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One-pot synthesis of stable phosphorus ylides by three-component reaction between arylglyoxals, phosphines and barbituric or Meldrum's acid

Mahsa Latifi and Mohammad Anary-Abbasinejad*

Department of chemistry, Vali-e-Asr University, Rafsanjan, 77176, Iran

Email: m.anary@vru.ac.ir

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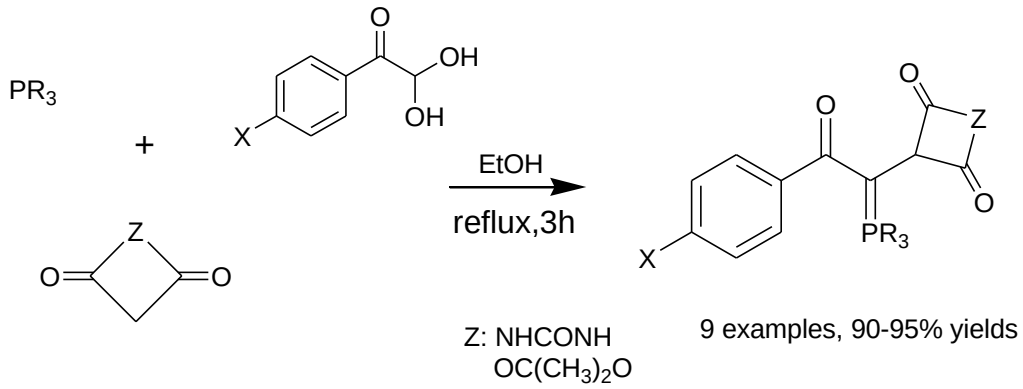
Abstract

An efficient one-pot method for the synthesis of new substituted phosphorus ylides is described via three-component reaction between arylglyoxals, C–H acids such as barbituric acid and Meldrum's acid and triphenylphosphine or tri-*n*-octylphosphine. This reaction was carried out in boiling ethanol in the absence of any catalyst to afford the products in good to excellent yields.



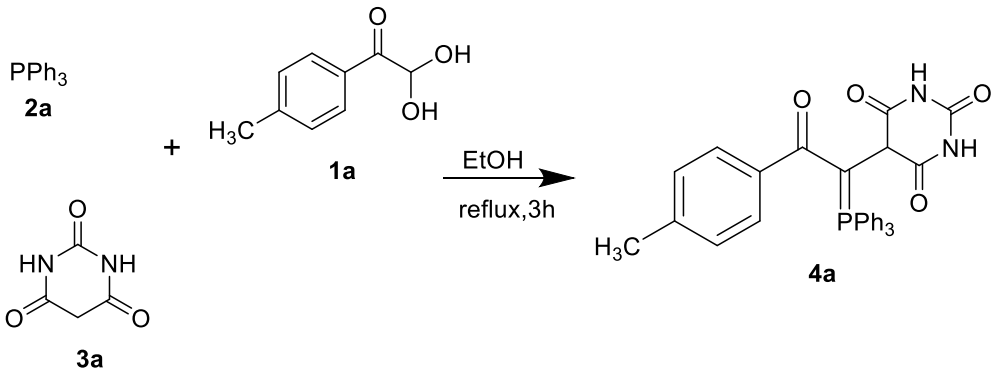
Keywords: Arylglyoxals, phosphorus ylides, triphenylphosphine, barbituric acid, Meldrum's acid

Introduction

Phosphorus ylides are important reactive intermediates in organic synthesis, and are also main starting materials used in syntheses of a number of natural products. They are important intermediates in synthesis of heterocyclic compounds by the Wittig reaction. These heterocyclic compounds have been employed in a wide range of medicinal chemistry because of their diverse biological activities, such as antibacterial, anticonvulsant, antiflammatory, anti-pain, antitumor, and antifungal activities.[1-6] Although many ylides are commercially available, it is often necessary to create them synthetically. Phosphorus ylides are commonly obtained from deprotonation of phosphonium salts which, in turn are produced by the reaction of alkyl halides with phosphine nucleophiles. Phosphonium salts are also prepared by the nucleophilic addition of phosphines to electron-deficient olefines and by other methods.[1-6] Three-component reaction of triphenylphosphine, electron-deficient acetylene diesters and acidic organic compounds has also been previously reported for synthesis of stable 1,2- and 1,4-phosphorus ylides.[7] In continuation of our previous works on synthesis of phosphorus and nitrogen ylides,[8,9] here we have developed a simple and efficient method for preparation of stable phosphorus ylides by a three-component reaction between arylglyoxals, phosphines, and C–H acidic organic compounds such as Meldrum's acid or barbituric acid.

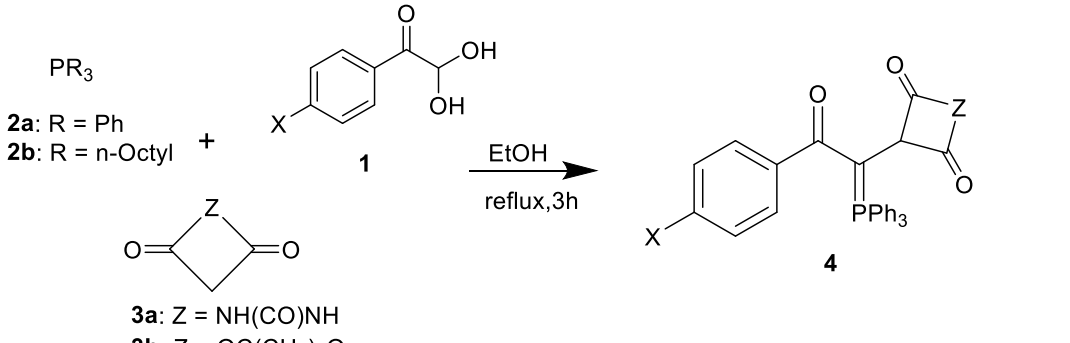
Results and Discussion

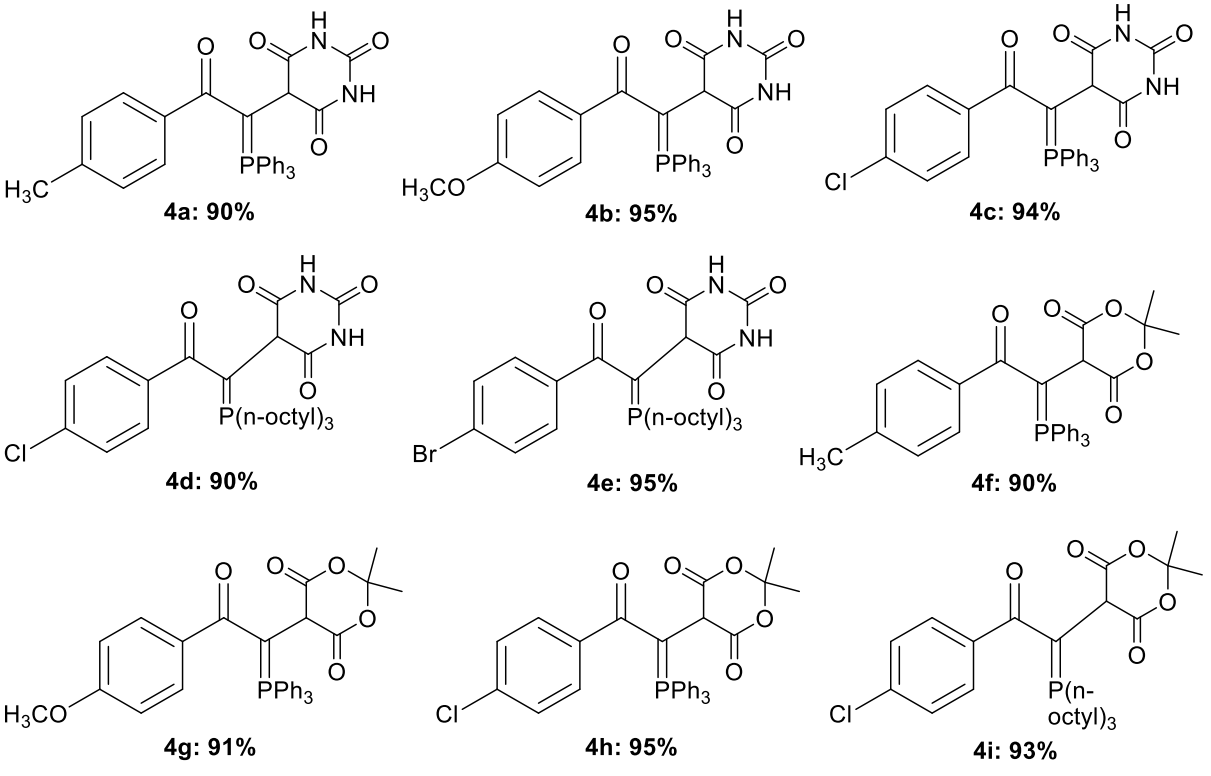
In order to investigate the three-component reaction of arylglyoxals, C-H acidic organic compounds and phosphines at first we studied the reaction between 4-methylphenylglyoxal monohydrate **1a**, barbituric acid **3a** and triphenylphosphine **2a** in ethanol as solvent (Scheme 1). A mixture of 4-methylphenylglyoxal monohydrate and barbituric acid **3a** was stirred in ethanol at room temperature. After thirty minutes triphenylphosphine **2a** was added and the mixture was stirred in boiling ethanol for 3 hours. The reaction course was monitored by TLC. After 3 hours the product was filtered off and washed with ethyl acetate to afford 5-(2-oxo-2-(*p*-tolyl)-1-(triphenylphosphoranylidene)ethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **4a** in 95% yield. To explore the scope of this reaction, various arylglyoxals were reacted with triphenylphosphine or trioctylphosphine and barbituric acid and the related ylides **4b-e** were obtained in good yields. The reaction was also examined with aryglyoxals, Meldrum's acid and triphenylphosphine or trioctylphosphine and the related phosphorus ylides **4f-i** were isolated in high yields. The reaction was also carried out with linear 1,3-dicarbonyl compounds such as acetylacetone or methyl acetoacetate, but no product could be isolated from the complex reaction mixture. We also could not isolate any product from the reaction of dimedone with arylglyoxals and triphenylphosphine.



Scheme 1. Three-component reaction between 4-methylphenylglyoxal monohydrate, triphenylphosphine and barbituric acid for synthesis of stable phosphorus ylide

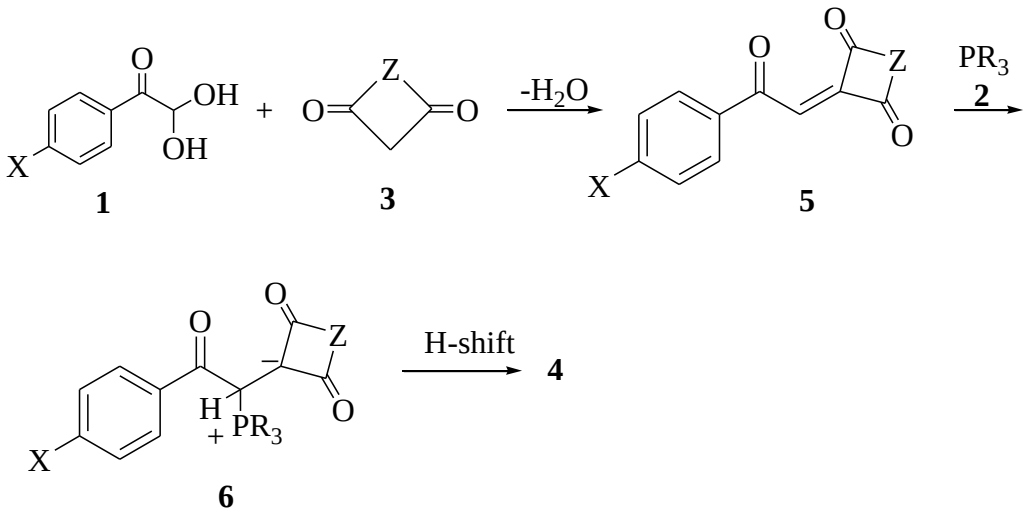
Table 1. Synthesis of stable phosphorus ylides by three-component reaction between arylglyoxal monohydrates, phosphines and C–H acidic organic compounds





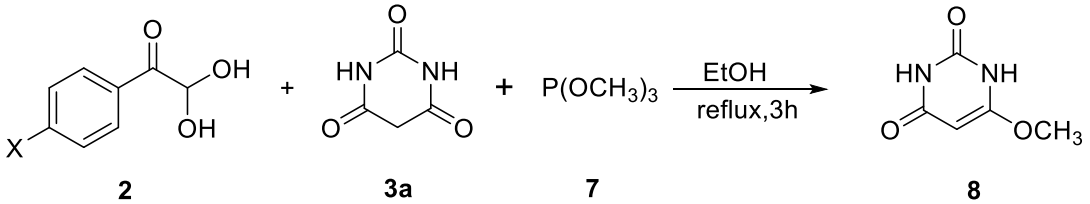
The structures of products **4a–i** were deduced from their elemental analyses and their infrared (IR), ^{1}H NMR, and ^{13}C NMR spectral data. The IR spectrum of **4a** exhibited absorption bands at 1678 cm^{-1} for carbonyl groups. The N-H stretching absorption band becomes visible at 3437 cm^{-1}. The 500-MHz ^{1}H NMR spectrum of **4a** showed a single signal at 2.32 ppm for the methyl group. The proton of CH was observed at 6.94 ppm as a doublet signal ($^{3}J_{PH}$ =7.9 Hz), and the aromatic protons exhibited multiplets at 7.21–7.83 ppm. The NH proton resonated at 9.36 ppm as a single signal. The ^{13}C NMR spectra of **4a** showed fourteen distinct signals in agreement with the proposed structure. The ylide carbon was observed at 50.3 ppm as a doublet with ^{13}C-^{31}P coupling constant of 58.7 Hz. The ^{31}P NMR spectrum of compound **4a** showed a signal at 23.2 ppm for phosphorus atom.

The suggested mechanism for formation of the phosphorus ylides **4a-i** is shown in Scheme 2. The Knoevenagel condensation of arylglyoxal monohydrate **1** and C-H acid **3** afforded the enone intermediate **5**. The Michael addition of triphenylphosphine to **5** lead to zwitterionic intermediate **6** which then converted to product **4a** by a proton shift (Scheme 2).

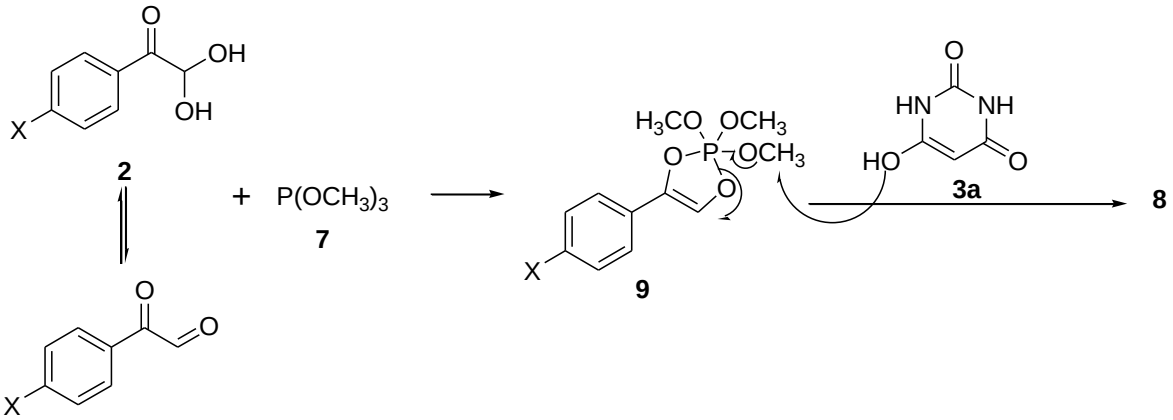


Scheme 2. The suggested mechanism for formation of the phosphorus ylides **4a-i**

We also investigate the reaction of trimethyl phosphite, arylglyoxals and barbituric acid. The only isolated product was the O-methylated barbituric acid **8** which was obtained in 95% yield. No product could be isolated from similar treatment with Meldrum's acid. A rational mechanism for formation of compound **8** is presented in Scheme 4. The addition of trimethyl phosphite to arylglyoxal afforded the dioxaphospholane intermediate **9** which can methylate barbituric acid **3a** to afford the isolated product **8**.



Scheme 3. The reaction of trimethyl phosphite, arylglyoxals and barbituric acid



Scheme 4. Suggested mechanism for formation of compound **8** from the reaction of trimethyl phosphite, arylglyoxals and barbituric acid

Conclusions

In conclusion we report here an efficient one-pot method for synthesis of new substituted phosphorus ylide derivatives by a three-component reaction between arylglyoxals, C–H acids such as barbituric acid or Meldrum's acid and phosphines. The advantages of the method are the available simple starting materials, simple and neutral reaction conditions, simple isolation and purification of products and high yields of products.

Experimental Section

General. All solvents and chemicals except arylglyoxals were purchased from commercial sources and used without further purification. The utilized arylglyoxals were prepared by the SeO_2-oxidation of the related aryl methylketones on the basis of the reported procedure, and used as their monohydrates.[10] Melting points were determined on a Melt-Tem II melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-470 spectrometer. All of the NMR spectra were recorded on a Varian model UNITY Inova 500 MHz (^{1}H: 500 ^{13}C: 125 MHz) NMR spectrometer. Chemical shifts of ^{1}H, ^{13}C NMR are reported in parts per million (ppm) from tetramethylsilane (TMS) as an internal standard in DMSO-d6 as a solvent.

General procedure. A mixture of arylglyoxal (1 mmol) and C-H acid (1 mmol) in ethanol (15 mL) was stirred at room temperature for 30 min. Then, triphenylphosphine or trioctylphosphine (1 mmol) was added to this mixture. The reaction mixture was then stirred at reflux temperature for 3 h. The solvent was removed under reduced pressure, and the residue was washed by ethyl acetate (2 x 10mL) to afford the pure product.
5-(2-Oxo-2-(*p*-tolyl)-1-(triphenylphosphoranylidene)ethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4a). Yield: (95%); White powder; mp 220–223°C. IR (KBr) (vmax, cm^{-1}): 3437 (NH), 1678 (C=O). ^{1}H NMR (d$_6$-DMSO): δ 2.32 (s, 3H, CH_3), 6.94 (1H, d, $^3J_{PH}$ 7.9 Hz, CH), 7.21–7.83 (m, 19H, arom-H), 9.36 (s, 2H,2NH). ^{13}C NMR (d$_6$-DMSO): δ 21.1 (CH_3), 50.3 (d, $^1J_{PC}$ 58.7 Hz, C=P), 120.8 (d, $^2J_{PC}$ 82.7 Hz, CH), 128.1, 128.6 (arom-C), 129.07 (d, $^2J_{PC}$ 12.1 Hz), 131.4 (d, $^3J_{PC}$ 9.8 Hz), 132.4 (d,^{4} J_{PC} 3.2 Hz), 133.5 (arom-C), 134.2 (d, $^1J_{PC}$ 19.5 Hz), 151.5 (arom-C), 163.5 (C=O), 195.6 (C=O). ^{31}P NMR (d$_6$-DMSO): δ 23.2. Anal. calcd for $C_{31}H_{25}N_2O_4P$: C 71.53, H 4.84, N 5.38. Found: C 71.66, H 4.53, N 5.22.

5-(2-(4-Methoxyphenyl)-2-oxo-1-(triphenylphosphoranylidene)ethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4b). Yield: (95%);White powder; mp 225–227 °C. IR (KBr) (vmax, cm^{-1}): 3432 (NH), 1705, 1678 (C=O). ^{1}H NMR (d_6-DMSO): δ 3.79 (s, 3H, OCH_3), 6.88 (1H, d , $^3J_{PH}$ 14.2Hz, CH), 6.92–7.83 (m, 19H, arom-H) ,9.30 (s, 2H,2NH). ^{13}C NMR (d_6-DMSO): δ 31.1 (OCH_3), 51.1 (d, $^1J_{PC}$ 58.3 Hz, C=P), 113.9 (arom-C) , 121.5 (d, $^2J_{PC}$ 82.5 Hz,CH), 129.2 (d, $^4J_{PC}$ 3.0 Hz), 129.5 (d, $^2J_{PC}$ 11.6 Hz), 130.8,133.9 (arom-C), 134.6 (d, $^1J_{PC}$ 19.6 Hz), 134.7 (d, $^3J_{PC}$ 9.6 Hz), 152.0 (arom-C),163.7,163.9 (C=O), 195.6 (C=O). ^{31}P NMR (d_6-DMSO): δ 25.9. Anal. calcd for $C_{31}H_{25}N_2O_5P$: C 69.40, H 4.70, N 5.22. Found: C 69.65, H 4.43, N 5.32.

5-(2-(4-Chlorophenyl)-2-oxo-1-(triphenylphosphoranylidene)ethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4c). Yield: (94%); White powder; mp 217–221 °C. IR (KBr) (vmax, cm−1): 3425 (NH), 1691 (C=O).
^{1}H NMR (d_6-DMSO): δ 6.98 (1H, d, $^3J_{PH}$ 14.2Hz, CH),7.46–7.88 (m, 19H, arom-H),9.36 (s, 2H,2NH). ^{13}C NMR (d_6-DMSO): δ 52.8 (d, $^1J_{PC}$ 58.3 Hz, C=P), 121.3 (d, $^2J_{PC}$ 82.5 Hz), 128.6 (arom-C), 129.1 (d, $^4J_{PC}$ 3.0 Hz), 129.5 (d, $^2J_{PC}$ 11.9 Hz), 130.3,134.0 (arom-C) , 134.2 (d, $^1J_{PC}$ 19.6 Hz), 134.7 (d, $^3J_{PC}$ 9.8 Hz), 152.0 (arom-C),163.9 (C=O), 196.0 (C=O). Anal. calcd for $C_{30}H_{22}ClN_2O_4P$: C 66.61, H 4.10, N 5.18. Found: C 66.65, H 4.13, N 5.30.

5-(2-(4-Chlorophenyl)-2-oxo-1-(trioctylphosphoranylidene)ethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4d). Yield: (90%); White powder; mp 163–167◦C. IR (KBr) (vmax, cm^{-1}): 3342 (NH), 1703,1633 (C=O). ^{1}H NMR (d -DMSO): δ 1.21-2.31 (m, 51H,tri-n-octyl), 5.58 (1H, d, $^3J_{PH}$ 14.2Hz, CH),7.48 (2H, d, $^3J_{HH}$ 8.5 Hz), 7.70 (2H, d, $^3J_{HH}$ 8.5 Hz), 9.4 (2H, s, 2NH). ^{13}C NMR (d_6-DMSO): δ 14.3, 19.1 (d, $^1J_{PC}$ 47.0 Hz), 21.9 (d, $^4J_{PC}$ 3.75 Hz), 22.5, 28.57 (d, $^2J_{PC}$ 23.7 Hz), 30.87 (d, $^3J_{PC}$ 14.1 Hz),31.6, 52.5 (d, $^1J_{PC}$ 58.3 Hz, C=P), 121.3 (d, $^2J_{PC}$ 82.5 Hz, CH), 128.3, 128.5 130.0, 152.0 (arom-C) , 164.3 (C=O), 196.6 (C=O). Anal. calcd for $C_{36}H_{58}ClN_2O_4P$: C 66.59, H 9.00, N 4.31. Found: C 66.65, H 9.13, N 4.20.

5-(2-(4-Bromophenyl)-2-oxo-1-(trioctylphosphoranylidene)ethyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione(4e). Yield: (95%); Yellow powder; mp 151–154°C. IR (KBr) (vmax, cm^{-1}): 3308 (NH),1725 (C= O). ^{1}H NMR ($CDCl_3$): δ 1.21-2.38 (m, 51H,tri-n-octyl), 5.47 (1H, d, $^3J_{PH}$ 14.2Hz, CH),7.52 (2H, d, $^3J_{HH}$ 8.1 Hz), 7.58 (2H, d, $^3J_{HH}$ 8.3 Hz), 9.1 (2H, s, 2NH). ^{13}C NMR ($CDCl_3$): δ 14.0, 19.7 (d, $^1J_{PC}$ 41.5 Hz), 21.68, 22.5 (d, $^4J_{PC}$ 5 Hz), 28.8 (d, $^2J_{PC}$ 12.2 Hz), 29.0, 31.7 (d, $^3J_{PC}$ 15.6 Hz), 52.5 (d, $^1J_{PC}$ 58.3 Hz, C=P), 121.3 (d, $^2J_{PC}$ 82.5 Hz, CH), 128.3, 128.5 130.0, 152.0 (arom-C) , 164.3 (C=O), 196.6 (C=O). Anal. calcd for $C_{36}H_{58}BrN_2O_4P$: C 62.33, H 8.43, N 4.04. Found: C 62.37, H 8.51, N 4.22.

2,2-Dimethyl-5-(2-oxo-2-(*p*-tolyl)-1-(triphenylphosphoranylidene)ethyl)-1,3-dioxane-4,6-dione (4f). Yield: (90%); Orange powder; mp 192–195 °C. IR (KBr) (vmax, cm^{-1}): 1666, 1615 (C= O). ^{1}H NMR (d_6-DMSO): δ 1.18 (s, 6H, $2CH_3$), 2.32 (s, 3H, CH_3), 7.60 (1H, d,$^3J_{PH}$ 13.2 Hz, CH), 7.22–7.88 (m, 19H, arom-H). ^{13}C NMR (d_6-DMSO): δ 21.6 (CH_3), 26.0 (CH_3), 50.8 (d, $^1J_{PC}$ 60.2 Hz, C=P), 66.5 (C), 121.7 (d, $^2J_{PC}$ 83.0 Hz, CH), 128.8 (arom-C), 129.2 (d, $^4J_{PC}$ 4.8 Hz), 129.6 (d, $^2J_{PC}$ 12.0 Hz), 132.9 (d, $^3J_{PC}$ 7.7 Hz),133.6 (d, $^1J_{PC}$ 19.6 Hz, CH),134.0 (d, $^4J_{PC}$ 3 Hz), 134.5 (d, $^3J_{PC}$ 9.6 Hz), 144.0 (arom-C), 164.5 (C=O), 196.6 (C=O). Anal. calcd for $C_{33}H_{29}O_5P$: C 73.87, H 5.45. Found: C 73.77, H 5.55.

5-(2-(4-Methoxyphenyl)-2-oxo-1-(triphenylphosphoranylidene)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione. (4g). Yield: (91%); White powder; mp 182–184°C. IR (KBr) (vmax, cm−1):1654,16114 (C= O). ^{1}H NMR (d_6-DMSO): δ 1.20 (s, 6H, $2CH_3$), 3.80 (s, 3H, OCH_3), 6.95 (1H, d, $^3J_{PH}$ 8.7Hz, CH), 7.59–7.88 (m, 19H, arom-H). ^{13}C NMR (d_6-DMSO): δ 26.0 (CH_3), 31.1 (OCH_3), 50.1 (d, $^1J_{PC}$ 60.2 Hz, C=P), 66.6 (C), 113.9 (arom-C) , 121.8 (d, $^2J_{PC}$ 82.9 Hz, CH), 128.1 (d, $^3J_{PC}$ 9.3Hz), 129.2 (arom-C) , 129.6 (d, $^2J_{PC}$ 11.6 Hz), 131.1 (arom-C) , 133.1 (d, $^1J_{PC}$ 19.6 Hz), 133.9 (d, $^4J_{PC}$ 2.9 Hz), 134.5 (d, $^3J_{PC}$ 9.7 Hz), 163.7, 164.5 (C=O), 195.4 (C=O). Anal. calcd for $C_{33}H_{29}O_6P$: C 71.73, H 5.29. Found: C 73.77, H 5.55.

5-(2-(4-Chlorophenyl)-2-oxo-1-(triphenylphosphoranylidene)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4h). Yield: (95%); White powder; mp 200–203°C. IR (KBr) (vmax, cm−1):1670,1617 (C=O). ^{1}H NMR (d_6-DMSO): δ = 1.18(s, 6H, $2CH_3$),7.12 (1H, d, $^3J_{PH}$ 13.5Hz, CH), 7.49–7.88 (m, 19H, arom-H), 9.36 (s, 2H,2NH). ^{13}C NMR (d_6-

DMSO): δ 25.9 (CH_3), 50.1 (d, $^1J_{PC}$ 60.1 Hz, C=P), 66.5 (C), 121.1 (d, $^2J_{PC}$ 83.5 Hz, CH), 128.7 (arom-C), 129.2 (d, $^3J_{PC}$ 7.5 Hz), 129.7 (d, $^2J_{PC}$ 12.0 Hz), 130.6 (d,^{4} J_{PC} 5.1 Hz) ,133.6 (d, $^1J_{PC}$ 19.6 Hz),134.0 (d, $^4J_{PC}$ 2.9 Hz), 134.5 (d, $^3J_{PC}$ 9.8 Hz, CH), 138.4 (arom-C), 164.5, 165.8 (C=O), 196.2 (C=O). Anal. calcd for $C_{32}H_{26}ClO_5P$: C 69.01, H 4.71. Found: C 69.77, H 4.53.

5-(2-(4-chlorophenyl)-2-oxo-1-(trioctylphosphoranylidene)ethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione(4i). Yield: (93%); Yellow powder; mp 130–132°C. IR (KBr) (vmax, cm−1): 1727,1637 (C=O). ^{1}H NMR ($CDCl_3$): δ 1.25-2.50 (m, 57 H,tri-n-octyl, CH_3), 5.44 (1H, d, ^{3} J_{PH} 13.3 Hz, CH), 7.37 (2H, d, ^{3} J_{HH} 8.4 Hz), 7.83 (2H, d, ^{3} J_{HH} 10.7 Hz), 9.1 (2H, s, 2NH). ^{13}C NMR ($CDCl_3$): δ 14.0, 19.8 (d, $^1J_{PC}$ 44.1 Hz), 22.41 (d, $^4J_{PC}$ 5 Hz),22.5, 26.3, 28.8 (d, $^2J_{PC}$ 10.7 Hz), 31.0 (d, $^3J_{PC}$ 14.9 Hz), 31.65, 52.5 (d, $^1J_{PC}$ 58.3 Hz, C=P), 65.8 (C), 101(arom-C), 121.3 (d, $^2J_{PC}$ 82.5 Hz, CH), 128.7, 129.8 139.7, 165.0 (C=O), 196.6 (C=O). Anal. calcd for $C_{38}H_{62}ClO_5P$: C 68.60, H 9.39. Found: C 68.77, H 9.13.

6-methoxypyrimidine-2,4(1*H*,3*H*)-dione (9). Yield: (90%); Yellow powder; mp 341–345°C. IR (KBr) (vmax, cm−1): 3006 (NH), 1715,1678 (C=O). ^{1}H NMR (d6-DMSO): δ = 3.75 (3H, s, OCH_3), 4.92 (1H, S, CH), 10.7 (1H, s, NH), 11.2 (1H, s, NH).

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