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A NEW SYNTHESIS OF VINYLPHOSPHONIUM SALTS. APPLICATION FOR DEUTERIUM LABELING (1)

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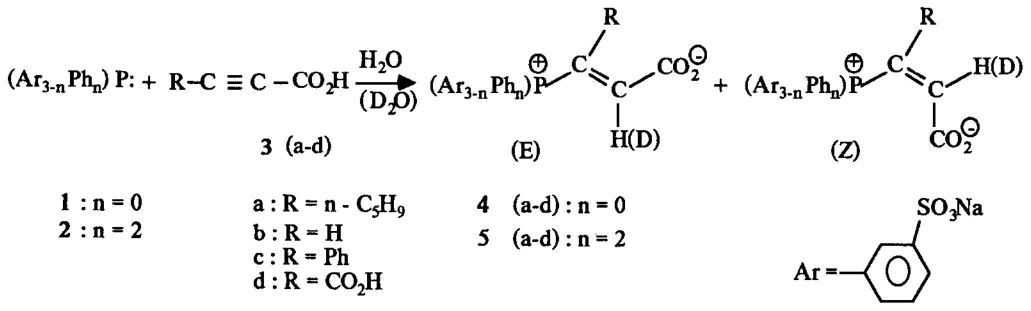
Summary : Nucleophilic additions of water-soluble phosphines on α-alcynic acids afford new vinylphosphonium salts which are easily transformed into specifically deuteriated olefins or phosphine oxides by using sequentially H_2O or D_2O.

Vinylphosphonium salts, useful intermediates in organic chemistry, can be prepared from phosphines and unsaturated halides or by modification of alkylphosphonium salts (2,3). Transient vinylphosphonium salts have also been identified (4) or postulated (5) when phosphines are added on alcynes in protic or aqueous solvents. They readily decompose, by alcoholysis, into alkoxyphosphonium ylids or vinylethers (4). We have recently shown (1) that reactions between activated olefins and hydrosoluble phosphines occured readily in water because the equilibria were displaced by protonation of the carbanionic intermediates. In this paper we describe the reaction of "triphenylphosphine meta-trisulfonate" 1 (TPPTS) (6) and "diphenylphosphine meta-monosulfonate" 2 (DPM) (7) with various α-acetylenic carboxylic acids 3 in the presence of water. These reactions lead in all cases to the quantitative production of water-soluble vinylphosphonium salts 4 and 5 which can be isolated and fully characterized. Compounds 4 and 5 are useful intermediates to prepare regiospecifically deuteriated olefins or new vinyl phosphine oxides.

Our method allows the synthesis (more efficiently than by published procedures (8)) at will of α,β-dideuterio- and α- or β-monodeuterio-fumaric (or cinnamic) acids in quasi-quantitative yield, rapidly and at room temperature. The recovery and the purification of the organic products are very easy because the phosphine oxide produced is water-soluble.

Reactions between the phosphines **1** and **2** and the acetylenic acids **3** are performed in water in a concentrated solution for TPPTS **1** or in a dilute solution for DPM **2**.



3 (a-d)

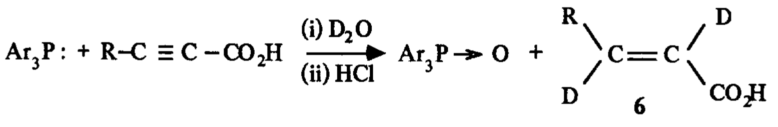
1 : n = 0
2 : n = 2

a : R = n - C_5H_9
b : R = H
c : R = Ph
d : R = CO_2H

4 (a-d) : n = 0
5 (a-d) : n = 2

The choice of the phosphine depends on wether the vinylphosphonium must be isolated in water, in deuterium oxide or in organic solvents for further synthetic purposes. By monitoring the reaction rates using ^{31}P NMR spectroscopy, it is found that electron-withdrawing groups accelerate the nucleophilic addition (9). On the other hand a mixture of Z (the more abundant) and E isomers is always produced, the structure of which are proved by ^{31}P chemical shifts and $^3J_{P\text{-}H}$ values (10). With acetylenic acids, zwitterionic salts are formed because the hydroxide ions produced by the reaction of the intermediate carbanions on water are neutralized by the carboxylic acid function. In D_2O, the vinylphosphonium salts are specifically deuteriated at the β-carbon (10).

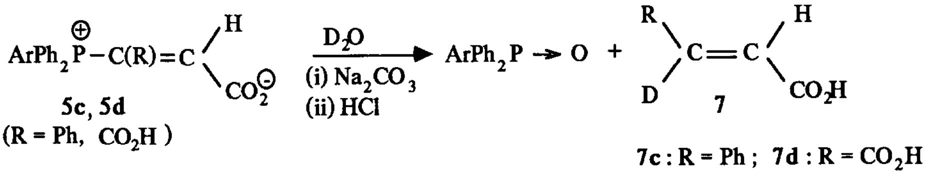
The stability and the reactivity of the vinylphosphonium salts are strongly dependent on the nature of R group and on the degree of sulfonation. The trisulfonated vinylphosphonium salts **4c** and **4d** are readily oxidized in water to afford phosphine oxide and fumaric (or cinnamic) acid with two deuterium atoms on the double bond when D_2O is used (11).



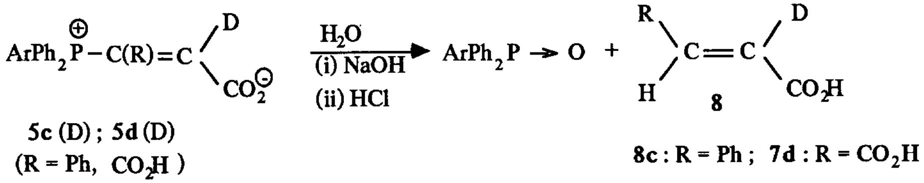
6

6c : R = Ph ; **6d** : R = CO_2H

The monosulfonated vinylphosphonium salts **5c** and **5d** (deuteriated or not) can be isolated and oxidized either in H_2O or D_2O by addition of NaOH or NaOD. These sequences lead to monodeuteriated fumaric acid **7d** and to regiospecifically monodeuteriated cinnamic acid **7c** and **8c** (12).

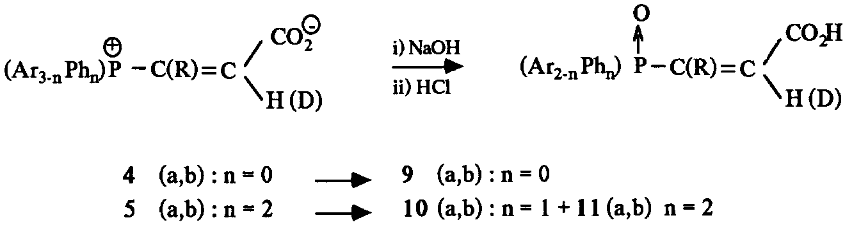

5c, 5d (R = Ph, CO_2H)

7c : R = Ph ; 7d : R = CO_2H


5c (D) ; 5d (D) (R = Ph, CO_2H)

8c : R = Ph ; 7d : R = CO_2H

Upon addition of NaOH to an aqueous solution of vinylphosphonium salts **4a**, **4b**, **5a** and **5b**, an aromatic grouping is removed and vinylphosphine oxides are produced. An hydrosoluble phosphine oxide, **9a** or **9b**, is obtained from the trisulfonated salts **4a** or **4b**. However, the monosulfonated salts **5a** or **5b** afford a mixture of monosulfonated oxides **10a** or **10b** and vinyldiphenylphosphine oxides **11a** or **11b** (13,14).


4 (a,b) : n = 0 ⟶ 9 (a,b) : n = 0

5 (a,b) : n = 2 ⟶ 10 (a,b) : n = 1 + 11 (a,b) n = 2

These vinyl phosphonium salts and phosphine oxides can be deuteriated at the β-carbon ; they are of interest to prepare, for instance, regioselectively deuteriated heterocycles by nucleophilic addition followed by an internal Wittig reaction (15-17). On the other hand they can be used to obtain various trisubstituted phosphorus derivatives (18,19), sulfonated or not and bearing also other functionalities.

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8 - Reaction between triphenylphosphine and dimethyl acetylene dicarboxylate in THF-D_2O (1%) (5) afford 70 % of impure dideuteriodimethyl fumarate after refluxing for several hours. Similarly methyl phenylpropiolate leads to methyl cinnamate in 40 % yield after refluxing 2-3 days.

9 - The reaction times between **1** (**2**) and **3** are respectively : **3a** : 10 h (12 h) ; **3b** : 10 mn (20 mn) ; **3c** : 1 h (1 h 30) ; **3d** : 5 mn (5mn).

10 - ^{31}P NMR (32.38 MHz), H_2O, δ ppm : **4a** : 23.5 (Z, 75 %), 26.9 (E, 25 %) ; **5a** : 22.5 (Z, 80 %), 26.1 (E, 20 %) ; **4b** : 17.1 (Z, 70 %), 19.9 (E, 30 %) ; **5b** : 16.0 (Z, 80 %), 18.9 (E, 20 %) ; **4c** : 23.5 (Z, 85 %), 25.1 (E, 15 %) ; **5c** : 23.2 (Z, 70 %), 24.7 (E, 30 %) ; **4d** : 26.6 (Z, 20 %), 28.0 (E, 80 %) ; **5d** : 24.5 (Z, 25 %), 25.4 (E, 75 %).

^{1}H NMR (90 MHz) D_2O, H vinyl, δ ppm : **4a** : 7.45 ($^3J_{P\text{-}H}$ = 36 Hz, Z), 7.03 ($^3J_{P\text{-}H}$ = 25 Hz, E) ; **5a** : 7.23 (half doublet, Z), 6.94 ($^3J_{P\text{-}H}$ = 25 Hz, E) ; **4b** : 7.37 ($^3J_{P\text{-}H}$ = 37 Hz, $^3J_{H\text{-}H}$ = 3 Hz, Z), 6.97 ($^3J_{P\text{-}H}$ = 22 Hz, $^3J_{H\text{-}H}$ = 17 Hz, E) ; **5b** : 7.35 ($^3J_{P\text{-}H}$ = 34 Hz, $^3J_{H\text{-}H}$ = 3 Hz, Z), 7.01 ($^3J_{P\text{-}H}$ = 22 Hz, $^3J_{H\text{-}H}$ = 17 Hz, E). For compounds **4c, d** and **5c, d** the signal of the vinylic proton is masked by the aromatic multiplet. The ^{31}P NMR spectra of the corresponding deuteriated vinylphosphonium are identical ; ^{1}H NMR study of the deuteriated compounds shows the disappearance of the vinylic proton.

11 - The acids **6c, 6d** are precipitated by addition of HCl and filtrated. Isotopic purities determined by mass spectrometry are respectively 95.8 % and 95.5 % for **6c** and **6d**. The acidic protons of **3c** and **3d** have not been exchanged before use.

12 - Isotopic purities determined by mass spectrometry of monodeuteriated olefins are : 94.3 % for **7c** and **8c** (R = Ph) and 93.5 % for **7d** (R = CO_2H).

13 - ^{31}P NMR, 32.38 MHz, δ ppm (H_2O) : **9a** : 38.32 ; **9b** : 38.54 ; **10a** : 38.77 ; **10b** : 36.81 ; **11a** : 27.19 ($CDCl_3$) ; **11b** : 25.23 ($CDCl_3$).

14 - The phosphine oxides **11a** or **11b** are not water-soluble and precipitate at pH = 1. They are separated by filtration ; compounds **10** (**a** or **b**) are obtained by removal of water.

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