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-inflammatory [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
on the aromatic electrophilic substitution reaction between the conjugate base of substituted phenols and a vinylphosphonium 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 acetylenedicarboxylate (DEAD) in the presence of trimethyl phosphate. 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-dihydroxyacetophenone, 4-chloro-2-methylphenol, 4-chloro-3,5-dimethylphenol, 4-hydroxypyridine, 2-hydroxypyridine, 3-hydroxypyridine, or 8-hydroxyquinoline leads to functionalized 4-carboxymethyl-2-oxo-2H-chromenes 1a-e and azacoumarins 2-5 Scheme 1. The reactions of tertiary phosphorus (trimethyl phosphite, triethyl phosphate 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 phosphate 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, 1H NMR and 13C 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 1H NMR and 13C 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 basis of the chemistry of trivalent phosphorus nucleophiles [6,7], it is reasonable to assume that compound 1a results from an initial addition of trimethyl phosphate 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 phosphate, 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 phosphate was identified as methyl 7-acetyl-6-hydroxy-2-oxo-2H-chromene-4-carboxylate (1e). Structure of 1e was assigned of this product on the basis of its 1H and 13C 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.
(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-hydroxyquinoline 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-2H-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-2H-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 synthesis 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 (1H) and 75 (13C) MHz on a Bruker Avance DPX-300 MHz NMR instrument with CDCl₃ 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-2H-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 °C for 10 min. The reaction mixture was then allowed to warm up to room temperature and refluxed for 20 h. The solven 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) (νmax/cm-1): 3421 (OH), 1724 (C=O), 1578 (C=C), 1232 and 1247 (C-O). 1H NMR: δ = 3.80 (s, 3H, OMe), 5.05 (s, br, OH), 6.43 (s, CH), 6.46 (dd, CH, 3JHH = 6 Hz, 4JHH = 3 Hz), 6.52 (dd, CH, 3JHH = 6 Hz, 4JHH = 3 Hz), 7.14 (t, CH, 3JHH = 6 Hz, 4JHH = 6 Hz) ppm. 13C 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 C11H10O5 (220.18): C, 60.00; H, 3.66; O, 36.33 %.

Methyl 5-hydroxy- 7-methyl- 2-oxo-2H- chromene-4-carboxylic acid (1b)

Yellow crystals, yield: 0.77 g (84 %), m.p. 119-120 °C. IR (KBr) (νmax/cm-1): 1731 (C=O), 1463 (C=C), 1236 and 1253 (C-O). 1H NMR: δ = 2.34 (s, 3H, Me), 3.95 (s, 3H, OMe), 6.44 (s, CH), 6.65 (s, CH), 6.70 (s, CH), 11.84 (s, 1H, OH) ppm. 13C 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 C12H10O5 (234.2): C, 61.54; H, 4.30; O, 34.16 %.

Methyl 7-acetyl- 6-hydroxy- 2-oxo-2H-chromene-4-carboxylic acid (1c)

Yellow crystals, yield: 0.69 g (75 %), m.p. 131-132 °C. IR (KBr) (νmax/cm-1): 1727 and 1650 (C=O), 1487 (C=C), 1222 and 1239 (C-O). 1H 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. 13C 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 C13H11O6 (262.21): C, 59.55; H, 3.84; O, 36.61 %.

Methyl 6-chloro- 8-methyl- 2-oxo-2H-chromene-4-carboxylic acid (1d)

Yellow crystals, yield: 0.72 g (78 %), m.p. 94-96 °C. IR (KBr) (νmax/cm-1): 1773 and 1736 (C=O), 1468 (C=C), 1174 and 1191 (C-O). 1H NMR: δ = 3.20 (s, 3H, Me), 2.82 (dd, CH, 3JHH = 6 Hz, 4JHH = 3 Hz), 3.14 (dd, CH, 3JHH = 6 Hz, 4JHH = 3 Hz), 3.73 (s, 3H, OMe), 3.92 (dd, CH, 3JHH = 3 Hz, 4JHH = 3 Hz), 7.15 (s, CH), 7.17 (s, CH) ppm. 13C NMR: δ = 16.1 (Me), 31.4 (CH), 41.6 (CH2), 53.4 (OMe), 120.8 (CH), 122.6 (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 C16H12ClO4 (252.65): C, 57.05; H, 3.59; Cl, 14.03; O, 25.33 %.

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

Yellow crystals, yield: 0.85 g (90 %), m.p. 108-110 °C. IR (KBr) (νmax/cm-1): 1776 and 1738 (C=O), 1459 (C=C), 1182 and 1196 (C-O). 1H NMR: δ = 2.44 (s, 6H, 2Me), 3.82 (s, 3H, OMe), 6.51 (s, CH), 6.87 (s, CH) ppm. 13C 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 C13H11ClO4 (266.68): C, 58.55; H, 4.16; Cl, 13.29; O, 24.00 %.

Ethyl 2-oxo-2H-pyrano [2,3-b] pyridine-4-carboxylic acid (2)

Light yellow crystals, yield: 0.79g (85%), m.p. 105-106 °C. IR (KBr) (νmax/cm-1): 1731 (C=O), 1462 (C=C), 1253 (C-O). 1H NMR: δ = 1.34 (t, 3H, Me), 4.17 (q, 2H, CH2), 7.01 (t, CH, 3JHH = 9 Hz), 7.13 (s, CH), 7.59 (dd, CH, 3JHH = 9 Hz, 4JHH = 6 Hz), 8.02 (dd, CH, 3JHH = 9 Hz, 4JHH = 6 Hz) ppm. 13C NMR: δ = 31.3 (Me), 53.6 (CH2), 112.2 (CH), 120.4 (CH), 124.2 (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 C13H12NO4 (219.19): C, 60.27; H, 4.14; N, 6.39; O, 29.20 %.

Ethyl 2-oxo-2H-pyrano [3,2-c] pyridine-4-carboxylic acid (3)

Yellow crystals, yield: 0.82 g (86 %), m.p. 100-101 °C. IR (KBr) (νmax/cm-1): 1730 (C=O), 1435 (C=C), 1246 (C-O). 1H NMR: δ = 1.37 (t, 3H, Me), 4.21 (q, 2H, CH2), 6.95 (d, CH, 3JHH = 9 Hz), 7.29 (s, CH), 7.85 (s, CH), 7.93 (d, CH, 3JHH = 9 Hz) ppm. 13C NMR: δ = 26.2 (Me), 53.6 (CH2), 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 C12H12NO4 (219.19): C, 60.27; H, 4.14; N, 6.39; O, 29.20 %.
Ethyl 2-oxo-2H-pyra[3,2-b] pyridine-4-carboxylate (4)

Yellow crystals, yield: 0.79 g (81 %), m.p. 102-103 °C.

IR (KBr) (\nu_{max}/cm^{-1}): 1729 (C=O), 1455 (C=C), 1236 (C-O).

\textsuperscript{1}H NMR: \delta = 3.35 (t, 3H, Me), 4.19 (q, 2H, CH₂), 6.83 (s, CH), 7.54 (dd, CH), 3\textsubscript{J}HH = 6 Hz, 4\textsubscript{J}HH = 3 Hz), 7.72 (t, CH, 3\textsubscript{J}HH = 6 Hz), 8.68 (dd, CH, 3\textsubscript{J}HH = 6 Hz, 4\textsubscript{J}HH = 3 Hz). ppm. \textsuperscript{13}C NMR: \delta = 21.4 (Me), 59.5 (CH₂), 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 C₁₁H₁₅NO₄ (219.19): C, 66.91; H, 4.12; N, 5.20; O, 23.77 %.

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