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SYNTHESIS OF SPECIFICALLY DEUTERATED 1,3-DIETHOXYCARBONYLALLYLIDENETRIPHENYLPHOSPHONIUM YLIDE

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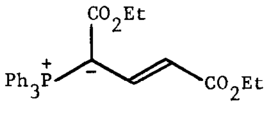
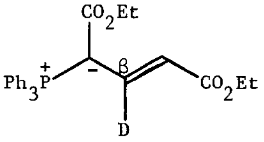
Abstract: Methods for the specific introduction of deuterium labels in the β- and γ-positions of the title allylidenephosphonium ylide, without deuterium scrambling, have been developed.

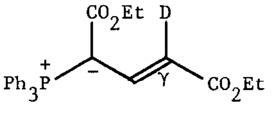
In a recent contribution[1] from our laboratory we communicated the unusual *retro*-Michael fragmentation of the allylidenephosphonium ylide (1) to yield ethoxycarbonylmethylenetriphenylphosphonium ylide (2) and ethyl propynoate, during its condensation with p-chlorobenzaldehyde. During our detailed investigation of this fragmentation-condensation reaction, the synthesis of the specifically deuterated allylidenephosphonium ylides (3) and (4) became desirable.



(1)



(3)



(4)

For the synthesis of the β-deuterated phosphonium ylide (3) the Michael addition of the ylide (2) to ethyl 3-deuteriopropynoate (5) was envisioned. The deuterio-ester (5) was very efficiently synthesized by a newly developed method which is, according to our experience, superior to the existing literature procedures.[2,3] Ethyl propynoate in dichloromethane was treated, under phase transfer conditions (tetrabutylammonium iodide, TBAI), with a three molar excess of deuterium oxide which contained a catalytic quantity of sodium deuteroxide. After stirring for one hour at room temperature, the organic phase was separated and the deuterium exchange procedure repeated twice. ^{1}H n.m.r. analysis of the dried organic phase revealed that it contained ethyl 3-deuteriopropynoate (5) with a deuterium content of >97%. Although the deuterio-ester (5) could be isolated in almost quantitative yield without appreciable deuterium loss by fractional distillation, we found that the β-deuteriophosphonium ylide (3) could very conveniently be synthesized by the addition of one mole equivalent of the ylide (2) to the dichloromethane solution of (5) without its prior isolation. The β-deuteriophosphonium ylide (3) was produced under these reaction conditions in 80% recrystallized yield,[4] m.p. 148°C (from ethyl acetate), δ($CDCl_3$) 6,30 (1 H, s), with specific deuterium incorporation in the β-position of >90% according to ^{1}H n.m.r. analysis.

$$\mathrm{H{-}C{\equiv}C{-}CO_2Et} \xrightarrow[\mathrm{CH_2Cl_2/TBAI}]{\mathrm{D_2O/\bar{O}D}} \underset{(5)}{\mathrm{D{-}C{\equiv}C{-}CO_2Et}} \xrightarrow[(2)]{\mathrm{Ph_3\overset{+}{P}{-}\overset{-}{C}H{-}CO_2Et}} (3)$$

For the synthesis of the γ-deuterated phosphonium ylide (4), acid catalyzed, regiospecific deuterium exchange of the allylidenephosphonium ylide (1) was invoked. The phosphonium ylide (1) in dichloromethane was treated with a nine molar excess of deuterium oxide which contained half a mole equivalent of deuterium chloride. The organic phase was separated and successively treated with an equal volume of deuterium oxide, an equal volume of deuterium oxide which contained half a mole equivalent of sodium deuteroxide, and again with a fresh portion of deuterium oxide. The residue from the dried (potassium carbonate) organic phase was recrystallized from ethyl acetate to produce the γ-deuteriophosphonium ylide (4) in 66% yield[4] with a specific deuterium incorporation of >90% according to ^1H n.m.r. analysis, m.p. 148°C $\delta(CDCl_3)$ 6.97 (1 H, d, J_{PH} 17.3 Hz). Treatment of the organic phase with an equivalent amount of base (sodium deuteroxide), after acid catalyzed deuterium exchange, was an essential operation in order to avoid deuterium loss.

Michael addition of the deuterated phosphonium ylide (6) to ethyl propynoate, also proved to be an efficient method for the synthesis of the γ-deuteriophosphonium ylide (4). The phosphonium ylide (2) in dichloromethane was treated with a five molar excess of deuterium oxide, the organic phase separated and the deuterium exchange procedure repeated twice. Separation of the organic layer was followed by in situ treatment of the deuterated phosphonium ylide (6) with one mole equivalent of ethyl propynoate at or below room temperature. The dichloromethane solution was treated as above with half a mole equivalent of sodium deuteroxide in deuterium oxide, washed with deuterium oxide and dried. According to ^1H n.m.r. analysis, the γ-deuterated allylidenephosphonium ylide (4) was produced under these reaction conditions with a regiospecific deuterium incorporation of >90%. The ylide (4) was sufficiently pure for in situ Wittig condensation with p-chlorobenzaldehyde without its prior isolation.

$$\underset{(2)}{\mathrm{Ph_3\overset{+}{P}\text{-}\overset{-}{C}H\text{-}CO_2Et}} \xrightarrow[\mathrm{CH_2Cl_2}]{\mathrm{D_2O}} \underset{(6)}{\mathrm{Ph_3\overset{+}{P}\text{-}\overset{-}{C}D\text{-}CO_2Et}} \xrightarrow{\mathrm{H\text{-}C{\equiv}C\text{-}CO_2Et}} (4)$$

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REFERENCES AND NOTES

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4. Yields were not optimized.

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