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ORIGINAL PAPER

Synthesis of functionalized 2,5-dihydro-1,2-oxaphospholes via one-pot three-component reaction

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Abstract An efficient one-pot synthesis of novel 2,5-dihydro-1,2-oxaphosphole derivatives via a three-component reaction of triphenyl phosphine, dialkyl acetylenedicarboxylates, and methyl (arylmethylidene) pyruvates has been reported. Carrying out the reaction in mild reaction conditions and synthesis of functionalized oxaphospholes are advantages of this approach.

Keywords 2,5-Dihydro-1,2-oxaphospholes · Methyl (arylmethylidene) pyruvate · One-pot three-component reaction · Pseudorotation

Introduction

Organophosphorus compounds are very important class of heterocyclic compounds widely used in organic synthesis [1–4], and they exhibit diverse interesting biological activities [5–10]. 1,2-Oxaphosphole derivatives are heterocyclic compounds which contain an O and a P atom in their molecules, with a variety of biological, industrial, and synthetic uses [11]. A large number of methods have been published describing novel syntheses of organophosphorus compounds [12–15]. Yavari et al. [16–21] reported that the reaction of triphenylphosphine with activated acetylenic compounds in the presence of ketones to access the corresponding oxaphospholes. Esmaeili et al. [22] used isatin for the synthesis of spirooxaphospholes. Recently, Zhu and co-workers reported the preparation of fluorinated oxaphospholes using aryl or styryl trifluoromethyl ketones [23]. The selection of the starting material has an essential role in this reaction. Methyl (arylmethylidene) pyruvates with three functional groups could be used as suitable starting materials in organic synthesis. They play an important role as an attractive starting material for the following reasons: (a) They have higher reactivity in comparison with usual β,γ-unsaturated α-ketones; (b) they contain active functional groups which can be used for further synthesis; and (c) their preparation is easy [24, 25].

As a part of our current studies on the development of new routes in synthesis of heterocycles via one-pot MCRs based on methyl (arylmethylidene) pyruvates [26–28], we report here a three-component reaction of triphenylphosphine **1**, dialkyl acetylenedicarboxylates **2,** and methyl (arylmethylidene) pyruvates **3** for the synthesis of polyfunctionalized 2,5-dihydro-1,2-oxaphospholes **4** at room temperature (Scheme 1).

Results and discussions

Recently, we have focused our research and development efforts on the preparation of new compound libraries containing biologically active heterocyclic skeletons. In this way, methyl (arylmethylidene) pyruvates **3** have been used as suitable starting materials. Existence of an active alkene in the structure of methyl (arylmethylidene)

Dedicated to Prof. M. Shamsipur on the occasion of his 65th birthday.

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Scheme 1 Synthesis of polyfunctional 2,5-dihydro-1,2-oxaphospholes via three-component reaction

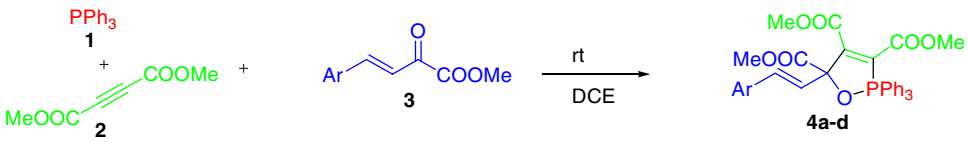
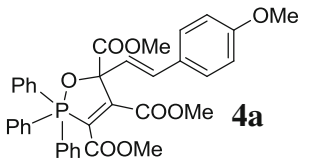
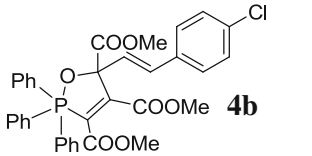
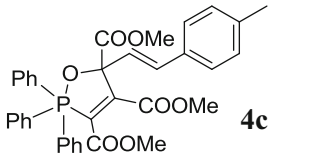
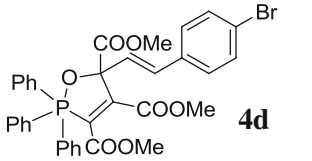


Table 1 Synthesis of 2,5-dihydro-1,2-oxaphosphole **4a–d** via three-component reaction

Entry	R	Ar	Product 4	Yield[a] (%)
1	Me	4-MeO–C_6H_4	 **4a**	67
2	Me	4-Cl–C_6H_4	 **4b**	77
3	Me	4-Me–C_6H_4	 **4c**	72
4	Me	4-Br–C_6H_4	 **4d**	82

Reaction conditions: 1.2 mmol **2**, 1.2 mmol PPh_3, 1 mmol methyl (arylmethylidene) pyruvate, 10 ml $C_2H_4Cl_2$, 5 h

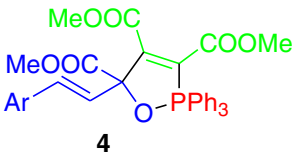
[a] Yield of isolated product

pyruvates could candidate them for the synthesis of complex molecules. Meanwhile, the molecule has additional ketone group which able to participate in further cyclization. They can be synthesized according to the known procedure by the reaction of aromatic aldehydes and pyruvic acid in an aqueous methanol solution in the presence of KOH [24].

We began our investigation with methyl (4-bromophenyl methylidene) pyruvate **3d**; its reaction with triphenylphosphine and dimethyl acetylenedicarboxylate in dichloroethane at room temperature was selected as the model reaction. The product was the desired oxaphosphole **4d** with 82 % yield.

The reaction was checked at different temperatures, increasing the temperature led to a mixture of products. The best yield was obtained at room temperature. Meanwhile, the ratio of reactants was optimized. The optimized mole ratios of the reactants are consistent with the 1.2:1.2:1 adducts of triphenylphosphine, dialkyl acetylenedicarboxylate, and methyl (arylmethylidene) pyruvates. The model reaction was checked in ethanol, methanol, dichloromethane, and THF. In all cases, the yields of product **4d** were between 45 and 55 %.

Typically, the reaction of dialkyl acetylenedicarboxylate with triphenylphosphine in the presence of methyl (arylmethylidene) pyruvates proceeded spontaneously at room temperature in dichloroethane and was completed within 5 h at room temperature. The results are summarized in Table 1. Our investigation showed that the existence of bromine substituent on the aromatic ring in methyl (arylmethylidene) pyruvates increases the yield of product.



4

The structures of the products **4a–d** were deduced from their HRMS (ESI) spectra and NMR spectroscopic data. The distinguished peak in the ^{1}H-NMR spectra of the products was indicated by two doublet signals at δ 6.70–6.90 ppm for the olefinic *trans* H-atoms with $J = 15.9$ Hz, and the methoxy groups resonated at δ 3.81–4.29 ppm. The ^{13}C-NMR spectra of **4d** showed a distinguished peak at δ 83.4 ppm, and the C=O groups appeared at δ 161.3, 165.2, 167.0 ppm. In ^{31}P-NMR data, a distinguished peak was shown at δ +30.49 ppm. Meanwhile, the structure of **4d** was confirmed by the X-ray crystallographic data. (Fig. 1).

Pseudorotation is a known property in some stable oxyphosphoranes, and the contribution of the conformational transmission effect has essential role in the barrier of pseudorotation in monocyclic oxyphosphoranes [29, 30]. In the synthesized compounds **4a-d**, existence of three phenyl groups and also three methyl ester groups could affect the pseudorotation in these compounds. In compounds **4a-d**, it is important to notice that the P atom is placed in the center of a trigonal bipyramidal ring and three aromatic groups, which are joined to it change their position frequently because of the berry pseudorotation in pentacoordinated phosphorus compounds, the aromatic picks are broad.

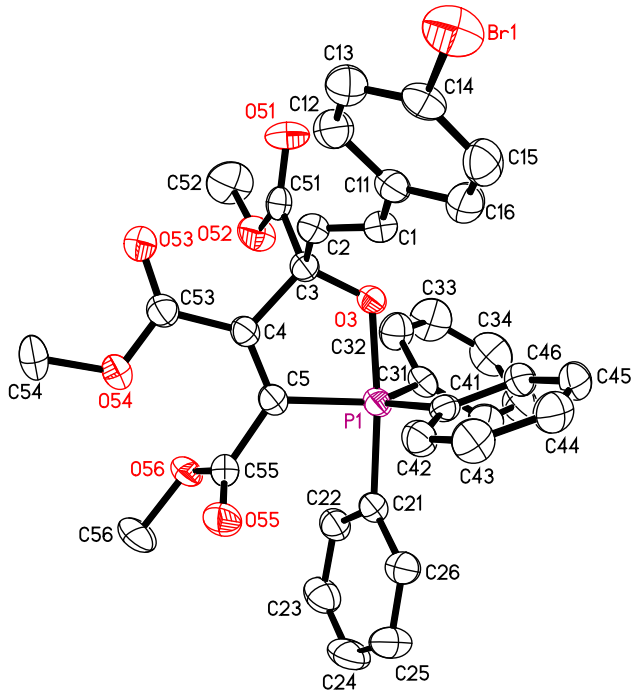


Fig. 1 ORTEP structure of compound **4d**

Mechanistically, it is conceivable that the reaction involves the initial formation of a 1,3-dipolar intermediate **A** which could be formed through reaction of triphenylphosphine and dialkyl acetylenedicarboxylate, and then it reacts with carbonyl group of methyl (arylmethylidene) pyruvates **3.** Cyclization of the zwitterionic intermediate **B** leads to the 2,5-dihydro-1,2-oxaphospholes. A tentative mechanism for this transformation is proposed in Scheme 2. Cyclization of this zwitterionic intermediate **B** leads to the 2,5-dihydro-1,2-oxaphospholes tricarboxylate **4a-d**.

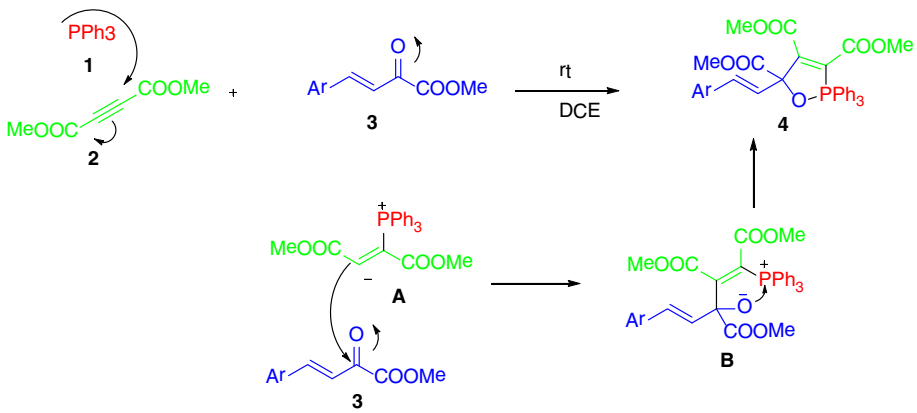
The formation of the products **4a-d** could be categorized as domino reactions. The reaction could proceed via a domino zwitterion formation/nucleophilic addition/cyclization reaction sequence. To the best of our knowledge, this is the first report for the synthesis of oxaphospholes using methyl (arylmethylidene) pyruvates. The present procedure has the advantage that the reaction is performed under neutral conditions and at room temperature, and the products have other active functional groups which could be used for further reactions.

Conclusions

In conclusion, an efficient approach for the one-pot synthesis of 2,5-dihydro-1,2-oxaphospholes via three-component reaction of dialkyl acetylenedicarboxylate, methyl (arylmethylidene) pyruvates and triphenylphosphine has been developed. Notably, high bond-forming efficiency, good to high yields, synthesis of polyfunctional compounds, carrying out the reaction at room temperature, and easy workup are advantages of this approach.

Experimental section

All solvents were anhydrous grade, unless otherwise noted. Starting materials were purchased from commercial suppliers and used without further purification, unless otherwise noted. Melting points were determined on an Electrothermal 9100 apparatus. Infrared spectra were recorded on an ABB FT-IR FTLA 2000 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were run on Bruker DRX-500 AVANCE and Bruker DRX-300 AVANCE spectrometer at 500 and 300 MHz for ^{1}H-NMR, and 125 and 75 MHz for ^{13}C-NMR, respectively. Chemical shifts are reported in ppm, relative to internal solvent peaks. Coupling constants *J* are reported in Hz. HR-ESI MS were obtained on a Bruker APEX-Qe ESI FT-ICR instrument.



Scheme 2 Proposed mechanism for the synthesis 2,5-dihydro-1,2-oxaphosphole

General procedure for the synthesis of 2,5-dihydro-1,2-oxaphospholes **4a–d**

To a stirred solution of dialkyl acetylenedicarboxylate (1.2 mmol) and methyl (arylmethylidene) pyruvates (1 mmol) in 1,2-dichloroethane (10 ml) was added dropwisely a solution of Ph_3P (1.2 mmol) at room temperature and the mixture was stirred for 5 h. The progress of reaction was monitored by TLC (eluent hexane/ethyl acetate 3:1). The solvent was removed under reduced pressure, and produced oil which was purified by prep TLC plates (Eluent hexane/ethyl acetate 3:1). Further purification was done by recrystallization in diethylether.

3,4-Dimethyl(*E*)-5-(4-methoxystyryl)-5-methyl-2,2,2-triphenyl-2,5-dihydro-1,2-oxaphosphole-3,4,5 tricarboxylate (**4a**)

0.418 g, 67 %, as a yellow oil. Rf (20 %AcOEt/hexane) 0.55. IR(neat): 1,786, 1,653, 1,600.^{1}H-NMR(500 MHz, $CDCl_3$): 3.80 (6H, *s*, MeO); 3.84 (3H, *s*, MeO); 4.29 (3H, *s*, MeO); 6.60 (1H, d, *J* 16.1 Hz, = CH); 6.69 (1H, *d*, $J = 16.1$, =CH); 6.86 (2H, *d*, $J = 8.7$, Ar); 7.35 (2H, *d*, $J = 8.7$, Ar); 6.86–7.68 (15H, *m*, Ar); ^{13}C-NMR(125 MHz, $CDCl_3$): 52.5 (MeO), 53.7 (MeO), 55.3 (MeO), 60.0 (MeO), 83.7, 114.0 (*d*, $^2J_{CP} = 26.7$, C_o of Ph_3P), 114.1, 119.4, 122.9, 125.3 (P–Ph), 127.8 (P–Ph), 128.1 (*d*, $^4J_{CP} = 6.3$, C_P of PPh_3), 128.4, 128.5 (d, $^3JCP = 14.4$, C*m* of Ph_3P), 128.6 (*d*, $^3J_{CP} = 12.5$, C*m* of Ph_3P), 131.8, 132.0 (*d*, $^3J_{CP} = 10.1$, C_m of Ph_3P),132.1, 132.2 (*d*, $^4J_{CP} = 2.5$, C_P of PPh_3), 147.7, 160.6, 161.4 (O=C–O), 165.4 (O=C–O), 167.3 (O=C–O); ^{31}P–NMR(121 MHz, $CDCl_3$): + 30.98. HRMS (ESI): $[M+H]^+$ found 625.19969. $C_{36}H_{34}O_8P$ requires 625.19987.

3,4-Dimethyl(*E*)-5-(4-chlorostyryl)-5-methyl-2,2,2-triphenyl-2,5-dihydro-1,2-oxaphosphole-3,4,5tricarboxylate (**4b**)

0.478 g, 76.6 %, as a yellow oil. Rf (20 % AcOEt/hexane) 0.47. IR (neat): 1,789, 1,751, 1,655. ^{1}H-NMR(500 MHz, $CDCl_3$): 3.80 (6H, *s*, MeO); 3.84 (3H, *s*, MeO); 4.28 (3H, *s*, MeO); 6.60 (1H, *d*, $J = 16.1$, =CH); 6.69 (1H, *d*, $J = 16.1$, =CH); 7.28 (2H, *d*, $J = 8.4$, Ar); 7.33 (2H, *d*, $J = 8.4$, Ar); 7.28–7.67 (15H, *m*, Ar). ^{13}C-NMR(125 MHz, $CDCl_3$): 52.5 (MeO), 53.9 (MeO), 60.0 (MeO), 83.4, 122.6, 125.5, 128.2, 128.3, 128.5 (*d*, $^2J_{CP} = 12.0$, C*o* of Ph_3P), 128.8, 128.9, 130.8, 132.1 (*d*, $^3J_{CP} = 9.8$, C_m of Ph_3P), 133.8 (*d*, $^1J_{CP} = 53.9$, C_{ipso} of PPh_3), 147.7, 161.3 (O=C–O), 165.2 (O=C–O), 167.0 (O=C–O). ^{31}P-NMR(121 MHz, $CDCl_3$): + 29.91. HRMS (ESI): $[M+H]^+$ found 629.15119. $C_{35}H_{31}^{35}ClO_7P$ requires 629.15153, $[M+H]^+$ found 631.14799. $C_{35}H_{31}^{37}ClO_7P$ requires 631.14829.

3,4,Dimethyl(*E*)-5-(4-methylstyryl)-5-methyl-2,2,2-triphenyl-2,5-dihydro-1,2-oxaphosphole-3,4,5tricarboxylate (**4c**)

0.438 g, 72 %, as a yellow oil; Rf (20 % AcOEt/hexane) 0.50. IR(neat): 1,792, 1,751, 1,653. ^{1}H-NMR(300 MHz, $CDCl_3$): 2.33 (3H, *s*, Me); 3.80 (3H, *s*, MeO); 3.84(3H, *s*, MeO); 4.29 (3H, *s*, MeO); 6.71 (2H, *s*, =CH); 7.13 (2H, *d*, $J = 8.0$, Ar); 7.27 (2H, *d*, $J = 8.0$, Ar); 7.13–7.32 (15H, *m*, Ar). ^{13}C-NMR(75 MHz, $CDCl_3$): 21.3 (Me), 52.5 (MeO), 53.7(MeO), 60.1 (MeO), 83.7, 120.7, 122.8, 127.0, 128.5 (*d*, $^2J_{CP} = 20.1$, C_o of PPh_3), 129.4, 132.0 (*d*, $^3J_{CP} = 16.2$, C_m of PPh_3), 132.1, 132.3 (*d*, $^3J_{CP} = 12.5$, C_m of PPh_3), 132.6, 138.7, 147.7, 161.4 (O=C–O), 165.4 (O=C–O), 167.3 (O=C–O). ^{31}P-NMR(121 MHz, $CDCl_3$): + 30.22. HRMS (ESI): $[M+H]^+$ found 609.20364. $C_{36}H_{34}O_7P$ requires 609.

3,4,Dimethyl(*E*)-5-(4-bromostyryl)-5-methyl-2,2,2-triphenyl-2,5-dihydro-1,2-oxaphosphole-3,4,5tricarboxylate (**4d**)

0.551 g, 82 %, as a colorless crystal.m.p 155–160 °C. Rf(20 %AcOEt/hexane) 0.43. IR(neat): 1,791, 1,655. ^{1}H-NMR(300 MHz, $CDCl_3$): 3.81 (3H, *s*, MeO); 3.85 (3H, *s*, MeO); 4.29 (3H, *s*, MeO); 6.68 (1H, *d*, $J = 15.9$, = CH); 6.75 (1H, *d*, $J = 15.9$, =CH); 7.27 (2H, *d*, $J = 7.2$, Ar); 7.44 (2H, *d*, $J = 7.2$, Ar); 7.30–7.90 (15H, *m*, Ar). ^{13}C-NMR(75 MHz, $CDCl_3$): 52.6 (MeO), 53.8 (MeO), 60.1 (MeO), 83.4, 122.5, 122.6, 122.7, 127.5 (*d*, $^2J_{CP} = 21.0$, C_o of PPh_3), 128.6, 130.8, 131.4 (*d*, $^3J_{CP} = 14.6$, C_m of PPh_3), 131.8, 132.0 (*d*, $^1J_{CP} = 71.6$, C_{ipso} of PPh_3), 134.3, 147.7, 161.3 (O=C–O), 165.2 (O=C–O), 167.0 (O=C–O). ^{31}P-NMR (121 MHz, $CDCl_3$): +30.49. HRMS (ESI): $[M+H]^+$ found 673.09864. $C_{35}H_{31}^{79}BrO_7P$ requires 673.09866, $[M+H]^+$ found 675.09704. $C_{35}H_{31}^{81}BrO_7P$ requires 675.09712.

Colorless crystal (polyhedron), dimensions $0.34 \times 0.11 \times 0.04$ mm^3, crystal system triclinic, space group $P\bar{1}$, $Z = 4$, $a = 8.7881(7)$ Å, $b = 18.3827(15)$ Å, $c = 20.7030(17)$ Å, $\alpha = 108.300(2)$ deg, $\beta = 90.223(2)$ deg, $\gamma = 101.620(2)$ deg, $V = 3{,}102.2(4)$ Å^3, $\rho = 1.442$ g/cm^3, $T = 200(2)$ K, $\theta_{max} = 24.01$ deg, radiation Mo Kalpha, $\lambda = 0.71073$ Å, 0.5 deg MeOga-scans with CCD area detector, covering the asymmetric unit in reciprocal space with a mean redundancy of 4.5, and a completeness of 97.7 % to a resolution of 0.95 Å, 37471 reflections measured, 8,174 unique (R(int) = 0.0333), 6,451 observed [$I > 2\sigma(I)$], intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS [31] based on the Laue symmetry of the reciprocal space, $\mu = 1.43$ mm^{-1}, $T_{min} = 0.65$, $T_{max} = 0.94$, structure solved by direct methods and

refined against F^2 with a full-matrix least-squares algorithm using the SHELXTL (version 2008/4) software package [32], 815 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.03 for observed reflections, final residual values $R1(F) = 0.042$, $wR(F^2) = 0.094$ for observed reflections, residual electron density -0.59 to $0.77\ e\text{Å}^{-3}$. CCDC 911088 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting information

Supplementary data associated with this article including full experimental detail, ^1H and ^{13}C spectra can be found via the "Supplementary Content" section of this article's webpage.

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