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Trimethyl phosphite mediated simple synthesis of coumarins and azachromenes through the reaction of phenols and dimethyl acetlendicarboxylate

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ABSTRACT

Protonation of the reactive intermediates produced in the reaction between Trimethyl Phosphite and dimethyl acetylenedicarboxylate by resorcinol 5-methylresorcinol 2,5 -dihyroxyasetophenone, 4 - chlro - 2 -methvlphenol, 2 - hydroxypyridine, or 4 - hydroxypyridine - leads tovinylphosphonium salts, which undergo michail addition with the conjugate basi of the OH-acid to produce functionalized 2-oxo-2H-chromenes (coumarins) and azachromenes in good yields.

KEYWORDS

2-Oxo-2H-chromenes;
Azacoumarins;
Acetylenic ester;
Aromatic substitution;
Trimethyl phosphate.

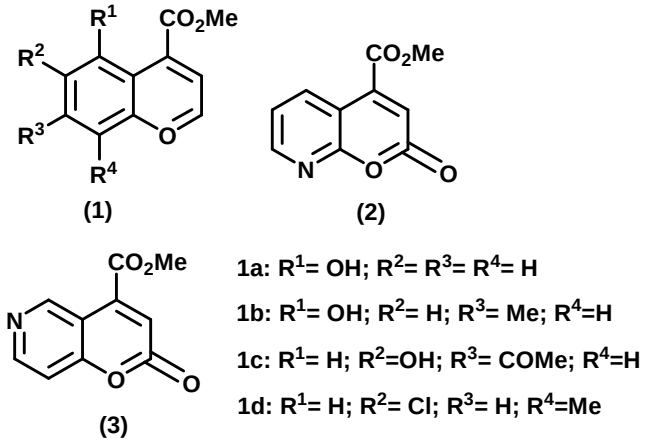
INTRODUCTION

2-Oxo-2H-chromens (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 uncleus is of current interest. Coumarins have been synthesized by several methods including von pechman[7], Knovenagel[8], and Reormatsky[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 phenols or hydroxyridines and dimethy actylendicarboxylate (DMAD) in the presence of trimethyl phosphate. This reaction leads to functionalized 2-oxo-2H-chromenes (coumarins) or azacoumarins. Thus, rection of DMAD and trimethyl phosphate in the presence of resorcinol, 5-methylresorcinol, 2,5-dihydroxyacetophenone, 4-chloro-2-methylphenol, 4-hydroxypyridine or 2-hydroxypyridine leads to functionalized 40 carboxymethyl-2-oxo-2H-chromenes 1a-d and azacoumarins 2 and 3, (see Scheme 1). The reactions of teriaryl phosphorus compounds with DMAD and, on occasion, other acetylenic systems have been dixcussed with emphasis upon the synthesis of phosphorus heterocycles[12].

RESULT AND DISCUSSION

The reaction of DMAD with resorcinol in the pres-



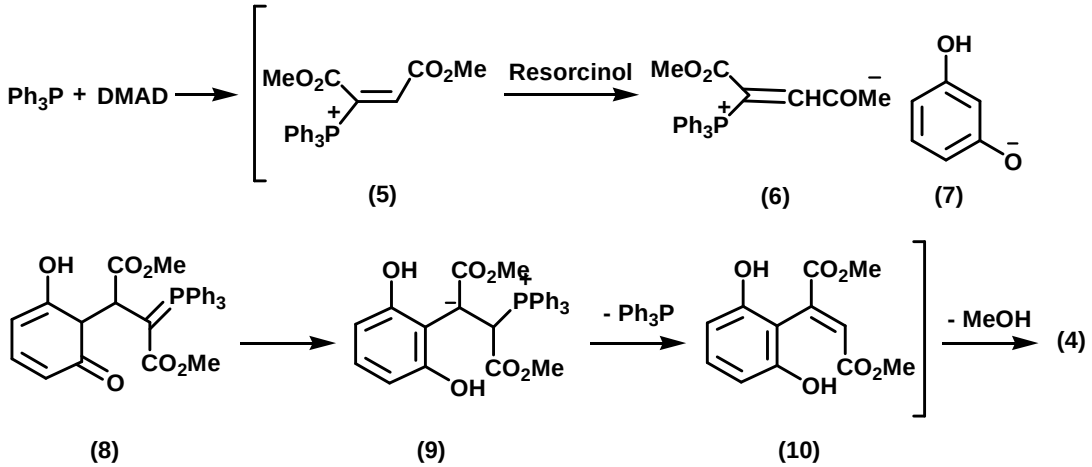
Scheme 1

ence of trimethyl phosphate was carried out on toluene at reflux temperature. The light-yellow obtained from the reaction mixture was identified as methyl 5-hydroxy-2oxo-2h-chromene-4-carboxylate (1a) (Scheme 1). The structure of 1a was deduced from its elemental analyses and its IR, ^{1}HNMR and ^{13}CNMR spectral data[13]. The mass spectrum of this compound displayed molecular ion peak at m/z = 436. 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-caroxylate (1b). The ^{1}H and ^{13}CNMR spectra of 1b are similar to those 1a except for the aromatic residue, which exhibits characteristic signals with appropriate chemical shifts (see Experimental section).

A plausible explanation for the formation of 1a is proposed in Scheme 2. On the basis of the chemistry of trivalent phosphorus uncleophiles[6,7], it is reasonable to assume that compound **(4)** results from an initial addition of trimethyl phosphate to the acetylenic ester.

Subsequent protonation of the 1:1 adduct 4 by the NH-acid leads to 5. Then, the positively charged ion might be attacked by the conjugate base of resorcinol to produce the compound **(6)**, which converted to 7 by [1.2]-H^{+} shift. The intermediate 8, formed by elimination of trimethyl phosphate, is 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 (1C) (Scheme 1). Structure 1c was assigned to the isolated product on the basis of its ^{1}HNMR and ^{13}CNMR spectra. Using 4-chloro-2-methlphenol as the proton source/uncleophile leads to pale yellow crystals identified as methyl 6-chloro-8-methyl-2-oxo-chromene-4-carboxylate (1d) (Scheme 1). Compounds **(1b-1d)** are formed by a mechanism similar to that outlined for 1a (see Scheme 2).



Scheme 2

The reaction of one equivalent of 2-hydroxypyridine or 4-hydroxypyridine with two equivalents of one DMAD in the presence of two equivalents of trimethyl phosphate was two carried out in refluxing CH_2Cl_2. The orange oil separated from reaction mixtures were identified as methyl 2-oxo-2h-pyrano[2,3-b]pyridine-4-carboxylate(2) or methyl 2-oxo-2H-pyrano[3,2-c]pyridine-4-carboxylate(3) (Scheme 1).

In conclusion the presented reactions provide 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 reac-

tion 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 multi-stepapproaches[14]. The present coumarin synthesis complements the older established methods and offers significant advantages for the synthesis of coumarins having acid sensitive functional groups. 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 an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHNO Rapid analyzer. IR spectra were recorded on a shimadzu IR-460 spectrometer. Mass spectra were recorded on a FINNIGAN-MAT 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 Aldrich silica gel 100 mesh chromatography plates were prepared from silica gel 60 mesh.

Preparation of coumarin derivatives examplified on methyl 5-Hydroxy-2-oxo-2H-chromene-4-carboxylate(1a); Typical procedure

To a stirred solution of trimethyl phosphate (4 mmol) and resorcinol (2mmol) in toluene (17mL) was added drop wise a mixture of DMAD (4mmol) in toluene (3ml) at -5^{0}C for 10 min. the reaction mixture was then allowed reduced pressure and the residue was purified by column chromatography using n-hexane-EtOAc as eluent to produce 3 as pale yellow oil, yield: 0.77g(94). IR (KBr) (υ_{max}/cm^{-1}): 3421(OH), 1724(C=O), 1598(C=C), 1232 and 1287(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) ppm. ^{13}CNMR: 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 (%) = 439 (M^++1, 7), 326 (100), 298(74), 230 (58), 57(47), 41(38) Anal. Calculated for $C_{20}H_{22}N_2O_9$ (436.4): C, 55.04; H, 5.54; N, 6.42. Founded C, 55.26; H 5.71; N, 6.46%.

Methyl 5- hydrocxy7 - methyl-2-oxo-2H-chromene-4-carboxylate (1b)

Yield 0.47g (57%). IR (KBr) (υ_{max}/cm^{-1}); 1731 (C=O), 1463 (C=C), 1286 and 1273 (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}CNMR: δ = 22.5 (Me), 54.2 (OMe), 103.6 (CH), 115.4(CH), 117.9(C), 128.6(C), 129.4 (CH) m133.2(C), 157.4(2C), 168.3 (C), 170.3 (C) ppm. MS: m/z 9%) = 436(M^++1, 7), 326 (100), 298(74), 230 (58), 57 (47), 41 (38). Anal. Calculated for $C_{20}H_{22}N_2O_9$ (436.4): C, 55.04; H, 5.54; N, 6.42. Founded: C, 55.26; H, 5.71; N, 6.46%.

Methyl7-acetyl-6-hydroxy-2-oxo-2H-chromene-4-carboxylate (1c)

Yellow oil, yield: 0.42g (52%). IR (KBr) (υ_{max}/cm^{-1}): 1727 and 1650 (C=O), 1487 (C=C), 1287 and 1222 (C-O). ^{1}HNMR: 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}CNMR 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=O) ppm. MS:m/z(%) = 436(M^++1,7), 326(100), 298(74), 230(58), 57(47), 41(38). Anal Calculated for $C_{20}H_{22}N_2O_9$ (436.4), C: 55.04; H, 5.54; N, 6.42. Founded: C: 55.26; H, 5.71; N, 6.46%.

Methyl6-chloro080methyl-2-oxo-2H-chromene-4-carboxylate (1d)

Pale yellow crystals (from 2:1 n-hexane-EtOAc), m.p. 94-96 ^{0}C; yield: 0.71g (87%). IR (KBr) (υ_{max}/cm^{-1}): 1773 and 1736 (C=O), 1468 (C=C), 1191 and 1154 (C-O). ^{1}HNMR: δ = 2.30 (s, 3H, Me), 2.82 (dd, CH, $^3J_{HH}$=6 Hz, $^3J_{HH}$= 3Hz), 3.14(dd, CH, $^3J_{HH}$=6Hz. $^3J_{HH}$=3Hz), 3.37 (s, 3H, OMe), 3.92(dd, CH, $^3J_{HH}$==3Hz, $^3J_{HH}$=3Hz), 7.15(s, CH), 7.17(s, CH) ppm. ^{13}CNMR: 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 (EI, 70 eV): m/z (%) = 196 (M^++2, 8), 194 (M^+, 34), 149(34), 139(28), 103(36), 77(100), 63(30), 59(36), 57 (76), 51 (78), 43(94), 41(98). MS: m/z (%) = 436 (M^++1, 7), 326(100). 298(74), 230(58), 57(47) m 41(38). Anal. Calculated for

$C_{20}H_{22}N_2O_9$(436.4): C, 55.04; H, 5.54; N, 6.42. Founded: C, 55.26; H, 5.71; N, 6.46%.

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

Light yellow oil, yield: 0.47g (90%).IR(KBr) (υ_{max}/ cm^{-1}): 1731(C=O), 1462(C=C), 1273(C-O). ^{1}HNMR: δ = 3.87 (s, 3H, OMe), 7.01(t, Ch, $^3J_{HH}$=9Hz), 7.13(s, CH), 7.59(dd, CH, $^3J_{HH}$=9Hz, $^4J_{HH}$=6Hz)ppm. ^{13}C NMR: δ = 53.6 (OMe), 111.2(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(%) = 436(M^++1, 7), 326(100), 298(74), 230(58), 57(47), 41(38). Anal. calculated for $C_{20}H_{22}N_2O_9$ (436.4): C, 55.04; H, 5.54; N, 6.42, founded: C, 55.26; H, 5.71; N, 6.46%.

Methyl2-oxo-2H-pyrano [3, 2-c] pyridine-4-carboxylate (3)

Pale yellow oil, yield: 0.69g (84%). IR (KBr) (υ_{max}/ cm^{-1}): 1731 (C=O), 1435(C=C), 1264(C-O). ^{1}HNMR: δ = 3.87 (s, 3H, OMe), (d, CH, $^3J_{HH}$=9Hz), 7.29(s, CH), 7.85(s,Ch), 7.93(d, CH, $^3J_{HH}$=9Hz) ppm. ^{13}CNMR: δ = 53.6 (OMe), 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), m/z (%) = 436 (M^++1, 7), 326(100), 298(74), 230(58), 57($&), 41(38). Anal. calculated for $C_{20}H_{22}N_2O_9$ (436.4): C, 55.4; H, 5.54; N, 6.42. founded: C, 55.26; H, 5.71; N, 6.46%.

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