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Three-component Synthesis and Characterization of New Stabilized Phosphorus Ylides

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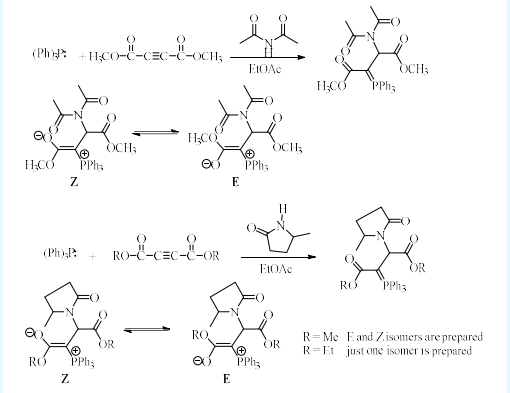
Abstract: New stabilized phosphoranes were obtained from the equimolar ratio of -NH acids, dialkyl acetylenedicarboxylates and triphenylphosphine. The reaction was carried out in ethyl acetate at room temperature and accomplished after an hour. The reaction of 5-methyl-2-pyrolidone and *N,N*-dimethylacetamide with dimethyl acetylenedicarboxylate in the presence of triphenylphosphine led to the Z and E regioisomeric products, while the reaction of 5-methyl-2-pyrolidone with diethyl acetylenedicarboxyle provided the corresponding phosphorane as the sole product.



Keywords: Phosphorus ylides, Dialkyl acetylenedicarboxylates, 5-Methyl-2-pyrrolidone, Dimethyl-*N,N*-diacetamide, Ph_3P.

1. Introduction

Phosphorus ylides are 1,2-dipolar compounds with a negative charge on the carbon atom which, is stabilized by the neighboring phosphonium moiety.[1] Three main methods have been developed for the synthesis of phosphorus ylides; a) deprotonation of phosphonium salts; b) three-component reaction of phosphines, dialkyl acetylenedicarboxylates and organic nucleophiles; and c) other methods such as transylidation reactions. The versatile reactivity of phosphorus ylides enables their use as starting precursors for the synthesis of many important organic compounds, such as natural substrates,[2] and biological and medicinally active compounds. [3] Stabilized phosphorus ylides are different from nonstabilized ylides, since they can be easily handled due to the additional stabilization created from delocalization of the negative charge. The synthesis and application of stabilized phosphorus ylides have been widely studied.[4,5] There are many investigations about the reaction between triphenylphosphine, acetylenic esters and -NH acids for the synthesis of many important organic compounds.[4,5] Treatment of some -NH acids such as *N*-aminophthalimide,[6] 2-acetylpyrrole,[7] hydantoin,[8] *N*-methylurea,[9] arylsulfonamides,[10] 6-azauracil[11] and carbendazim[12] with 1:1 triphenylphosphine-dialkyl acetylenedicarboxylate adducts have provided new stabilized phosphorus ylides. In recent years, the synthesis of phosphorus ylides has been developed from the reaction of acetylenic esters with a phosphine compound in the presence of a proton source such as C–H groups.[13,14] In some cases, the ylide product is not stable and cannot be isolated, so it acts as an intermediate and due to the reactions, the related product is observed.[15] Esmaili *et al.* investigated the reaction of triphenylphosphine, dialkyl acetylenedicarboxylate and 2-aminothiophenol. Reaction of dimethyl and diethyl acetylenedicarboxylate provided the desired ylide product. Nevertheless, the reaction of isopropyl and *tert*-butyl acetylenedicarboxylate leads to 1,4-benzothiazine derivative and triphenylphosphine is recovered unreacted.[16]

Stabilized phosphorus ylides also take part in important organic reactions as catalyst and ligand.[17] Recently, the *N,N*-diethylacetamide derived phosphorane was reported as an organocatalyst for cyanosilylation of ketones using TMSCN.[18] The use of a class of the cyclopalladated benzo[h]quinolinate mixed with phosphonium-phosphine ylides as a catalyst in Suzuki coupling reaction has been

evaluated. This mixed new complex has shown efficient catalytic applications.[19] Zakarianezhad *et al.* investigated the mechanism of the reaction between triphenylphosphine and dialkyl acetylenedicarboxylate in the presence of NH-acid, such as benzotriazole[20] and 2-mercapto thiazoline[21] based on the quantum mechanical calculations. Herein, we are going to introduce three new stabilized phosphorus ylides. The reaction of two amides, i.e.,5-methyl-2-pyrrolidone and dimethyl-*N,N*-diacetamide with dialkyl acetylenedicarboxylates in the presence of triphenylphosphine was evaluated.

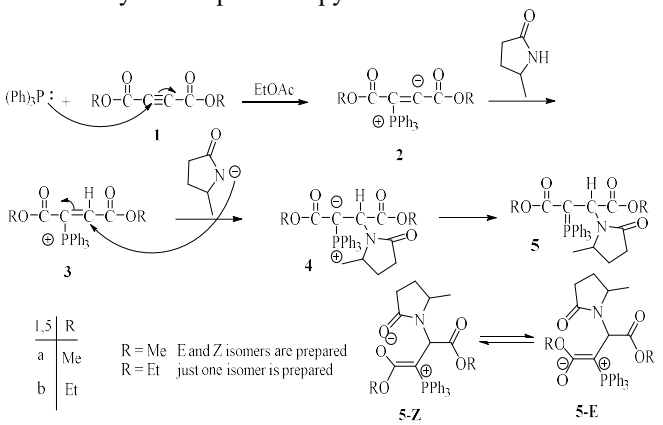
2. Results and Discussion

In this study, the reaction of amide derivatives with Ph_3P and dialkyl acetylenedicarboxylates were evaluated. At first, the treatment of 5-methyl-2-pyrrolidone with Ph_3P and dimethyl acetylenedicarboxylates was investigated. The reaction proceeded well at room temperature in ethyl acetate and was complete after one hour. The structures of the products were deduced from their elemental analyses, IR, ^1H, ^{31}P and ^{13}C NMR spectra. The ^1H and ^{13}C NMR spectra of the product clearly indicated the formation of phosphorane and were consistent with the presence of two geometric isomers (Scheme 1). Assignment of configuration (Z) to the minor geometrical isomer is based on the ^1H chemical shift of the OR moiety, which is expected to be shielded as a result of the anisotropic effect of the phenyl groups.

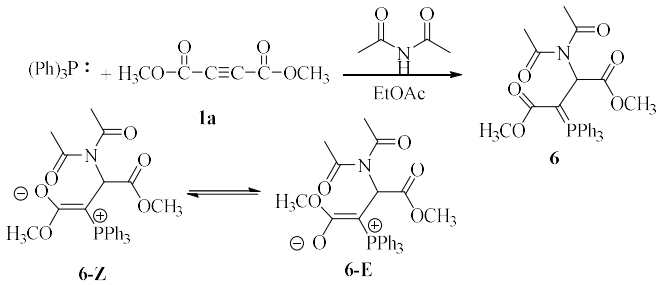
Then the reaction of 5-methyl-2-pyrrolidone and diethyl acetylenedicarboxylates in the presence of Ph_3P was investigated. Here again the reaction was carried out at room temperature in ethyl acetate and was completed within one hour. The structure of the product was identified from its elemental analyses, IR, ^1H, ^{31}P and ^{13}C NMR spectra. The reaction of 5-methyl-2-pyrrolidone with diethyl acetylene dicarboxylate in the presence of Ph_3P resulted in the corresponding phosphorene as the sole product, and no regioisomeric products were observed (Scheme 1).

The reaction of dimethyl-*N,N*-diacetamide with dimethyl acetylenedicarboxylates and Ph_3P was also studied. This reaction was also carried out at room temperature in ethyl acetate for one hour. The structure of the product was determined using IR and NMR spectroscopic methods of elemental analysis. Here again Z and E regioisomers were obtained (Scheme 2).

The first step of the reaction is the Michael addition reaction of triphenylphosphine to dialkyl acetylenedicarboxylates **1** and formation of the intermediate ۲ and subsequent protonation of the highly reactive 1:1 adduct by acidic hydrogen attached to cyclic nitrogen atom and formation of vinyl triphenylphosphonium cation ۳ followed by attack of heterocyclic nitrogen anion of 5-methyl-2-pyrrolidone on the vinyl triphenylphosphonium cation to form the phosphorane ٤. The ylide moiety of the phosphorane is strongly conjugated with the adjacent carbonyl group, therefore the product exists as two regioisomers. Rotation about the partial double bond in E and Z geometrical isomers is slow on the NMR timescale at ambient temperature, so the existence of the product can be observed by NMR spectroscopy.



Scheme 1. Synthesis and mechanism of the formation of dimethyl 2-(2-methyl-5-oxopyrrolidin-1-yl)-3-(triphenylphosphoranylidene)succinate



Scheme 2. Formation of dimethyl 2-(*N,N*-diacetamide-1-yl)-3-(triphenylphosphoranylidene)succinate

3. Experimental

Chemicals were purchased from Fluka and Merck Chemical Companies. Melting points (m.p.) were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Testcan shimodzu FTIR8000. ^1H and ^{13}C NMR spectra were measured with a BRUKER DRX 400 AVAVCE at 400 and 100 MHz, respectively. Elemental analyses were obtained using ThermoFinnigan Flash EA 1112 Series.

Synthesis of dimethyl 2-(2-methyl-5-oxopyrrolidin-1-yl)-3-(triphenylphosphoranylidene)succinate:

To a magnetically stirred solution of Ph_3P (0.26 g, 1 mmol) and 5-methyl-2-pyrrolidone (96.72 µL, 1 mmol) in EtOAc (4 mL), a solution of dimethyl acetylenedicarboxylate (122.5 µL,1 mmol) in EtOAc (1 mL) was added dropwise at -10 ºC during 10 min. Then, the mixture was allowed to

warm up to room temperature and the mixture was stirred for an hour. The product was precipitated. The precipitate was filtered under vacuum and several times was washed with cold ether (2-3 mL). The product was obtained as a white pure solid.

Dimethyl 2-(2-methyl-5-oxopyrrolidin-1-yl)-3-(triphenylphosphoranylidene)succinate 5a

White solid; m.p. 198-200 ºC; yield 0.49 g, 99%; IR (neat) (ν_{max}, cm^{-1}): 3058, 2947, 1744, 1661; Anal. Calcd. for ($C_{29}H_{30}NPO_5$): C, 69.17; H, 6.00; N, 2.78; Found: C, 69.10; H, 6.06; N, 2.73%.

Minor isomer (Z)-**5a** (43%), ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.85-2.15 (m, 2H, O-C-$\underline{CH_2}$) 2.17-2.42 (m, 2H, N-C-$\underline{CH_2}$), 3.١٣ and 3.٥٦ (6H, 2s, 2OCH_3); 3.67-3.82 (m, 4H, N-$\underline{CHCH_3}$), 4.72 (d, $^2J_{H\text{-}P}$ = 17.2 Hz, 1H, P-C-$\underline{CH}$), 7.51-7.72 (m, 15H, 3 C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 18.42 (s, N-C-$\underline{CH_2}$), 31.43 (s, CO-$\underline{CH_2}$), 40.96 (d, $^1J_{C\text{-}P}$ = 134 Hz, $\underline{C}$=P) 44.83 (s, $\underline{CH}CH_3$), 42.97 and 52.16 (2s, 2O$\underline{CH_3}$), 54.29 (d, $^2J_{C\text{-}P}$ = 17.0 Hz, P-C-$\underline{CH}$), 126.84 (d, $^1J_{C\text{-}P}$ = 91.52 Hz, C_{ipso}), 128.93 (d, $^3J_{C\text{-}P}$ = 12.0 Hz, C_{meta}), 132.20 (d, $^4J_{C\text{-}P}$ = 2.0 Hz, C_{para}), 133.60 (d, $^2J_{C\text{-}P}$ = 4.0 Hz, C_{ortho}), 169.86 (d, $^3J_{C\text{-}P}$ = 13.0 Hz, C=O ester), 172.56 (d, $^2J_{C\text{-}P}$ = 13.0 Hz, C=O ester), 174.01 (s, C=O amide); ^{31}P NMR(300 MHz, $CDCl_3$) δH: 23.94.

Major isomer (E)-**5a** (56%), ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.85-2.15 (m, 2H, O-C-$\underline{CH_2}$) 2.17-2.42 (m, 2H, N-C-$\underline{CH_2}$), 3.١٣ and 3.٥٦ (6H, 2s, 2OCH_3); 4.75 (d, $^2J_{H\text{-}P}$ = 18.8 Hz, 1H, P-C-$\underline{CH}$), 3.674-3.82 (m, 4H, N-$\underline{CHCH_3}$), 7.51-7.72 (m, 15H, 3 C_6H_5); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 18.42 (s, N-C-$\underline{CH_2}$), 31.43 (s, CO-$\underline{CH_2}$), 40.96 (d, $^1J_{C\text{-}P}$ = 134 Hz, $\underline{C}$=P), 44.44 (s, $\underline{CH}CH_3$) 44.83 (s, $CH\underline{CH_3}$), 42.97 and 52.16 (2s, 2O$\underline{CH_3}$), 53.85 (d, $^2J_{C\text{-}P}$ = 17.0 Hz, P-C-$\underline{CH}$), 126.84 (d, $^1J_{C\text{-}P}$ = 91.52 Hz, C_{ipso}), 128.93 (d, $^3J_{C\text{-}P}$ = 12.0 Hz, C_{meta}), 132.20 (d, $^4J_{C\text{-}P}$ = 2.0 Hz, C_{para}), 133.60 (d, $^2J_{C\text{-}P}$ = 4.0 Hz, C_{ortho}), 170.76 (d, $^3J_{C\text{-}P}$ = 18.0 Hz, C=O ester), 172.49 (d, $^2J_{C\text{-}P}$ = 13.0 Hz, C=O ester), 174.01 (s, C=O amide); ^{31}P NMR(400 MHz, $CDCl_3$) δH: 24.27.

Diethyl 2-(2-methyl-5-oxopyrrolidin-1-yl)-3-(triphenylphosphoranylidene)succinate 5b

White solid; m.p. 214-216ºC; yield 0.50 g, 95%; IR (neat) (ν_{max}, cm^{-1}): 3053, 2970, 1738, 1682; Anal. Calcd. for ($C_{31}H_{34}NPO_5$): C, 70.04; H, 6.44; N, 2.63; Found: C, 70.10; H, 6.46; N, 2.73%.

Only one rotamer **5b**, ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: ٠,٣٧ (s, 3H, CH_3), 1.23 (t, $^3J_{HH}$ = 6 Hz, 6H, 2O-C-$\underline{CH_3}$), 1.79-2.0 (m, 2H, CH_2), 2.09-2.25 (m, 2H, CH_2), 3.58-3.64 (m, 1H, CH), 3.82-4.09 (m, 4H, 2OCH_2), 4.61 (d, $^3J_{HP}$ = 18 Hz, 1H, CH), 7.41-7.61 (m, 15H, 3 C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 13.97 ($\underline{CH_3}$), 14.27 (2$OCH_2\underline{CH_3}$), 18.4 ($\underline{CH_2}$), 31.3 ($\underline{CH}CH_3$), 44.8 ($\underline{CH_2}$), 60.8 ($O\underline{CH_2}CH_3$), 127.1 (d, $^1J_{C\text{-}P}$ = 91.52 Hz, C_{ipso}), 128.77 (d, $^3J_{C\text{-}P}$ = 12.25 Hz, C_{meta}), 132.1 (d, $^4J_{C\text{-}P}$ = 2.79 Hz, C_{para}), 133.59 (d, $^2J_{C\text{-}P}$ = 9.83 Hz, C_{ortho}), 169.5 (C=O amide), 171.82 (d, $^3J_{C\text{-}P}$ = 12.93 Hz, C=O ester), 173.94 (s, C=O ester); ^{31}P NMR(300 MHz, $CDCl_3$) δH: 24.27.

Dimethyl 2-(*N*,*N*-diacetamide-1-yl)-3-(triphenylphosphoranylidene)succinate 6

Yellow powder; m.p. 184-185 ºC; yield 0.48 g, 95%; IR (neat) (ν_{max}, cm^{-1}): 3053, 2942, 1746, 1670; Anal. Calcd. for ($C_{28}H_{28}NPO_6$): C, 66.52; H, 5.58; N, 2.77; Found: C, 66.44; H, 5.59; N, 2.79%.

Minor isomer (Z)-**6** (40%), ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.99 (s, 6H, 2 $\underline{CH_3}$C=O), 3.17 and 3.72 (6H, 2s, 2O-$\underline{CH_3}$), 4.57 (d, $^3J_{HP}$ = 9 Hz, 1H, CH), 7.42-7.75 (m, 15H, 3 C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 23.34 (s, 2CH_3), 43.46 (d, $^1J_{C\text{-}P}$ = 127.2 Hz, P-$\underline{C}$-CH), 51.57 (d, $^2J_{C\text{-}P}$ = 17.55 Hz, P-C-$\underline{CH}$),49.02 and 52.26 (2s, 2OCH_3), 126.06 (d, $^1J_{C\text{-}P}$ = 93.03 Hz, C_{ipso}),128.70 (d, $^3J_{C\text{-}P}$ = 12.85 Hz, C_{meta}),132.12 (d, $^4J_{C\text{-}P}$ = 2.79 Hz, C_{para}), 132.82 (d, $^2J_{C\text{-}P}$ = 9.83 Hz, C_{ortho}), 168.59 (s, C=O amide), 170.47 (d, $^3J_{C\text{-}P}$ = 13.08 Hz, C=O ester), 173.85 (s, C=O ester); ^{31}P NMR(300 MHz, $CDCl_3$) δH: 23.02.

Major isomer (E)-**6** (55%), ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.99 (s, 6H, 2 $\underline{CH_3}$C=O), 3.59 and 3.72 (6H, 2s, 2O-$\underline{CH_3}$), 4.62 (d, $^3J_{HP}$ = 9 Hz, 1H, CH), 7.42-7.75 (m, 15H, 3 C_6H_5); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C: 23.34 (s, 2CH_3), 43.46 (d, $^1J_{C\text{-}P}$ = 127.2 Hz, P-$\underline{C}$-CH), 51.57 (d, $^2J_{C\text{-}P}$ = 17.55 Hz, P-C-$\underline{CH}$),49.02 and 52.26 (2s, 2OCH_3), 126.06 (d, $^1J_{C\text{-}P}$ = 93.03 Hz, C_{ipso}),128.70 (d, $^3J_{C\text{-}P}$ = 12.85 Hz, C_{meta}),132.12 (d, $^4J_{C\text{-}P}$ = 2.79 Hz, C_{para}), 132.82 (d, $^2J_{C\text{-}P}$ = 9.83 Hz, C_{ortho}), 168.59 (s, C=O amide), 170.47 (d, $^3J_{C\text{-}P}$ = 13.08 Hz, C=O ester), 173.85 (s, C=O ester). ^{31}P NMR (300 MHz, $CDCl_3$) δH: 22.08.

4. Conclusions

In conclusion, we have reported the synthesis of three new phosphorus stabilized ylides upon the reaction of 5-methyl-2-pyrolidone and *N*,*N*-dimethylacetamide with methyl- and ethyl acetylenedicarboxylate in the presence of triphenylphosphine. The ylides resulting from the reaction of the mentioned amides with dimethyl acetylenedicarboxylate exist as Z and E regioisomeric products, whereas the reaction of 5-methyl-2-pyrolidone with diethyl acetylene dicarboxyle produces only one ylide. This report offers a mild, simple and efficient reaction condition. Ease of product separation, excellent product yields and short reaction time are the prominent features of this research.

Declaration of Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

Sepideh Ahmadi: Methodology, Data curation. Enayatollah Bahman Jahromi: Supervision, Writing-Original draft preparation.

Supporting Information

The Supporting Information is available free of charge athttp://www.org.chem.res./doi: XXXX

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