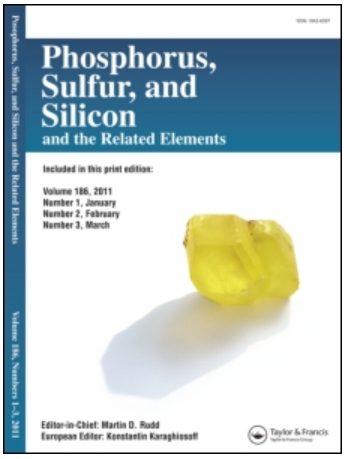

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Novel Phosphoranes Containing Urea Derivatives: Synthesis and Characterization

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Novel Phosphoranes Containing Urea Derivatives: Synthesis and Characterization

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N-Acetyl-N′-methyl urea or ethyl urea in the presence of an acetylenic ester and a desired phosphine functioned as a NH-acid and added to the triple bond in a chemoselective reaction. One of the obtained products underwent lactonization to the corresponding imidazolidine containing ylide moiety when heated in the presence of a base such as triethyl amine.

Keywords N-Acetyl-N′-methyl urea; chemoselective reaction; phosphoranes

INTRODUCTION

The various families of phosphorus compounds are particularly exciting because of indications that they may generate many opportunities for applied chemistry. The phosphoranes are good examples of such molecules that apply in the synthesis of organic compounds.[1–5] They are of interest as building blocks for the preparation of alkenes,[6] heterocyclic compounds,[7,8] and natural products.[9] In addition, imidazolidine-2,4-diones and their derivatives show interesting medicinal activities since they have indicated therapeutic applications in drugs, such as HIV protease inhibitors,[10] antiarrhythmic properties,[11] antihypertensive activity,[12] phenytion for the action of different types of epileptic seizures,[13] nilutamide,[14] a nonsteroidal orally active antiandrogen in the therapy of metastatic prostate cancer, and azimilide[15] as an antiarrhythmic.

In spite of the fact that the applications of phosphorus ylides in the synthesis of drugs[16] and organic compounds and the application of imidazolidines in organic chemistry as heat-resistant polymera for electrical conductors[17] and their interesting biological activities,[18] there is

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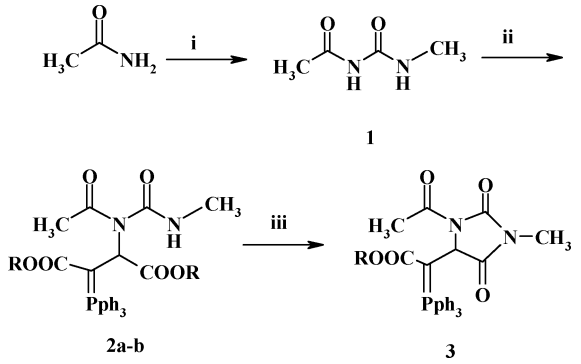
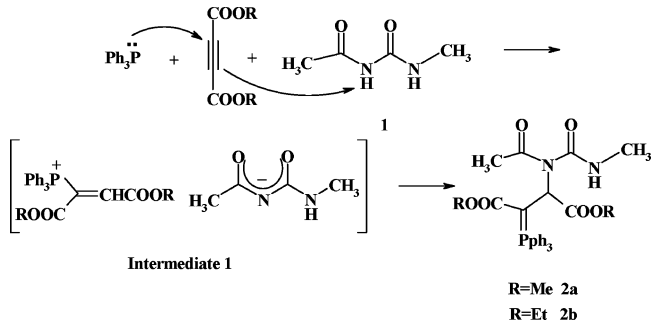
still a search for the preparation of new compounds of these families, and this has become an attractive strategy for synthetic chemists to produce such materials in an effective manner from available precursors. Here, we present our findings towards this goal (Scheme 1).



SCHEME 1 Synthesis of imidazolidine-2,4-dione derivatives: (i) Br_2/KOH; (ii) Ph_3P, DMAD or DEAD; (iii) Et_3N, heat.

RESULTS AND DISCUSSION

Acetamide reacted with bromine in the presence of KOH to give N-acetyl-N′-Methyl urea **1**[19] via a Hoffmann rearrangement.[20–22] The formation of compounds **2a–b** may be explained in terms of the Michael addition of Ph_3P to the triple bond of the acetylenic esters, and subsequent protonation of the formed carbanion by NH acid in a chemoselective manner to give intermediate **1**. This intermediate readily undergoes a second Michael addition to give an imide including polyfunctional groups. The mechanism is shown in Scheme 2.



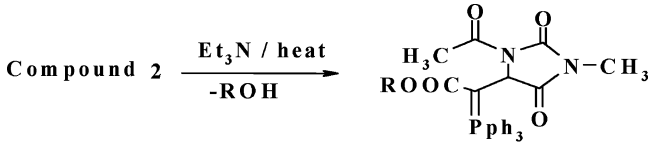
SCHEME 2

Due to much the greater acidity of the NH group of the imide relative to the NH group in an amide moiety, no other products were formed under these conditions. The structures of compounds **2a–b** are assigned based on their IR, ^{1}H NMR, and ^{13}C NMR spectra and elemental CHN-analyses data. The ^{1}H and ^{13}C NMR spectroscopic data for these compounds exhibit a mixture of two rotational isomers.[23–25] The main reason for this phenomenon is related to the resonance of the carbanion of the ylide moiety with the adjacent carbonyl group of the ester. The ratio of rotational isomers was determined from the ^{1}H NMR spectrum. As an example, the ^{1}H NMR spectrum of compound **2a** exhibits the mixture of these isomers as 80% and 20% for *Z* and *E* isomers, respectively.

The spectrum of compound **2a** shows six sharp lines (δ 1.98, 2.05, 3.05, 3.52, 3.76, 3.78) arising from the methyl of acetyl groups and methoxy protons along with signals from the N-methyl protons at δ 2.88 and 2.83, which appear as two doublets ($^3J_{NH-H} = 4.8$) and the methine protons at δ 5.04 and 5.00, which appear as two doublets ($^3J_{PH} = 17.7$) for the major and minor geometrical isomers, respectively. The ^{13}C NMR spectrum of compound **2a** is in agreement with the proposed structure. The ^{1}H and ^{13}C NMR spectra of **2b** are similar to those of compound **2a**, except for the signals from the ester groups, which appear as characteristic resonance lines with the corresponding chemical shifts.

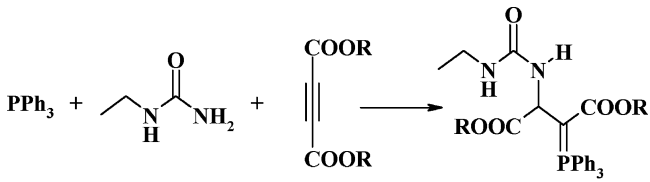
Synthesis of Imidazolidine-2,4-dione Derivative

When compounds **2a–b** were subjected to ring closure by heating in the presence of a base such as triethyl amine, only **2a** was exclusively lost methanol to produce imidazolidine-2,4-dione derivative **3**.



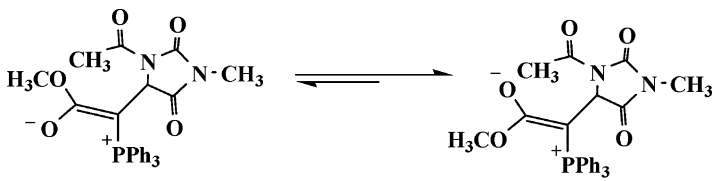
3

Since the other derivatives of compound **3** did not form in the same reaction conditions, the reaction of N-ethyl urea, dialkyl acetylenedicarboxylate, and Ph_3P was employed for synthesis of compounds **4a** and **4b** in a chemoselective reaction manner.



Similarly compounds **4a–b** were subjected to ring closure upon heating in the presence of triethylamine; however, no reaction was observed even a prolonged period. Although the reason of this observation is not clear to us, it is possible that the steric hindrance of the ethyl substituent could be a factor.

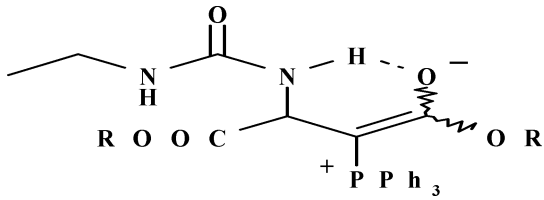
Structure **3** was assigned on the basis of its elemental analyses and IR, ^{1}H, and ^{13}C NMR spectral data. Compound **3** did not show the absorption band of the NH group in the IR spectrum at 3354 cm^{-1}, while this absorption was detected in the IR spectrum of **2a**. ^{1}H NMR and ^{13}C NMR spectra of compound **3** revealed a mixture of two rotational isomers (Scheme 3).



SCHEME 3

In the ^{1}H NMR spectrum of compound **3**, protons of the acetyl groups appeared as two singlets at δ 2.51and 2.49 along with two signals arising from the methoxy groups at δ 3.10 and 3.46 for the **3Z** and **3E** isomers, respectively. Protons of N-methyl groups appeared as two singlets at δ 3.05 and 3.07. The ^{1}H NMR spectra of **2a** and **3**, which we believe are the result of ring closure of **2a**, are quite different. N-methyl protons of **3** appeared as two singlets, whereas in the ^{1}H NMR spectrum of **2a**, these protons appeared as two doublets due to the spin–spin splitting of the NH proton. The ^{13}C NMR spectrum of compound **3** is in agreement with the proposed structure.

The structures of compounds **4a–b** were deduced from their IR, ^{1}H NMR, and ^{13}C NMR spectra and elemental CHN-analyses data. The ^{1}H and ^{13}C NMR spectral data for these compounds exhibit a mixture of two rotational isomers, and the ratio of the *Z* isomer is extremely high in comparison to the *E* isomer. Probably the high yield of the *Z* isomer compared to the *E* isomer is the result of hydrogen bonding via a six-membered ring as shown:



4 (Z)

CONCLUSION

In conclusion, N-acetyl N′-methyl urea was used as a precursor for the synthesis of only one imidazolidine-2,4-dione derivative. The conversion of ylides to imidazolidine-2,4-dione derivatives depended on the substituent that was presented into the reactants. When the reactant contains a methyl substituent, the reaction produces the expected product. Although ylides were obtained in the first step of the reaction, when bigger groups than methyl were used as a substituent on the acetylenic ester or urea, the reaction does not go further even after refluxing the reaction mixture for a long period.

EXPERIMENTAL

All common reagents and solvents were used as obtained from commercial suppliers without further purification. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-500 AVANCE (^{1}H NMR at 500 MHz, and ^{13}C NMR at 125.77 MHz). Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. Elemental CHN analyses were performed by the University of Tarbiat Moalem using a Heracus CHN-O Rapid analyzer. IR spectra were measured on a Mattson 1000 FT-IR spectrometer. Throughout this section, * = for two rotamers.

Dimethyl 2-Acetyl(methylamino)carbonyl)amino-3-(1,1,1-triphenyl-λ^5-phosphanylidene) Succinate 2a: General Procedure

At ambient temperature, dimethyl acetylenedicarboxylate (0.24 mL, 2 mmol) was added dropwise to a stirred solution of triphenylphosphine (0.53 g, 2 mmol) and acetyl methyl urea (0.23 g, 2 mmol) in a mixture of hexane/ethyl acetate (3:2). After the addition was complete (approximately 30 min), the mixture was stirred for an additional 1 h and was subsequently filtered. The solid collected in the filter was washed thoroughly with ethyl acetate to give a white powder.

0.99 g, mp 162–163°C, yield 95%; IR (KBr) (ν_{max}, cm^{-1}): 1741, 1716, 1666, and 1641 (C=O). Isomer (Z) (80%) ^{1}H NMR ($CDCl_3$): δ 1.98 (s, CH_3), 2.88 (d, $^3J_{NH-H} = 4.8$ Hz NCH_3), 3.05 and 3.78 (s, 2 OCH_3), 5.04 (1H, d, $^3J_{PH} = 17.7$ Hz, P=C–CH), 7.38–7.69 (30H, m, Ar)* , 6,95 (1H, br.s, NH)*. ^{13}C NMR ($CDCl_3$): δ 22.90 (CH_3), 27.42 (NCH_3), 39.96 (d, $^1J_{PC} = 123.5$, P=C), 49.20 and 52.69 (2 OCH_3), 57.35 (d, $^2J_{PC}$ =16.8 Hz P=C-CH), 125.96 (d,$^1J_{PC} = 91.9$ Hz, C^{ipso}), 128.67(d, $^3J_{PC} = 12.5$ Hz, C^{meta}), 132.28 (d,$^4J_{PC} = 2.6$ Hz, C^{para}), 133.62 (d,$^2J_{PC} = 9.8$ Hz, C^{ortho}), 156.62 and 169.29 (C=O), 170.24 (d, $^2J_{PC} = 12.7$ Hz, C=O)*, 173.22 (d,$^3J_{PC} = 14.6$Hz, C=O)*. Isomer (E) (20%), ^{1}H NMR ($CDCl_3$) : δ 2.05 (s, CH_3), 2.83 (d, $^3J_{HH}$ 4.8 Hz, NCH_3), 3.52 and 3.76 (s, 2 OCH_3), 5.01 (1H, d, $^3J_{PH} = 17.6$ Hz, P=C-CH). ^{13}C NMR ($CDCl_3$): δ 22.35 (CH_3), 27.40 (NCH_3), 50.25 and 52.20 (2 OCH_3), 56.77 (d, $^2J_{PC} = 16.8$ Hz P=C-CH), 125.48 (d,$^1J_{PC} = 90.7$ Hz, C^{ipso}), 128.44 (d,$^3J_{PC} = 12.1$ Hz, C^{meta}), 131.86 (d, $^4J_{PC} = 2.5$ Hz, C^{para}), 133.78 (d,$^2J_{PC} = 9.7$ Hz, C^{ortho}). Anal. Calcd. For $C_{28}H_{29}N_2O_6P$ (520): C, 64.61; H, 5.57; N, 5.38%. Found: C, 64.42; H, 5.11; N, 5.41%.

Diethyl 2-Acetyl (Methyl Amino) Carbonyl) Amino-3-(1,1,1-triphenyl-λ^5-phosphanylidene) Succinate 2b

1.03 g, mp 160–162°C, yield 92%; IR (KBr) ($\nu_{max,}$ cm^{-1}): 1765, 1741, 1690, and 1641 (C=O). Isomer (Z) (88.2%), ^{1}H NMR ($CDCl_3$): δ 0.45 (t, 3H, $^3J_{HH} = 7.0$ Hz, CH_3), 1.32 (t, 3H, $^3J_{HH} = 7.1$ Hz, CH_3), 2.00 (s, CH_3), 2.89 (d, $^3J_{NH-H} = 4.7$ Hz, CH_3), 3.57–4.36(8H, m, 4OCH_2)*, 5.04 (1H, d, $^3J_{PH} = 18.3$ Hz, P=C-CH), 7.45°7.72 (30H, m, Ar)* .^{13}C NMR ($CDCl_3$): δ 13.98, 14.22 and 22.89 (3 CH_3), 27.48 (NCH_3), 39.87 (d, $^1J_{PC} = 122.3$, P=C)*, 57.35 (d, $^2J_{PC} = 16.9$ Hz P=C-^{13}CH), 57.92 and 61.41 (2 OCH_2)*, 126.17 (d,$^1J_{PC} = 91.8$ Hz, C^{ipso})*, 128.58 (d,$^3J_{PC}$ = 12.3 Hz, C^{meta})*, 132.21 (d, $^4J_{PC} = 2.6$ Hz, C^{para})*, 133.71 (d,$^2J_{PC} = 9.8$ Hz, C^{ortho})*, 156.75 and 169.23 (2 C=O), 169.77 (d, $^2J_{PC} = 12.6$ Hz, C=O)*, 172.71 (d,$^3J_{PC} = 14.3$Hz, C=O)*. Isomer, (E) (11.8%),^{1}H NMR

($CDCl_3$): δ 1.16 (t, 3H, $^3J_{HH} = 6.9$ Hz, CH_3), 1.36 (t, 3H, $^3J_{HH} = 7.2$ Hz, CH_3), 1.97 (s, CH_3), 2.91 (d, $^3J_{NH-H} = 5.0$ Hz, CH_3), 5.00 (1H, d, $^3J_{PH} = 17.1$ Hz, P=C-CH).^{13}C NMR ($CDCl_3$): δ 13.99, 14.83 and 22.40 (3 CH_3), 26.45 (NCH_3), 56.77 (d, $^2J_{PC} = 16.6$ Hz P=C-^{13}CH). Anal. Calcd. for $C_{30}H_{33}N2O_6P$ (548): C, 65.69; H, 6.02; N, 5.10%. Found: C, 65.50; H, 6.0; N, 5.04%.

Methyl 2-(3-Acetyl-1-methyl-2,5-dioxo-4-imidazolidinyl)-2-(1, 1,1-triphnyl-λ^5-phosphanylidene) Acetate 3

Compound **2a** (0.52 g, 1 mmol) was heated in boiling triethyl amine for 30 min, and compound **3** was subsequently filtered. The solid collected in the filter was washed thoroughly with ethyl acetate to give a white powder.

0.29 g, mp 180 °C (dc), yield 70%; IR (KBr) (ν_{max}, cm^{-1}): 1790, 1741, 1690, and 1641 (C=O). Isomer (Z): (66%) ^{1}H NMR ($CDCl_3$): δ 2.51 (s, CH_3), 3.05 (s, NCH_3), 3.11 (s, OCH3), 4.20 (1H, d, $^3J_{PH} = 12.9$, Hz, P=C-CH), 7.49–7.81 (30H, m, Ar)* .^{13}C NMR ($CDCl_3$): δ 24.87 (CH3), 25.34 (NCH_3), 40.39 (d, $^1J_{PC} = 134.3$ Hz, P=C), 48.93 (OCH_3), 60.88 (d, $^2J_{PC} = 18.4$Hz P=C-CH), 125.78 (d,$^1J_{PC} = 93.4$ Hz, C^{ipso}), (128.52 (d,$^3J_{PC} = 12.3$ Hz, C^{meta}), 132.01 (d, $^4J_{PC} = 2.4$ Hz, C^{para}), 134.14 (d,$^2J_{PC} = 8.4$ Hz, C^{ortho}), 154.77 (C=O), 168.99 (d, $^2J_{PC} = 12.9$ Hz, C=O), 169.20 (C=O), 173.97 (d,$^3J_{PC} = 5.8$ Hz, C=O). Isomer (E) (34%), ^{1}H NMR ($CDCl_3$): δ 2.49 (s, CH_3), 3.07 (s, NCH_3), 3.4 (s, OCH_3), 4.27(1H, d, $^3J_{PH} = 13.9$ Hz, P=C-CH). ^{13}CNMR ($CDCl_3$): δ 24.70 (CH_3), 25.34 (NCH_3), 40.82 (d, $^1J_{PC} = 142.5$ Hz, P=C), 50.23 (OCH_3), 59.93 (d, $^2J_{PC} = 18.1$ Hz, P=C-CH), 126.47 (d, $^1J_{PC} = 80.4$ Hz, C^{ipso}). 128.59 (d,$^3J_{PC} = 12.2$ Hz, C^{meta}), 134.21 (d,$^2J_{PC} = 10.2$ Hz, C^{ortho}), 132.12 (d, $^4J_{PC} = 2.3$ Hz, C^{para}), 154.87 and 168.78 (2 C=O), 169.4 (d, $^2J_{PC} = 18.2$ Hz, C=O), 174.02 (d,$^3J_{PC} = 5.53$ Hz, C=O). Anal. Calcd For $C_{27}H_{25}N_2O_5P$ (488): C, 66.39; H, 5.12; N, 5.73%. Found: C, 65.75; H, 5.51; N, 5.28%.

Dimethyl 2-{[(Methyl Amino) Carbonyl]amino}-3-(1,1,1-triphenyl-λ^5-phosphanylidene) Succinate 4a

This compound was prepared by using the method as described for the preparation of compound **2a**.

0.95 g, mp 119–120°C, yield 97%); IR (KBr) (ν_{max}, cm^{-1}): 1741, 1716, 1691, and 1617 (C=O). Isomer (Z) (96%) ^{1}H NMR ($CDCl_3$): δ 1.05 (3H, t, $^3J_{HH} = 7.1$ Hz, CH_3), 3.11 and 3.61 (6H, s,2 OCH_3), 3.13–3.20 (4H, m, 2 NCH_2)*, 4.52–4.63 (2H, m, P=C-CH)*, 5.70 (2H, d,$^3J_{HH} = 8.4$ Hz, NH), 6.15 (4H, br.s, $2NH_2$)*, 7.45–7.72 (30H, m,

Ar)*. ^{13}C NMR ($CDCl_3$): δ 15.44 ($2CH_3$)*, 35.23 (2 N-CH_2)*, 43.94 (d, $^1J_{PC}$ 125.6 Hz, P=C)*, 48.99, 51.96 (2 OCH_3), 52.79 (d, $^2J_{PC}$ = 16.9 Hz P=C-CH)*, 126.98 (d,$^1J_{PC}$ = 92.4 Hz, C^{ipso}), 128.54 (d,$^3J_{PC}$ = 12.3 Hz, C^{meta})*, 132.08 (d, $^4J_{PC}$ = 2.6 Hz, C^{para})*, 133.82 (d,$^2J_{PC}$ = 9.9 Hz, C^{ortho})*, 157.63 (C=O), 170.75 (d, $^2J_{PC}$ =13.8 Hz, C=O)*, 174.30 (d,$^3J_{PC}$ = 12.6 Hz, C=O)*. Isomer (E) (4 %),^{1}H NMR ($CDCl_3$): δ 1.24 (t, $^3J_{HH}$ = 7.1 Hz, CH_3), 3.51 and 3.61 (2 OCH_3).^{13}C NMR ($CDCl_3$): δ , 49.93 and 51.95 (2 OCH_3), 126.27 (d, $^1J_{PC}$ = 87.5 Hz, C^{ipso}) Anal. Calcd. For $C_{27}H_{29}N_2O_5P$ (492): C, 65.8; H, 5.8; N, 5.69%. Found: C, 66.39; H, 5.97; N, 5.80%.

Diethyl 2 -{[(Methyl Amino) Carbonyl]amino}-3-(1,1,1-triphenyl-λ^5-phosphanylidene) Succinate 4b

(0.93 g, mp 174–175°C, yield 90%); IR (KBr) (ν_{max}, cm^{-1}): 1741, 1716, 1691, and 1617 (C=O). Isomer (Z) (88%)^{1}H NMR ($CDCl_3$): δ 0.43 (t, 3H, $^3J_{HH}$ = 7.1 Hz, CH_3), 1.11 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.17 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3), 3.13–3.21 (4H, m, 2 CH_2N)*, 3.63–4,13 (8H, m, OCH_2)*, 4.42–4.47 (2H, m, P=C-CH)*, 5.65 (2H, d,$^3J_{HH}$ = 6.9 Hz, NH) 6.12 (4H, br.s, 2 NH_2)*, 7.42–7.72 (30H, m, Ar)* .^{13}C NMR ($CDCl_3$): δ 13.89, 14.13 and 15.49 (3 CH_3), 35.24 (NCH_3), 43.69 (d, $^1J_{PC}$ = 128.4 Hz, P=C)*, 52.81 (d, $^2J_{PC}$ = 16.4 Hz P=C-^{13}CH), 57.62 and 60.88 (2 OCH_2), 126.85 (d,$^1J_{PC}$ = 91.8 Hz, C^{ipso}), 128.44 (d,$^3J_{PC}$ = 12.3 Hz, C^{meta}), 131.96 (d, $^4J_{PC}$ = 2.4 Hz, C^{para}), 133.93 (d, $^2J_{PC}$ = 9.8 Hz, C^{ortho})*, 157.70 (C=O), 170.32 (d, $^2J_{PC}$ = 13.8 Hz, C=O)*, 174.52 (d,$^3J_{PC}$ = 12.6 Hz, C=O). Isomer (E) (12%), ^{1}H NMR ($CDCl_3$): 1.21 (t, 3H, $^3J_{HH}$ = 6.9 Hz, CH_3), 1.23 (t, 3H, $^3J_{HH}$ = 7.0 Hz, CH_3), 1.24 (t, 3H, $^3J_{HH}$ = 6.9 Hz, CH_3). ^{13}C NMR ($CDCl_3$): δ 14.14 and 15.11 (2 CH_3), 35.25 (NCH_2), 52.25 (d, $^2J_{PC}$ 16.2 Hz, P=C-^{13}CH), 58.03 and 60.86 (2 OCH_2) 126.40 (d, $^1J_{PC}$ = 92.4 Hz, C^{ipso}), 128.63 (d, $^3J_{PC}$ = 8.8 Hz, C^{meta}), 132.04 (C^{para}), 157.42(C=O). Anal. Calcd. For $C_{29}H_{33}N_2O_5P$ (520): C, 66.9; H, 6.3; N, 5.4%. Found: C, 67.39; H, 6.43; N, 5.25%.

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