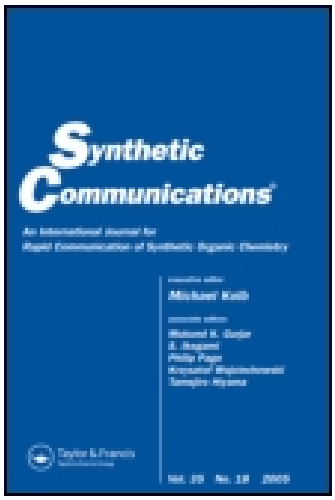

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Synthesis of Novel Phosphoric Esters of Flavone and Isoflavone by Atherton–Todd Reaction

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ABSTRACT

7-hydroxyflavone, chrysin, 4′-chloro-7-hydroxyisoflavone and 4′-fluo-7-hydroxy-isoflavone were phosphoylated by the Atheron–Todd reaction. The expected phosphates are obtained in good yields.

Key Words: Phosphoric esters; Flavone; Isoflavone; Atherton–Todd reaction.

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Phosphates and phosphoroamidates have wide bio-activities. Ester and amides of phosphoric acid play a vital role in many biological process and they appear to be synthesized and to undergo interconversion in living organisms with great ease.[1] With respect to introducing these functionalities into biomolecules, Atherton–Todd reaction is a useful synthetic approach. It involves the oxidation of diakyl phosphates with chlorocarbons into dialkyl or trialkyl phosphates. The versatility of the reaction results from the fact that the initial products in the reaction are the highly reactive dialkyl chlorophosphates, which in the presence of amines or alcohols are converted in situ into the corresponding dialkyl phosphoramides or trialkyl phosphates, respectively.[2] Among several methods, which have been used to prepare DIPP protected amino acids, Zhao's modification of the classical Atherton–Todd procedure, by mixing amino acid with diisopropylphosphite(DIPPH) in the presence of water, ethanol, carbon tetrachloride and triethyl amine, is very successfully one with good yields of objective products.[3]

In recent years, flavones and isoflavones have attracted increasing interests due to their various beneficial pharmacological effects.[4–6] We have been able to enlarge the scope of the Atherton–Todd reaction to flavone phosphorlation (Scheme 1). Our procedures are practical. The target products were obtained with good yields. All the structures of target products were determined by ESI-MS/MS, NMR and IR for the first time. The structure of phosphated chrysin was further confirmed by x-ray diffraction.

EXPERIMENTAL

IR spectra were recorded on a Shimadazuir-408. ^{1}H and ^{31}P NMR spectra were on a Bruker-DTX-400. Chemical shifts are expressed in parts per million positive values downfield from internal TMS (^{1}H) and external 85% H_3PO_4 (^{31}P). Coupling constants are expressed in Hertz.TLC was performed on silica gel plates and preparative chromatograph on columns of silica gel (200–300 mesh). MS were recorded on Bruke Esquire-3000.

Compound a. $C_{19}H_{19}O_6P$. 0.5253 g 7-hydroxyflavone was added to a solution of 40 mL ethanol and 10 mL triethylamine. The mixture was stirred until 7-hydroxyflavone was dissolved and then a solution of diethylphosphite (DEPH) and CCl_4 (0.3042 g DEPH + 10 mLCCl_4) was added dropwise with vigorous stirring in ice-water bath. The reaction proceeded for 24 hours at room temperature. The resulting salt of triethyl amine was precipitated. Then the organic phase was dried over $MgSO_4$ and evaporated in vacuo below 50°C. Then 10 mL water was added. The solution was extracted by ethyl acetate. The product was further purified by column chromatography ($CHCl_3 : CH_3CH_2OH = 100 : 1$). 0.7594 g white plate compound **a** was obtained. m.p 60–61°C.

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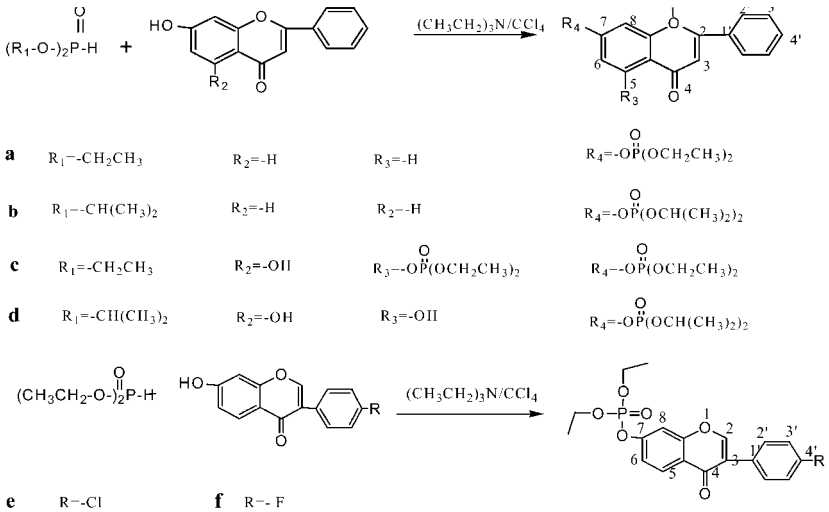

Scheme 1.

yield: 92%. Anal (Calcd)% for $C_{19}H_{19}O_6P$ (compound **a**): C 60.92 (60.96), H 5.05 (5.08), P 8.26 (8.29); ^{1}H NMR (400 MHz, CD_3Cl) δ: 8.23 (d, 1H, $J = 8.4$,), 7.92 (m, 2H, 2′-H), 7.54 (m, 4H, 3′-H, 4′-H, 8-H), 7.27 (d, 1H, $J = 8.3$, 6-H), 6.82 (s, 1H,3-H), 4.29(m, 4H, CH2), 1.41 (m, 6H, CH_3); ^{31}P NMR (400 MHz, D_2O), δ: -6.77; ESI-MS/MS, m/z 375 $[M + H]^+$, 374, 347 $[M\text{-}C_2H_4 + H^+]$, 319 $[M\text{-}2C_2H_4 + H^+]$. IR 1265 (PO).

Compound b. $C_{21}H_{23}O_6P$. 0.2310 g 7-hydroxyflavone was added to a solution of 20 mL ethanol and 10 mL triethylamine. The mixture was stirred until 7-hydroxyflavone was dissolved and then a solution of diisopropylphophite (DIPPH) and CCl_4 (0.166 g DIPPH + 10 mLCCl_4) was added dropwise with vigorous stirring in ice-water bath. The reaction proceeded for 24 hours at room temperature. The resulting salt of triethyl amine was precipitated. Then the organic phase was dried over $MgSO_4$ and evaporated in vacuo below 50°C. Then 10 mL water was added. The solution was extracted by ethyl acetate. The product was further purified by column chromatography ($CHCl_3 : CH_3CH_2$-OH = 80 : 1). 0.3705 g white plate compound **b** was obtained. m.p. 58–59°C. yield: 95%. Anal (Calcd)% for $C_{19}H_{19}O_6P$ (compound **b**): C 62.64 (62.68), H 5.73 (5.76), P 7.68 (7.70); ^{1}H NMR (400 MHz, CD_3Cl) δ: 8.22 (d, 1H, $J = 8.8$), 7.92 (m, 2H, 2′-H), 7.55 (m, 4H, 3′-H, 4′-H, 8-H), 7.27 (d, 1H, $J = 8.3$, 6-H), 6.81 (s, 1H,3-H), 4.81(m, 2H, CH), 1.35 (m, 12H, CH_3); ^{31}P NMR (400 MHz, D_2O), δ: -9.32; ESI-MS/MS, m/z 403 $[M + H]^+$, 361 $[M\text{-}C_3H_6 + H^+]$, 319 $[M\text{-}2C_3H_6 + H^+]$. IR 1265 (PO).

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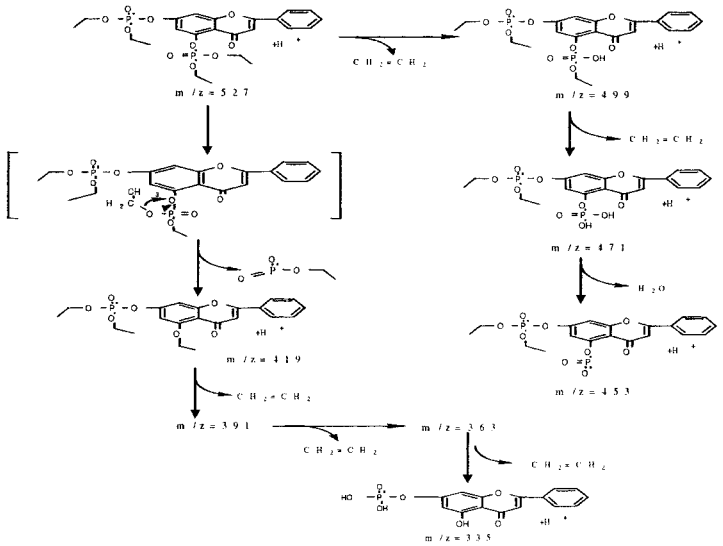

Scheme 2. Positive ion ESI mass spectral fragmentation pathway of protonated compound c.

Compound c. $C_{23}H_{28}O_{10}P_2$. 0.5631 g chrysin was added to a solution of 40 mL dioxane 10 mL triethylamine. The mixture was stirred until chrysin was dissolved and a solution of DEPH and CCl_4 (0.6120 g DEPH + 10 mLCCl_4) was then added dropwise vigorous stirring in ice-water bath. The reaction proceeded for 24 hours at room temperature. The resultiong salt of triethyl amine was precipitated. The filtrate was evaporated in vacuo below 50°C. Then 10 mL water was added. The solution was extracted by ethylacetate. The organic phase was dried over $MgSO_4$. The needle crystalline residue 1.026 g were separated out. m.p. 62–64°C. yield: 88%. Anal (Calcd)% for $C_{23}H_{28}O_{10}P_2$: C 52.44 (52.47) H 5.27 (5.31), P 11.74 (11.76); ^{1}H NMR (400 MHz, CD_3Cl) δ: 7.88 (d, 2H 2′-H $J = 7.6$ Hz), 7.54 (m, 3H, 3′-H, 4′-H), 7.41(s, 1H, 6-H), 7.26 (s, 1H,8-H), 6.69 (s,1H,3-H), 4.33 (m, 8H, −CH2), 1.41(m, 12H −CH3); ^{31}P NMR (400 MHz, D2O), δ: P-1: −7.078, P-2 : −7.1548; ESI-MS/MS, m/z 527 $[M + H]^+$, 499 $[M\text{-}C_2H_4 + H^+]$, 471 $[M\text{-}C_2H_4 + H^+]$, 453 $[M\text{-}C_2H_4\text{-}H_2O + H^+]$, 419 $[M\text{-}(O)_2POCH_2CH_3 + H^+]$, 391 $[M\text{-}(O)_2POCH_2CH_3\text{-}C_2H_4 + H^+]$, 363 $[M\text{-}(O)_2POCH_2CH_3\text{-}2C_2H_4 + H^+]$, 335 $[M\text{-}(O)_2POCH_2CH_3\text{-}3C_2H_4 + H^+]$. IR 1264 (PO). Structure of compound c was also confirmed by X-ray diffraction (Fig. 1).

Compound d. $C_{21}H_{23}O_7P$. 0.5063 g chrysin was added to a solution of 30 mL dioxane and 20 mL triethylamine. The mixture was stirred until

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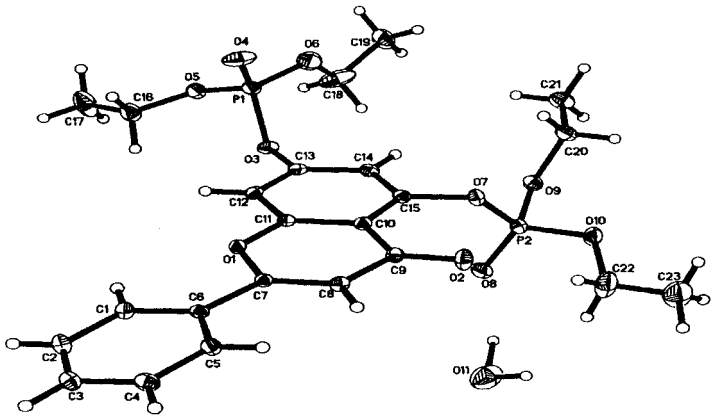

Figure 1. Crystal structure of compound c.

chrysin was dissolved and then a solution of DIPPH and CCl_4 (0.7747 g DIPPH + 10 mLCCl_4) was added dropwise with vigorous stirring in ice-water bath. The reaction proceeded for 24 hours at room temperature. The resulting salt of triethyl amine was precipitated. Then the organic phase was drived over $MgSO_4$. The filtrate was evaporated in vacuo below 50°C. Then 10 mL water was added. The solution was extracted by ethyl acetate. The product was further purified by column chromatography ($CHCl_3 : CH_3CH_2OH = 25 : 1$). 0.708 g white yellow compound **d** was obtained. m.p. 95–96°C. Yield: 85%. Anal (Calcd)% for $C_{21}H_{23}O_7P$ (compound **d**): C 60.25 (60.29), H 5.51 (5.54), O 26.75 (26.77), P 7.38 (7.40). ^{1}H NMR (400 MHz, CD_3Cl) δ: 12.7 (s, 1H, OH), 7.89 (d, $J = 8.16$, 2H, 2′-H), 7.55 (m, 3H, 3′-H, 4′-H), 7.01 (s, 1H, 6-H), 6.72 (s, 1H, 3-H), 6.66 (s, 1H, 8-H), .81(m, 2H), 1.38 (m,12H). ^{31}P NMR (400 MHz, D_2O), δ: P: −9.118. ESI-MS/MS: m/z: 419 $[M + H]^+$, 376 $[M\text{-}C_3H_6 + H^+]$, 334 $[M\text{-}2C_3H_6 + H^+]$. IR 1263 (PO).

Compound e. $C_{19}H_{18}ClO_6P$. 0.0955 g 4′-chloro-7-hydroxy-isoflavone was added to a solution of 10 mL ethanol and 2 mL triethylamine. The mixture was stirred until 4′-chloro-7-hydroxy-isoflavone was dissolved and then a solution of DEPH and CCl_4 (0.048 g DEPH + 5 mLCCl_4) were added dropwise with vigorous stirring in ice-water bath. The reaction proceeded for 24 hours at room temperature. The resulting salt of triethyl amine was precipitated. The organic phase was dried over $MgSO_4$. The filtrate was evaporated in vacuo below 50°C. Then 10 mL water was added. The solution was extracted by ethyl acetate. The product was further purified by column chromatography ($CHCl_3 : CH_3CH_2OH = 100 : 1$). 0.117 g white power compound **e** was obtained. m.p. 126–127°C yield: 81.7%. Anal (Calcd)% for $C_{19}H_{18}ClO_6P$

(compound **e**): C 55.80 (55.83), H 4.42 (4.44), Cl 8.63 (8.67), O 23.45 (23.48), P 7.55 (7.58). ^{1}H NMR (400 MHz, CD_3Cl) δ: 8.285 (d, $J = 8.8$, 1H, 5-H), 8.0 (s, 1H, 2-H), 7.50 (d, 2H, $J = 8.4$,2′-H), 7.43 (s, 1H), 7.42 (d, 2H, $J = 6.0$, 3′-H), 7.28 (d, 1H, $J = 8.8$, 6-H), 4.27 (m, $J = 5.2$, 4H), 1.39 (m, $J = 6.8$,6H). ^{31}P NMR (400 MHz, D_2O), δ: P: −7.061. ESI-MS/MS, m/z: 431 [M + Na^+], 403 [M-C_2H_4 + Na^+], 475 [M-$2C_2H_4$ + Na^+]. IR 1267 (PO).

Compound f. $C_{19}H_{18}FlO_6P$. 0.120 g 4′-fluo-7-hydroxy-isoflavone was added to a solution of 10 mL ethanol and 2 mL triethlyamine. The mixture was stirred until 4′-fluo-7-hydroxy-isoflavone was dissolved and then a solution of DEPH and CCl_4 (0.064 g DEPH + 3 mLCCl_4) were added dropwise with vigorous stirring in ice-water bath. The reaction proceeded for 24 hours at room temperature. The resulting salt of triethyl amine was precipitated. The filtrate was evaporated in vacuo below 50°C. Then 10 mL water was added. The solution was extracted by ethyl acetate. Then the organic phase was drived over $MgSO_4$. The filtrate was evaporated to give 0.1591 g white power compound **f**. m.p. 146–147°C. Yield: 86.6%. Anal (Calcd)% for $C_{19}H_{18}FO_6P$ (compound **f**): C 58.15 (58.17), H 4.60 (4.62), F 4.84 (4.84), O 24.45 (24.47), P 7.88 (7.90). ^{1}H NMR (400 MHz, CD_3Cl) δ: 8.30 (d, 1H, $J = 8.8$,5-H), 7.98 (s, 1H, 2-H), 7.54 (m, 2H, 2′-H), 7.42 (s, 1H, 8-H), 7.284 (d, 1H, $J = 8.84$, 6-H) 7.137 (m, 2H, 3′-H,), 4.27 (m, $J = 5.2$, 4H), 1.39 (m, $J = 6.8$, 6H). ^{31}P NMR (400 MHz, D_2O), ($\delta = 0$), δ: P: −7.055. ESI-MS/MS, m/z: 393 [M + H^+], 365 [M-C_2H_4 + H^+], 337 [M-$2C_2H_4$ + H^+]. IR 1266 (PO)

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