



Reaction Between Trimethyl phosphite, Dimethyl Acetylenedicarboxylate and 1,3-Dicarbonyl Compounds: An Efficient Method for the Synthesis of Dimethoxyphosphoryl Succinic Acid Dimethoxy Ester Derivatives

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The addition of a phosphorus nucleophile to an acceptor such as alkyne, certainly represents one of the most versatile and powerful tools for the formation of P-C bonds. This offers the possibility to access many diversely functionalized products. In this article, the reaction between trimethyl phosphite and dimethyl acetylenedicarboxylate (DMAD) with 1,3-dicarbonyl compounds such as dimedone, acetyl acetone and diethyl malonate proceeds smoothly to produce stable dimethoxyphosphoryl succinic acid dimethyl ester derivatives (**4**), (**11**) and (**12**) in excellent yields.

Key Words: Phosphite, Acetylenedicarboxylate, Dimedone, Phosphoryl succinic acid dimethyl ester.

INTRODUCTION

Phosphorus compounds have emerged to be tremendously important for many different areas in chemistry and especially in organic synthesis¹. Interest in the preparation of organophosphorus compounds has continued to expand in recent years. This is a direct result of developing applications for phosphorus compounds in numerous synthetic procedures as well as an understanding of the role of the element in biological systems. The several classical efforts in regard to applications of organophosphorus compounds-the preparation of insecticides, agricultural chemicals, flame retardants, medicinal agents and reagents for olefination reactions- continue to be highly active topics in organophosphorus chemistry². Organophosphorus compounds are being used as versatile intermediates in synthetic chemistry³⁻⁵. Especially, the structure of compounds which a carbon atom is directly bound to a phosphorus atom, are synthetic target of interest, not least because of their value for a variety of industrial, or biological activity and are useful in chemical synthesis. The physical properties and chemical reactivity of phosphate esters interlinks many areas in chemistry and biology. Introduction of a phosphate monoester into a molecule such as a drug candidate enhances the water solubility, hence altering its bioavailability⁶⁻⁸. Thus, a large number of methods have indicated novel synthesis of organophosphorus compounds. There are many studies on the reaction between trivalent phosphorus nucleophiles and α,β -unsaturated carbonyl compounds in the presence of a proton

source such as alcohol, phenol⁹⁻¹¹ or NH-acids¹². Moreover it is reported the diastereoselective synthesis of *meso*-bisphosphonates in the presence of 4-nitrophenol¹³. We described herein the synthesis of a new series of dimethoxyphosphoryl succinic acid dimethoxy ester derivatives (**4**), (**11**) and (**12**) from the reaction of trimethyl phosphite and dimethyl acetylenedicarboxylate (DMAD) in the presence of 1,3-dicarbonyl compounds such as dimedone, acetyl acetone and diethyl malonate.

EXPERIMENTAL

Most of the chemical compounds were commercially available and were purchased from Merck company and used without further purification. Melting points were determined on an electrothermal 9100 apparatus. The IR spectra were recorded on a Shimadzu 470 spectrometer. ¹H NMR spectra were appropriately recorded on a BRUKER FT-80 spectrometer. Elemental analyses were performed by using a Heraeus CHN-O-rapid analyzer. Their results were found to agree favourably with the calculated values.

Preparation of compound (4), (11), (12): To a stirred solution of 1,3-dicarbonyl compound (2 mmol) in 20 mL diethyl ether was added 2 mL trimethyl phosphite (2 mmol) and 2 mL dimethyl acetylenedicarboxylate (2 mmol) dropwise over 15 min at -5 °C. The reaction mixture was allowed to room temperature and stirred for 48 h. The solvent was evaporated and the residue was crystallized from ethanol to produce the pure product.

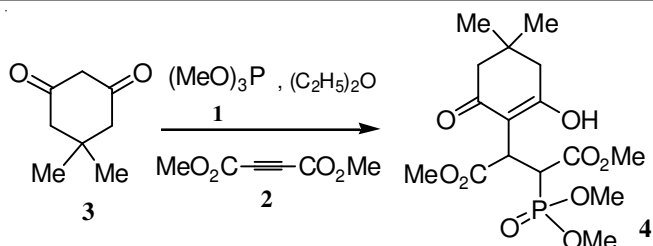
2-(Dimethoxy-phosphoryl)-3-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)succinic acid dimethyl ester (4): Whitecrystals, m.p. 171.3 °C, 0.73 g (91 % yield); Anal. calcd.: C, 46.83; H, 5.94. Found: C, 48.98; H, 6.42 %. IR (KBr, ν_{\max} , cm^{-1}): 3125-3450 (broad peak, OH), 1780 (C=O), 1630 (C=C), 1230 (P=O), 900 (POCH₃); ¹H NMR (80 MHz, CDCl₃): 1.09 (s, 6H, 2CH₃), 2.25 (m, 4H, 2CH₂), 3.59 (d, 3H, OCH₃(P(OCH₃))), 3.64 (s, 3H, OCH₃(COOCH₃)), 3.67 (s, 3H, OCH₃(COOCH₃)), 3.80 (d, 3H, OCH₃(P(OCH₃))), 4.00 (dd, 1H, ³J_{HH} = 9.00-12.00 Hz, ²J_{HP} ≈ 20 Hz, CH), 4.40 (dd, 1H, ³J_{HH} = 9.00-12.00 Hz, ³J_{HP} ≈ 10.00 Hz, CH) ppm.

2-(1-Acetyl-2-hydroxy-propenyl)-3-(dimethoxy-phosphoryl)succinic acid dimethyl ester (11): Orange crystals, m.p. 97 °C, 0.64 g (90 % yield); Anal. calcd.: C, 45.86; H, 6.18. Found: C, 44.32; H, 6.01 %. IR (KBr, ν_{\max} , cm^{-1}): 3370-3500 (broad peak, OH), 1720 (C=O), 1650 (C=C), 1259 (P=O), 850 (POCH₃); ¹H NMR (80 MHz, CDCl₃): 2.15 (s, 3H, CH₃), 2.25 (s, 3H, CH₃), 3.58 (s, 3H, OCH₃(P(OCH₃))), 3.59 (s, 3H, OCH₃(COOCH₃)), 3.70 (s, 3H, OCH₃(COOCH₃)), 3.80 (s, 3H, OCH₃(P(OCH₃))), 4.20 (dd, 1H, ³J_{HH} = 9.00-12.00 Hz, ²J_{HP} ≈ 20.00 Hz, CH), 4.80 (dd, 1H, ³J_{HH} = 9.00-12.00 Hz, ³J_{HP} ≈ 10.00 Hz, CH) ppm.

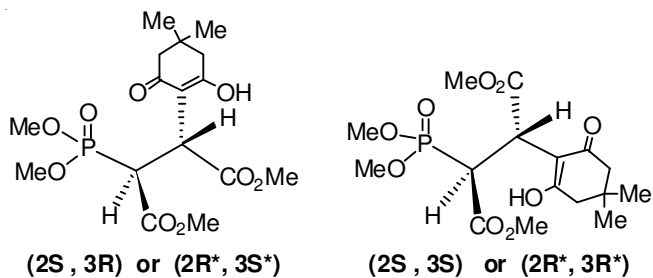
2-(1-Acetyl-2-ethoxy-2-hydroxy-vinyl)-3-(dimethoxy-phosphoryl)succinic acid dimethyl ester (12): Orange oil, 0.71 g (86 % yield); Anal. calcd.: C, 45.27; H, 6.38. Found: C, 44.97; H, 6.60 %. IR (KBr, ν_{\max} , cm^{-1}): 3300-3620 (broad peak, OH), 1729 (C=O), 1620 (C=C), 1248 (P=O), 781 (POCH₃); ¹H NMR (80 MHz, CDCl₃): 1.30 (t, 6H, 2CH₃), 3.35 (s, 6H, 2OCH₃(P(OCH₃))), 3.71 (s, 3H, OCH₃(COOCH₃)), 3.77 (s, 3H, OCH₃(COOCH₃)), 4.15 (q, 4H, 2CH₂), 4.40 (dd, 1H, ³J_{HH} = 9.00-12.00 Hz, ²J_{HP} ≈ 20 Hz, CH), 5.00 (dd, 1H, ³J_{HH} = 9.00-12.00 Hz, ³J_{HP} ≈ 10.00 Hz, CH) ppm.

RESULTS AND DISCUSSION

The reaction of trimethyl phosphite (1) and dimethyl acetylenedicarboxylate (2) in the presence of dimedone (3) as the proton source/nucleophile leads to 2-(dimethoxy-phosphoryl)-3-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)succinic acid dimethyl ester (4) in 91 % yields (Scheme-I). The reaction was completed by mixing diethyl ether with dimedone (3), then respectively trimethyl phosphite and dimethyl acetylenedicarboxylate (DMAD) were added slowly. The reaction was complete within 48 h. The structure of compound as 1:1:1 adducts was deduced from its elemental analyses, IR and ¹H NMR. The ¹H NMR spectrum of (4) in CDCl₃ exhibited two doublets recognized as arising for the two methoxy (δ = 3.59 and 3.80 ppm) groups. The two singlets at (δ = 3.64 and 3.67 ppm) belong to the ester methoxy protons. Observation of a doublet of doublet at (δ = 4.00 ppm, ³J_{HH} = 9.00-12.00 Hz, ²J_{HP} = 20.00 Hz) and (δ = 4.40 ppm, ³J_{HH} = 9.00-12.00 Hz, ³J_{HP} = 10.00 Hz) for the *vicinal* methine protons in (4), indicates the dominance of the *anti* arrangement. Since compound (4) possesses two stereogenic centers, two diastereomers with *anti* HCCH arrangement are possible (Scheme-II). Although we have not yet established the mechanism of the reaction between trimethyl phosphite and DMAD in the presence of dimedone in an experimental manner, a possible explanation is proposed in Scheme-III. On the basis of the



Scheme-I: Synthesis of 2-(dimethoxy-phosphoryl)-3-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)succinic acid dimethyl ester (4)



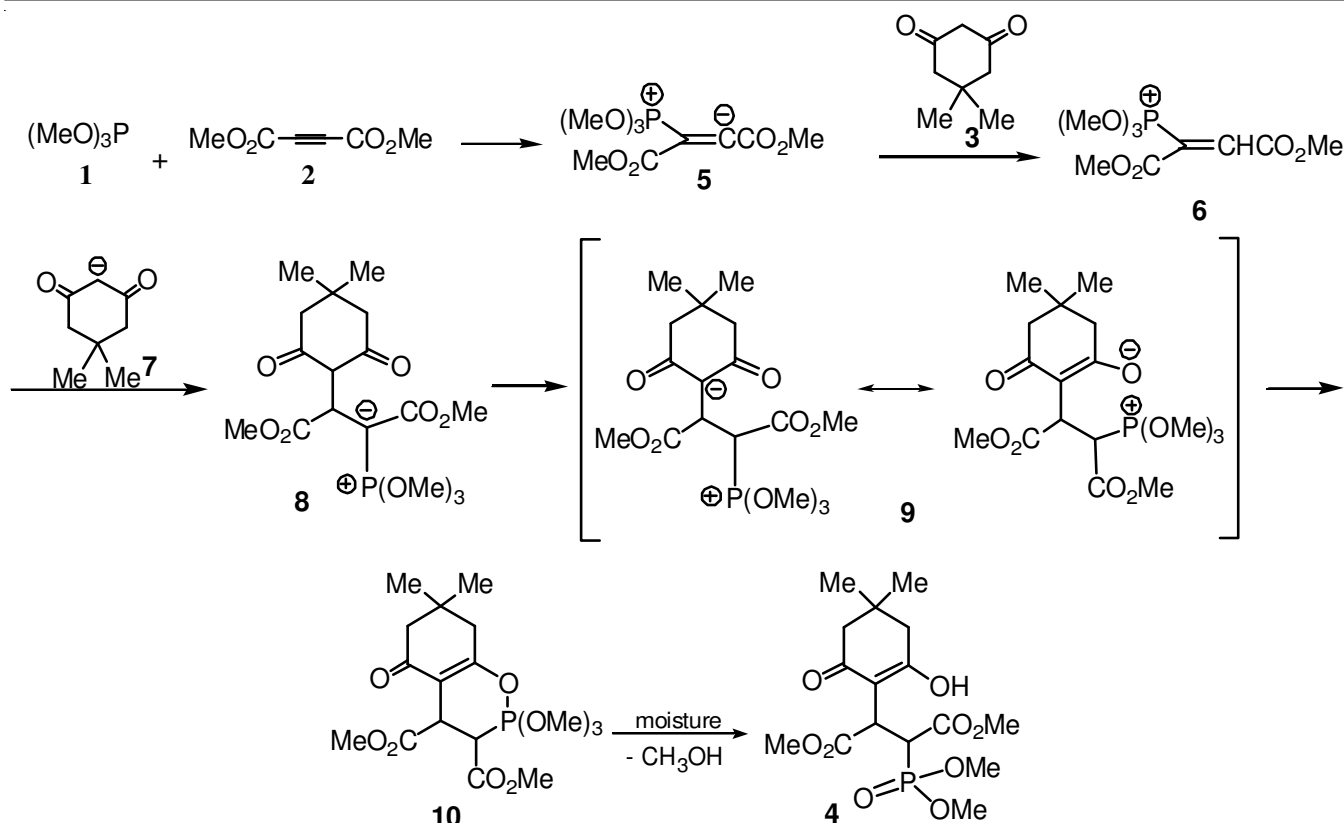
Scheme-II: Diastereomers of 2-(dimethoxy-phosphoryl)-3-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)succinic acid dimethyl ester (4)

well established chemistry of phosphorus nucleophiles^{4,5}, it is reasonable to assume that compounds (4) result from initial addition of trimethyl phosphite to the activated dimethyl acetylenedicarboxylate and subsequent protonation of the reactive 1:1 adduct by dimedone. Following on, the positively charged ion (6) is attacked by the anion of the 1,3-dicarbonyl ion (7) to produce compound (8) that is converted to compound (9). Then by attack of the oxygen atom of the anion to phosphorus cation, to generate compound (10), which is hydrolyzed to give compound (4). Since the reaction was carried out under an ordinary atmosphere, the conversion of compound (10) to (4) is presumably accomplished by the moisture from the air (Scheme-III). The reaction of trimethyl phosphite with DMAD in the presence of acetyl acetone and diethyl malonate gave (11) and (12) in high yields (Scheme-IV). Observation of ³J_{HH} = 9.00-12.00 Hz and ³J_{HH} = 9.00-12.00 Hz for the *vicinal* methine protons (11) and (12) compounds, show the dominance of the *anti* arrangement and (2S, 3R) or (2R, 3S) diastereoisomer respectively.

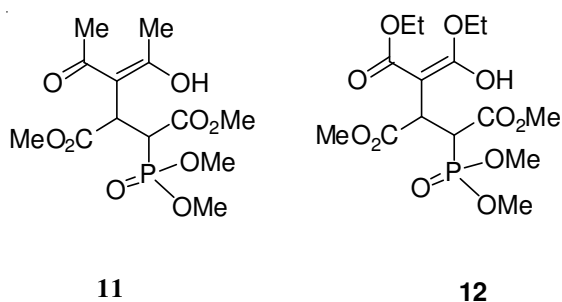
Finally, the reaction of trimethyl phosphite, dimethyl acetylenedicarboxylate (DMAD) and 1,3-dicarbonyl compounds such as dimedone, acetyl acetone and diethyl malonate provides a simple one-pot synthesis of stable dimethoxy-phosphoryl succinic acid dimethyl esters of potential synthetic and pharmaceutical interest. The present method carries the advantage that not only is the reaction performed under neutral conditions, but also the substances can be used without any activation or modification.

Conclusion

Dimethoxyphosphoryl succinic acid dimethoxy ester derivatives (4), (11) and (12) have been synthesized from the reaction of trimethyl phosphite, dimethyl acetylenedicarboxylate and 1,3-dicarbonyl compounds.



Scheme-III: A possible mechanism for synthesis of 2-(dimethoxy-phosphoryl)-3-(2-hydroxy-4,4-dimethyl-6-oxo-cyclohex-1-enyl)succinic acid dimethyl ester (4)



Scheme-IV: Structures of 2-(1-acetyl-2-hydroxy-propenyl)-3-(dimethoxy-phosphoryl)succinic acid dimethyl ester (11) and 2-(1-acetyl-2-ethoxy-2-hydroxy-vinyl)-3-(dimethoxy-phosphoryl)succinic acid dimethyl ester (12)

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