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Note

Synthesis of 2*H*-1-benzopyran derivatives with a strongly electron-withdrawing substituent at 6-position

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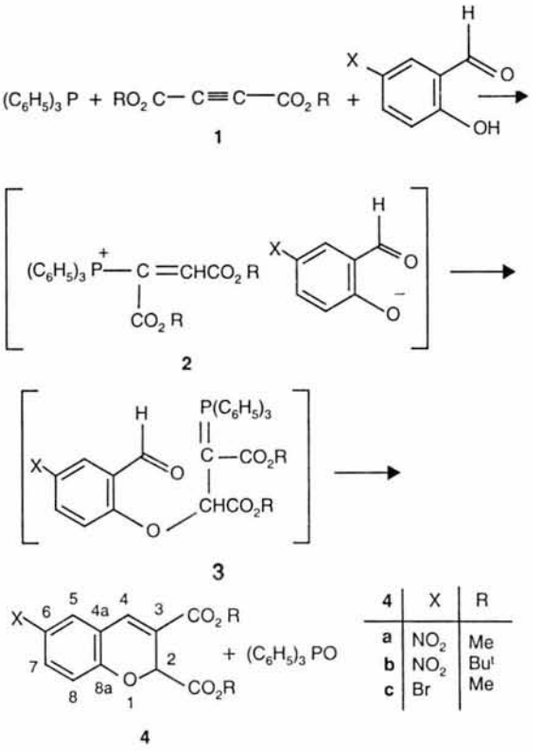
5-Bromo- and 5-nitro-2-hydroxybenzaldehyde react with the acetylenic ester **1** (R = Me and Bu^t) in the presence of triphenylphosphine to give the corresponding 6-substituted 2*H*-1-benzopyran-2,3-dicarboxylic esters **4**. Isolated yields in the one-pot preparation of compounds **4** are excellent. Reaction mechanism for the formation of compouds **4** is proposed. The structures of compounds **4a-c** have been confirmed by IR, MS and ^{1}H and ^{13}C NMR spectroscopy and elemental analyses.

2*H*-1-Benzopyrans (2*H*-chromenes) are important intermediates in the synthesis of many natural products[1] and medicinal agents[2] including some potassium-channel activating drugs[3,4]. A feature common to all these compounds is the presence of a strongly electron-withdrawing substituent at 6-position of the 2*H*-1-benzopyran ring[3,4]. Literature preparations of 2*H*-1-benzopyrans having electron-withdrawing substituents generally give low to moderate yields of product[5-7] and this prompted us to investigate improved procedures toward these compounds. Recently, we have established the utility of vinylphosphonium salts for heterocyclic synthesis[8,9]. In this note, we wish to report a practical and highly efficient procedure for preparing 2*H*-1-chromene derivatives **4a-c** with a strongly electron-withdrawing substituent at 6-position.

Many examples are known in which a heterocyclic alkene is formed from a phosphorane connected with a carbonyl group by a chain containing a heteroatom[10-13]. The formation of chromene **4** from salicylaldehyde, acetylenic ester and triphenylphosphine as reported here involves initial addition of triphenylphosphine to the acetylenic ester **1** and concomitant protonation of the 1:1 adduct, followed by attack of the anion of **2** to vinyl-triphenylphosphonium cation to form phosphorane **3**, which cyclises to **4** (Scheme I).

The structures of compounds **4a-c** were deduced from their elemental analyses and their ^{1}H and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at m/z 293, 377 and 326, respectively.



Scheme I

In conclusion, vinyltriphenylphosphonium salts have been shown to be useful precursors for preparing 2*H*-1-chromene derivatives with a strongly electron-withdrawing substituent at 6-position. The one-step nature of the present procedure makes it an interesting alternative to multistep approaches[12,13].

Experimental Section

Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Shimadzu IR-460 spectrometer; ^{1}H and ^{13}C NMR spectra on a JEOL EX-90A spectrometer at 90 and 22.6 MHz, respectively, and mass spectra on a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV.

General procedure for the preparation of 2*H*-1-benzopyrans 4a-c : To a magnetically stirred solution of triphenylphosphine (0.524 g, 2 mmoles) and 2-hydroxybenzaldehyde derivative (2 mmoles) in CH_2Cl_2 (12 mL) was added dropwise, a mixture of the acetylenic ester (2 mmoles) in CH_2Cl_2 (4 mL) at -10 °C over 15 min. The reaction mixture was then allowed to warm up to room temperature and stirred for 24 hr. The solvent was removed under reduced pressure and the viscous residue was purified by silica gel (Merck silica gel 60, 230-400 mesh) column chromatography using ethyl acetate-hexane (1:4) as eluent. The solvent was removed under reduced pressure and products **4a-c** were obtained as colourless crystals. The characterisation data of the chromenes **4** are given below.

Dimethyl 6-nitro-2*H*-1-benzopyran-2,3-dicarboxylate 4a : Colourless crystals, m.p. 143-44°C; yield 92%; IR(KBr) (ν_{max}, cm^{-1}): 1728(C=O), 1691(C=O), 1227(C-O) and 1198(C-O); ^1H NMR($CDCl_3$) : δ 3.73 and 3.89(6 H, 2 s, 2×OCH_3), 5.94(1 H, s, 2-H), 7.12(1 H, d, $J_{8H,7H}$=8.95 Hz, 8-H), 7.54(1 H, s, 4-H), 8.13(1 H, d, $J_{5H,7H}$=2.95 Hz, 5-H), 8.18(1 H, dd, $J_{7H,8H}$=8.95 $J_{7H,5H}$=2.95 Hz, 7-H); ^{13}C NMR ($CDCl_3$) : δ 52.57 and 52.97 (2 OCH_3), 72.56(C2);117.24, 124.73, 127.86 and 131.85(4 CH), 119.76 and 122.98(C3 and C4a), 142.73 (C6), 158.73(C8a), 163.86 and 168.38(2 C=O); MS (m/z, %): 293(M^+, 21); 234(M^+ -CO_2Me, 100), 188(M^+ -CO_2Me -NO_2, 78). Analysis: Calc. for $C_{13}H_{11}NO_7$ (293.24): C, 53.25; H, 3.78; N, 4.78. Found: C, 53.4; H, 3.4; N, 4.5%.

Di-*tert*-butyl 6-nitro-2*H*-1-benzopyran-2,3-dicarboxylate 4b : Colourless crystals, m.p. 145-46°C; yield 95%; IR(KBr) (ν_{max}, cm^{-1}): 1730(C=O), 1691(C=O), 1250(C-O); 1155(C-O). ^1H NMR($CDCl_3$) : δ 1.39 and 1.62 (18 H, 2 s, 2×CMe_3), 5.81(1H, s, 2-H), 7.09(1 H, d, $J_{8H,7H}$=9.84 Hz, 8-H), 7.41(1H, s, 4-H), 8.11(1H, d, $J_{5H,7H}$=2.86, 5-H), 8.16(1H, dd, $J_{7H,8H}$=9.84 $J_{7H,5H}$=2.86 Hz, 7-H); ^{13}C NMR ($CDCl_3$) : δ 29.16 and 29.36(6 CH_3 of 2×CMe_3); 74.44(C2), 83.60 and 84.62(2C of 2×CMe_3); 118.17, 125.75, 128.76 and 131.41(4 CH), 121.39 and 126.76 (C3 and C4a), 143.70(C6), 160.40(C8a), 163.94 and 168.38 (2 C=O); MS (m/z, %): 377(M^+, 26), 321(M^+ -CH_2=CMe_2, 27), 276(M^+ -CO_2Bu^t, 12), 265(M^+ -2 CH_2=CMe_2, 14), 219(M^+ -NO_2 -2 CH_2=CMe_2, 61), 175(M^+ -NO_2 -2CH_2=CMe_2 -CO_2,17). Analysis: Calc for $C_{19}H_{23}NO_7$ (377.40): C, 60.47; H, 6.14; N, 3.71. Found: C, 60.7; H, 6.0; N, 3.5%.

Dimethyl 6-bromo-2*H*-1-benzopyran-2,3-dicarboxylate 4c : Colourless crystals, m.p. 139-40 °C; yield 90%; IR(KBr) (ν_{max}, cm^{-1}): 1749(C=O), 1712(C=O), 1236(C-O), 1199(C-O). ^1H NMR($CDCl_3$) : δ 3.58 and 3.75 (6 H, 2 s, 2×OCH_3), 5.70 (1 H, s, 2-H), 6.78 (1 H, d, $J_{8H,7H}$ =8.21 Hz, 8-H), 7.20 (1 H, d, $J_{5H,7H}$=2.67, 5-H), 7.27 (1 H, dd, $J_{7H,8H}$=8.21 $J_{7H,5H}$=2.67 Hz, 7-H), 7.33(1 H, s, 4-H); ^{13}C NMR($CDCl_3$) : δ 52.10 and 52.51 (2 OCH_3), 71.92 (C2), 114.56 (C6), 119.12, 132.15, 132.65 and 135.10 (4 CH), 152.15 (C8a), 161.89 and 164.75 (2 C=O); MS (m/z, %): 328(M^+ + 2, 20), 326(M^+, 20.5), 267(M^+ - CO_2Me, 100), 188(M^+ - CO_2Me - Br, 60). Analysis: Calc. for $C_{13}H_{11}BrO_5$ (327.14): C, 48.13; H, 3.39. Found: C, 48.5; H, 3.1%.

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