. Calcd for $C_{11}H_8O_5$ (220.18): C, 60.00; H, 3.66; O, 36.33 %.

Methyl 5-hydroxy- 7-methyl- 2-oxo-2*H*- chromene-4-carboxylate (1b)

Yellow crystals, yield: 0.77 g (84 %), m.p. 119-120 °C. IR (KBr) (ν_{max}/cm^{-1}): 1731 (C=O), 1463 (C=C), 1236 and 1253 (C-O). ^{1}H NMR: δ= 2.34 (s, 3H, Me), 3.95 (s, 3H, OMe), 6.44 (s, CH), 6.52 (s, CH), 6.70 (s, CH), 11.84 (s, 1H, OH) ppm. ^{13}C NMR: δ= 22.5 (Me), 54.2 (OMe), 103.6 (CH), 115.4 (CH), 117.9 (C), 128.6 (C), 129.4 (CH), 133.2 (C), 157.4 (2C), 168.3 (C), 170.3 (C) ppm. MS: m/z (%) = 234.05 (100). Anal. Calcd for $C_{12}H_{10}O_5$ (234.2): C, 61.54; H, 4.30; O, 34.16 %.

Methyl 7-acetyl- 6-hydroxy- 2-oxo- 2*H*-chromene-4-carboxylate (1c)

Yellow crystals, yield: 0.69 g (75 %), m.p. 131-132 °C. IR (KBr) (ν_{max}/cm^{-1}): 1727 and 1650 (C=O), 1487 (C=C), 1222 and 1239 (C-O). ^{1}H NMR: δ = 2.64 (s, 3H, Me), 3.82 (s, 3H, OMe), 6.93 (s, CH), 7.11 (s, CH), 7.19 (s, CH), 11.88 (s, OH) ppm. ^{13}C NMR: δ = 28.7 (Me), 53.6 (OMe), 111.2 (CH), 118.1 (CH), 120.4 (2C), 133.2 (CH), 142.4 (C), 151.6 (C), 156.2 (C), 159.5 (C), 167.2 (C), 198.2 (C) ppm. MS: m/z (%) = 262.05 (100). Anal. Calcd for $C_{13}H_{10}O_6$ (262.21): C, 59.55; H, 3.84; O, 36.61 %.

Methyl 6-chloro- 8-methyl- 2-oxo- 2*H*-chromene-4-carboxylate (1d)

Yellow crystals, yield: 0.72 g (78 %), m.p. 94-96 °C. IR (KBr) (ν_{max}/cm^{-1}): 1773 and 1736 (C=O), 1468 (C=C), 1174 and 1191 (C-O). ^{1}H NMR: δ = 2.30 (s, 3H, Me), 2.82 (dd, CH, $^3J_{HH}$ = 6 Hz, $^4J_{HH}$ = 3 Hz), 3.14 (dd, CH, $^3J_{HH}$ = 6 Hz, $^4J_{HH}$ = 3 Hz), 3.73 (s, 3H, OMe), 3.92 (dd, CH, $^3J_{HH}$ = 3 Hz, $^3J_{HH}$ = 3 Hz), 7.15 (s, CH), 7.17 (s, CH) ppm. ^{13}C NMR: δ = 16.1 (Me), 31.4 (CH), 41.6 (CH_2), 53.4 (OMe), 120.8 (CH), 122.6 (C), 126.2 (C), 129.2 (CH), 131.4 (C), 148.8 (C), 166.0 (C), 171.1 (C) ppm. MS: m/z (%) = 252.02 (100). Anal. Calcd for $C_{12}H_9ClO_4$ (252.65): C, 57.05; H, 3.59; Cl, 14.03; O, 25.33 %.

Methyl 6-chloro-5,7-dimethyl-2-oxo-2*H*-chromene-4-carboxylate (1e)

Yellow crystals, yield: 0.85 g (90 %), m.p. 108-110 °C. IR (KBr) (ν_{max}/cm^{-1}): 1776 and 1738 (C=O), 1459 (C=C), 1182 and 1196 (C-O). ^{1}H NMR: δ = 2.44 (s, 6H, 2Me), 3.82 (s, 3H, OMe), 6.51 (s, CH), 6.87 (s, CH) ppm. ^{13}C NMR: δ= 14.4 (Me), 19.5 (Me), 52.4 (OMe), 117.3 (CH), 118.7 (CH), 131.8 (C), 132.8 (C), 135.5 (C), 138.4 (C), 148.2 (C), 152.5 (C), 161.3 (C), 169.2 (C) ppm. MS: m/z (%) = 266.03 (100). Anal. Calcd for $C_{13}H_{11}ClO_4$ (266.68): C, 58.55; H, 4.16; Cl, 13.29; O, 24.00 %.

Ethyl 2-oxo-2*H*-pyrano [2,3-*b*] pyridine-4-carboxylate (2)

Light yellow crystals, yield: 0.79g (85%), m.p. 105-106 °C. IR (KBr) (ν_{max}/cm^{-1}): 1731 (C=O), 1462 (C=C), 1253 (C-O). ^{1}H NMR: δ = 1.34 (t, 3H, Me), 4.17 (q, 2H, CH_2), 7.01 (t, CH, $^3J_{HH}$ = 9 Hz), 7.13 (s, CH), 7.59 (dd, CH, $^3J_{HH}$ = 9 Hz, $^4J_{HH}$ = 6 Hz), 8.02 (dd, CH, $^3J_{HH}$ = 9 Hz, $^4J_{HH}$ = 6 Hz) ppm. ^{13}C NMR: δ = 31.3 (Me), 53.6 (CH_2), 112.2 (CH), 120.4 (CH), 124.2 (C), 133.2 (CH), 142.4 (CH), 151.6 (C), 159.5 (C), 165.7 (C), 167.2 (C), 171.1 (C) ppm.

MS: m/z (%) = 219.05 (100). Anal. Calcd for $C_{11}H_9NO_4$ (219.19): C, 60.27; H, 4.14; N, 6.39; O, 29.20 %.

Ethyl 2-oxo-2*H*-pyrano [3,2-*c*] pyridine-4-carboxylate (3)

Yellow crystals, yield: 0.82 g (86 %), m.p. 100-101 °C. IR (KBr) (ν_{max}/cm^{-1}): 1730 (C=O), 1435 (C=C), 1246 (C-O). ^{1}H NMR: δ = 1.37 (t, 3H, Me), 4.21 (q, 2H, CH_2), 6.95 (d, CH, $^3J_{HH}$ = 9 Hz), 7.29 (s, CH), 7.85 (s, CH), 7.93 (d, CH, $^3J_{HH}$ = 9 Hz) ppm. ^{13}C NMR: δ = 26.2 (Me), 53.6 (CH_2), 111.2 (CH), 117.9 (C), 130.7(CH), 132.2 (CH), 151.1 (CH), 161.0 (C), 165.7 (C), 168.2 (C), 176.9 (C) ppm. MS: m/z (%) = 219.05 (100). Anal. Calcd for $C_{11}H_9NO_4$ (219.19): C, 60.27; H, 4.14; N, 6.39; O, 29.20 %.

Ethyl 2-oxo-2*H*-pyrano [3,2-*b*] pyridine-4-carboxylate (4)

Yellow crystals, yield: 0.79 g (8 5%), m.p. 102-103 °C. IR (KBr) (ν_{max}/cm^{-1}): 1735 (C=O), 1423 (C=C), 1227 (C-O). ^{1}H NMR: δ = 1.35 (t, 3H, Me), 4.19 (q, 2H, CH_2), 6.83 (s, CH), 7.54 (dd, CH, $^3J_{HH}$ = 6 Hz, $^4J_{HH}$ = 3 Hz), 7.72 (t, CH, $^3J_{HH}$ = 6 Hz), 8.68 (dd, CH, $^3J_{HH}$ = 6 Hz, $^4J_{HH}$ = 3 Hz) ppm. ^{13}C NMR: δ = 24.1 (Me), 59.5 (CH_2), 128.4 (CH), 128.9 (CH), 129.1 (CH), 132.4 (CH), 134.5 (C), 137.8 (C), 141.5 (C), 157.3 (C), 168.1 (C) ppm. MS: m/z (%) = 219.05 (100). Anal. Calcd for $C_{11}H_9NO_4$ (219.19): C, 60.27; H, 4.14; N, 6.39; O, 29.20 %.

Ethyl 2-oxo-2*H*-pyrano [3,2-*h*] quinoline-4-carboxylate (5)

White crystals, yield: 0.77 g (81 %), m.p. 126-127 °C. IR (KBr) (ν_{max}/cm^{-1}): 1729 (C=O), 1455 (C=C), 1236 (C-O). ^{1}H NMR: δ = 1.39 (t, 3H, Me), 4.25 (q, 2H, CH_2), 7.15 (s, CH), 7.45 (m, 2CH), 7.51 (d, CH, $^3J_{HH}$ = 6 Hz), 8.14 (dd, CH, $^3J_{HH}$ = 6 Hz, $^4J_{HH}$ = 3 Hz), 8.45 (dd, CH, $^3J_{HH}$ = 6 Hz, $^4J_{HH}$ = 3 Hz) ppm. ^{13}C NMR: δ = 12.3 (Me), 62.1 (CH_2), 115.1 (CH), 120.6 (C), 123.3 (CH), 124.1 (CH), 129.2 (CH), 130.5 (C), 132.8 (CH), 136.1 (C), 143.2 (CH), 151.6 (C), 158.7 (C), 164.2 (C), 168.5 (C) ppm. MS: m/z (%) = 269.07 (100). Anal. Calcd for $C_{15}H_{11}NO_4$ (269.25): C, 66.91; H, 4.12; N, 5.20; O, 23.77 %.

Received : 28th October 2007 ; Accepted : 30th December 2007

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