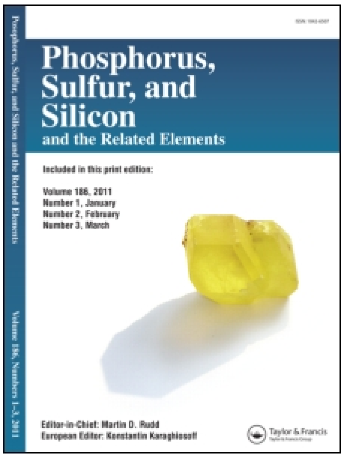

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Synthesis of Solanesyl Phosphonate

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Three solanesyl phosphonates were synthesized using standard Arbuzov reaction, and their structures were determined by ESI-MS, NMR, and IR.

Keywords Anti-cancer drug; arbuzov reaction; phosphonates; solanesyl phosphonate

INTRODUCTION

Solanesol, a long-chain terpenoid alcohol mainly existing in tobacco leaves, is the starting material for many high-value biochemicals, including Vitamin K analogues and co-enzyme Q10 which is useful in the treatment of heart diseases, cancers and ulcers. Solanesol itself can be used as cardiac stimulant, lipid antioxidant and antibiotics, and clinical trials are also developing the use of solanesol as an anti-cancer drug.[1]

Phosphonates have important applications in flame retardancy, organic synthesis, and biological applications.[2] Phosphate esters play an important role in a wide variety of structurally diverse natural and biologically active compounds, from glycolipids to nucleic acids.[3] Introduction of a phosphate group essentially changes the physical and chemical properties of the parent molecule, resulting in changes to the polarization and intermolecular bonding characteristics of that molecule. Within the pharmaceutical industry, phosphate esters are often used as pro-drugs to increase the water solubility and hence bio-availability of the agent,[4] such as the antiinflammatory agents dexamethasone and oxyphenbutazone.[5] The toxicity of phosphonates to aquatic organisms

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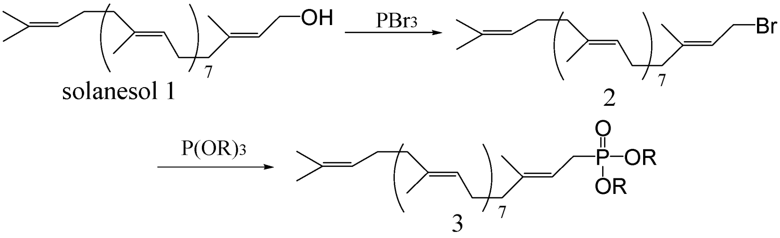
is low. Human toxicity is also low which can be seen in the fact that phosphonates are used to treat various diseases. Phosphonates are similar to phosphates except that they have a C—P bond in place of the C—O—P linkage. Due to their structural similarity to phosphate esters, phosphonates often act as inhibitors of enzymes due in part to the high stability of the C—P bond.

The Michaelis-Arbuzov reaction is a chemical reaction for the formation of phosphonates from trialkyl phosphites and alkyl halides. In the work described in this paper, three solanesyl phosphonates were synthesized using standard Arbuzov[6] reaction (Scheme 1), and their structures were determined by ESI-MS, NMR, and IR.



a R= $-CH_3$ **b** R= $-CH_2CH_3$ **c** R= $-CH(CH_3)_2$

SCHEME 1 Synthesis of solanesyl phosphonates.

EXPERIMENTAL

IR spectra were recorded on a Shimadazuir-408.^{1}H-NMR and ^{31}P-NMR spectra were on a Bruker-DTX-400, chemical shifts were expressed in parts per million positive values downfield from internal TMS (^{1}H) and external 85% H_3PO_4 (^{31}P), coupling constants were expressed in Hertz. MS was recorded on Bruker Esquire-3000 and Micromiss Q-Tof. Melting point was recorded on a microscopical determinator XT4 A (the thermometer was not adjusted).

Synthesis of Solanesyl Bromide 2[7]

Solanesol **1** 10.0 g was dissolved in 70 ml petroleum ether in a 250 ml three-necked flask. Then 14 ml pyridine was added into the flask, and the temperature was maintained at −5°C using an ice/salt bath. A solution of 2.2 g phosphorus tribromide in 15 ml of petroleum ether was added dropwise to the mixture over 1 h. Then the mixture was stirred and the temperature was maintained at −5°C for 3 h. The disappearance of the solanesol in the reaction solution was checked using TLC

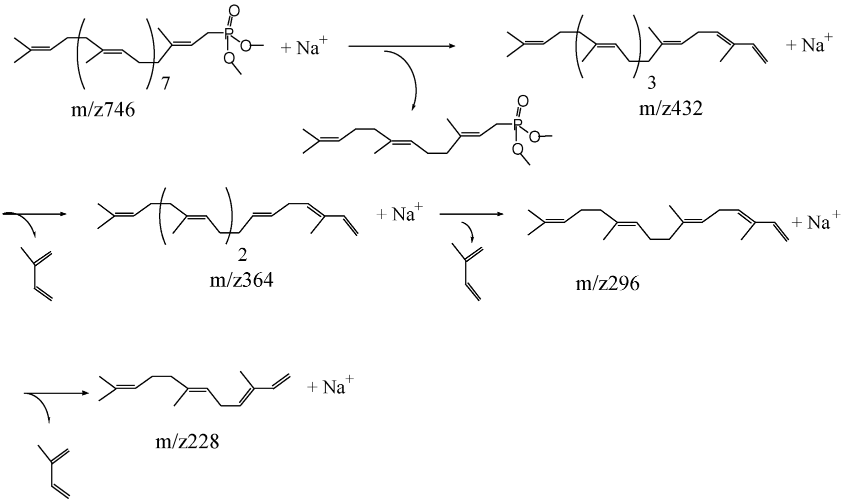
($CHCl_3$:CH_3OH = 1:1). 60 ml ice water was added to the reaction solution afterwards, and then extracted by 3 × 45 mL petroleum ether. The organic layer was washed with saturated sodium chloride solution and dried with anhydrous sodium sulphate. The crude solanesyl bromide **2** (6.7 g), a light-yellow liquid was finally obtained and then used in the next reaction without further purification.

Synthesis of Title Compound 3 through Arbuzov Reaction

5.0 g crude solanesyl bromide **2**, 35 ml toluene and 5.4 g trialkylphosphate were added to a 100 ml flask. The mixture was refluxed for 12 h. and then evaporated in vacuo below 50° to remove toluene and part of trialkylphosphate. The title compound **3,** a light-yellow liquid was obtained after being purified by column chromatography (petroleum ether: $CH_3COOCH_2CH_3$ = 1:1).

Compound 3a ($C_{47}H_{79}O_3P$)

^1H NMR ($CDCl_3$ 400 MHz) δ: 1.60~1.68 (30H, $-CH_3$), 2.04~2.08 (m, 32H, $-CH_2$), 2.52~2.59 (dd, J = 22.0, 7.6 Hz, 2H, $-CH_2$-P), 4.09~4.14 (m, 6H, $-OCH_3$), 5.08~5.13 (m, 9H, $-CH$); ESI-MS/MS, *m/z*: 723 $[M+H]^+$,746 $[M+Na]^+$, 432 $[M\text{-}C_{17}H_{31}O_3P+Na]^+$, 364 $[M\text{-}C_{22}H_{39}O_3P+Na]^+$, 296 $[M\text{-}C_{27}H_{47}O_3P+Na]^+$, 228$[M\text{-}C_{32}H_{55}O_3P+Na]^+$. A detail ESI-MS/MS fragmentation pathway of sodium adduct of compound 3a was shown in Scheme 2. A molecular



SCHEME 2 ESI-MS/MS fragmentation pathway of sodium adduct of compound 3**a.**

formula of $C_{47}H_{79}O_3P$ was determined from the molecular ion peak at m/z 723.5801 $[M+H]^+$ (calcd. for $C_{47}H_{79}O_3P$ 722.5767) obtained by ESIQ-TOF.

Compound 3b ($C_{49}H_{83}O_3P$)

^1H NMR ($CDCl_3$ 400 MHz) δ: 1.29~1.33 (t, 6H, $-CH_2\underline{CH_3}$), 1.60~1.68 (30H, $-CH_3$), 2.04~2.08 (m, 32H, $-CH_2$), 2.53~2.61 (dd, J = 22.0, 7.6 Hz, 2H, CH_2-P), 4.08~4.15 (m, 4H, $-O\underline{CH_2}CH_3$), 5.10~5.11 (m, 9H, -CH); ESI-MS, m/z: 751 $[M+H]^+$. A molecular formula of $_{49}H_{83}O_3P$ was determined from the molecular ion peak at m/z 751.6086 $[M+H]^+$ (calcd. for $_{49}H_{83}O_3P$ 750.6080) obtained by ESIQ-TOF.

Compound 3c ($C_{51}H_{87}O_3P$)

^1H NMR ($CDCl_3$ 400 MHz) δ: 1.30~1.35 (m, 12H, $-CH_3$), 1.60~1.68 (30H, $-CH_3$), 2.05~2.08 (m, 32H, 16-CH_2), 2.51~2.57 (dd, J = 21.9, 7.6 Hz, 2H, $-CH_2$-P), 4.60~4.70 (m, 2H, $-CH$), 5.10~5.13 (m, 9H, $-CH$); ESI-MS, m/z: 779 $[M+H]^+$. A molecular formula of $C_{51}H_{87}O_3P$ was determined from the molecular ion peak at m/z779.6389 $[M+H]^+$ (calcd. for $C_{51}H_{87}O_3P$ 778.6393) obtained by ESIQ-TOF.

The products described above were characterized by ^1H, ^{13}C, and ^{31}P NMR. An additional splitting of proton resonance of $-CH_2$-P group was observed. The signal from the two equivalent hydrogen atoms of the $-CH_2$-P group is split into *dd* peaks by adjacent hydrogen of the = CH- group and adjacent phosphorus atom. The spectra of phosphorus-containing compounds frequently show additional splitting of proton resonances due to ^{31}P-^1H coupling.

CONCLUSION

Three new solanesyl phosphonates were synthesized using standard Arbuzov[6] reaction. Their structures were determined by ESI-MS, NMR, and IR.

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