

SHORT
COMMUNICATIONS

Dimethyl 1-Hydroxy-3,7-dimethyl-2,6-octadienylphosphonate. Development of Synthetic Procedures

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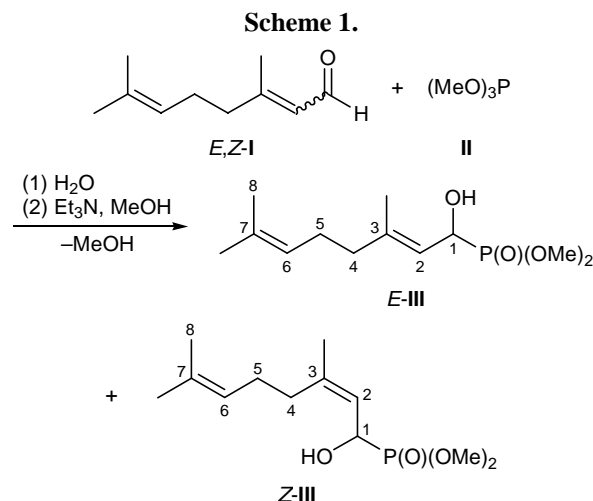
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With the goal of simulating phosphorylation of natural polyisoprenyl aldehydes which are promising low-molecular bioregulators [1–3], we examined reactions of citral (3,7-dimethyl-2,6-octadienal, a mixture of *E* and *Z* isomers) with trimethyl phosphite and dimethyl phosphonate in the presence of third-party reagents. We previously succeeded in reacting trimethyl phosphite with citral under fairly mild conditions (50°C, 1.5 h) in the presence of acid catalysts, e.g., acetic acid [4]. While developing methods of synthesis of unsaturated α -hydroxy phosphonates we tried to use other initiating agents. It is known that phosphorylation of lower aldehydes and ketones with neutral phosphites successfully occurs in the presence of an equimolar amount of water [5–7]. The behavior of dienals toward trialkyl phosphites in the presence in water remains unexplored. We examined the reaction of citral (**I**) with trimethyl phosphite (**II**) in the

presence of an equimolar amount of water. According to the ³¹P NMR data, under these conditions (~20°C) trimethyl phosphite undergoes hydrolysis to dimethyl phosphonate. Therefore, the same reaction was carried out following the Abramov version in the presence of a base catalyst. For this purpose, a dilute solution of triethylamine in ethanol was added to the reaction mixture, and the mixture was heated for 13.5 h at 60°C. As a result, we isolated dimethyl 1-hydroxy-3,7-dimethyl-2,6-octadienylphosphonate (**III**) as a mixture of *E* and *Z* isomers in an overall yield of 71% (Scheme 1); the physical constants and IR, ³¹P and ¹³C NMR, and mass spectra of the product were in agreement with the data reported in [4].

Taking into account that the formation of compound **III** in the above reaction involves intermediate conversion of **II** into dimethyl phosphonate (**IV**), we examined the reaction of **IV** with citral **I** in the presence of triethylamine at a reactant molar ratio of 4:2:8 in a dilute solution in methanol (Scheme 2). The reaction was complete in 16 h at 40–55°C, and phosphonate **III** was isolated in 88% yield.



By carrying out the reactions in a strongly dilute solution we succeeded in avoiding tarring and obtaining purer target product. Thus we have developed convenient procedures for the synthesis of 1-hydroxydienyl phosphonates in high yields, which provide a route to phosphorylated polyprenoids.

Dimethyl 1-hydroxy-3,7-dimethyl-2,6-octadienylphosphonate (III). *a.* Water, 0.5 g (27.8 mmol), was added dropwise to a mixture of 3.25 g (26.2 mmol) of phosphite **II** and 4.0 g (26.2 mmol) of citral (**I**) under stirring at $\sim 20^\circ\text{C}$ in a stream of dry argon. The mixture was stirred for 4 h at $\sim 20^\circ\text{C}$, a solution of 8.2 ml of triethylamine in 50 ml of methanol was added, and the mixture was stirred for 13.5 h at 60°C and evaporated under reduced pressure at 40°C (for 1 h at 0.5 mm and for 1 h at 0.02 mm). The residue was subjected to molecular film distillation at 165°C (0.03 mm) to isolate 4.9 g (71%) of phosphonate **III**, $n_D^{20} = 1.4855$; published data [4]: $n_D^{20} = 1.4850$. ^{31}P NMR spectrum, δ_P , ppm: 25.8 and 22.5 (intensity ratio $\sim 1:1$). Found, %: P 12.05. $\text{C}_{12}\text{H}_{23}\text{O}_4\text{P}$. Calculated, %: P 11.84.

b. A solution of 16.0 g (158.1 mmol) of triethylamine in 150 ml of anhydrous methanol was added dropwise to a mixture of 8.7 g (79.1 mmol) of dimethyl phosphonate (**IV**) and 6.0 g (39.4 mmol) of citral (**I**) under stirring at $\sim 20^\circ\text{C}$ in a stream of dry argon. The mixture was stirred for 16 h at $40\text{--}50^\circ\text{C}$ and evaporated under reduced pressure at 40°C (for 1 h at 0.5 mm and for 1 h at 0.03). Crude phosphonate **III**, 4.6 g (88%), was purified by molecular film distillation at 160°C (0.02 mm). Yield 2.4 g.

The IR spectra were recorded on a Bruker Vector-22 Fourier spectrometer from samples prepared as thin

films between KBr plates. The ^{31}P NMR spectra were obtained on a Bruker CXP-100 instrument (36.5 MHz, 85% H_3PO_4) from solutions in benzene. The ^{13}C NMR spectra (100.6 MHz) were measured on a Bruker MSL-400 spectrometer from solutions in CDCl_3 . The mass spectra were recorded on a Perkin-Elmer Turbo-mass Gold GC-MS system.

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