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Vinyltriphenylphosphonium salt mediated synthesis of 1,4-benzoxazine and coumarin derivatives

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Abstract—Protonation of the reactive 1:1 intermediate produced in the reaction between triphenylphosphine and dimethyl acetylenedicarboxylate by 2-aminophenol, 3-aminophenol, 4-aminophenol and 2-amino-3-hydroxypyridine leads to vinyltriphenylphosphonium salts, which undergo Michael addition with the conjugate base of the aminophenol or aminohydroxypyridine to produce highly functionalized heterocyclic compounds. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Coumarin and its derivatives continue to capture the attention of synthetic organic chemists, and a large number of coumarin ring syntheses and application of known methods to new problems in coumarin chemistry have been reported.[1–7] The coumarin nucleus is incorporated in many biologically active compounds and natural products.

We have recently described[8,9] a new and operationally convenient approach to the synthesis of coumarin derivatives based on the aromatic electrophilic substitution reaction between the conjugate base of substituted phenols and a vinyltriphenylphosphonium salt. As part of our current studies on the developement of new routes to heterocyclic and carbocyclic systems, we now report the reaction between aminophenols and dimethyl acetylenedicarboxylate (DMAD) in the presence of triphenylphosphine. Thus, the reaction of DMAD and triphenylphosphine in the presence of 2-aminophenol, 3-aminophenol, 4-aminophenol or 2-amino-3-hydroxypyridine leads to functionalized coumarins, 1,4-oxazines, or iminophosphorane[10] derivatives. The reactions of tertiary phosphorus compounds with DMAD and, on occasion, other acetylenic systems have been discussed with emphasis upon the synthesis of phosphorus heterocycles.[11]

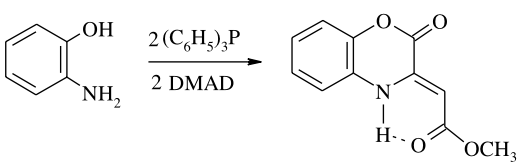
2. Results and discussion

2.1. 2-Aminophenol

The reaction of 2-aminophenol with 2 equiv. of DMAD in the presence of 2 equiv. of triphenylphosphine was carried out in refluxing toluene. The product was identified as methyl 2-[2-oxo-2*H*-1,4-benzoxazine-3(4*H*)-yliden]acetate (**1**) (see Scheme 1).

A compound identical with this product has been reported by Iwanami.[12] Proton NMR chemical shifts and melting point of the compound described in the paper supports its identity. Complete ^{1}H and ^{13}C NMR shifts for **1** are given in Section 4.

Compound **1** results from the initial addition of triphenylphosphine to DMAD and subsequent protonation of the reactive 1:1 adduct by 2-aminophenol. Then the positively charged ion is attacked by the nitrogen atom of the conjugate base of the phenol derivative to produce phosphorane **2**. The 2-oxo-2*H*-1,4-benzoxazine-3(4*H*)-ylidene derivative **1** is presumably produced by intramolecular lactonization of the unsaturated diester **4**, which is formed by proton-transfer reaction and elimination of triphenylphosphine (see Scheme 2).



1 (70%)

Scheme 1.

Keywords: aromatic substitution; ring formation; coumarin derivatives; triphenylphosphine; iminiphosphoranes; 2-oxo-2*H*-pyrano[2,3-*c*]-pyridines.

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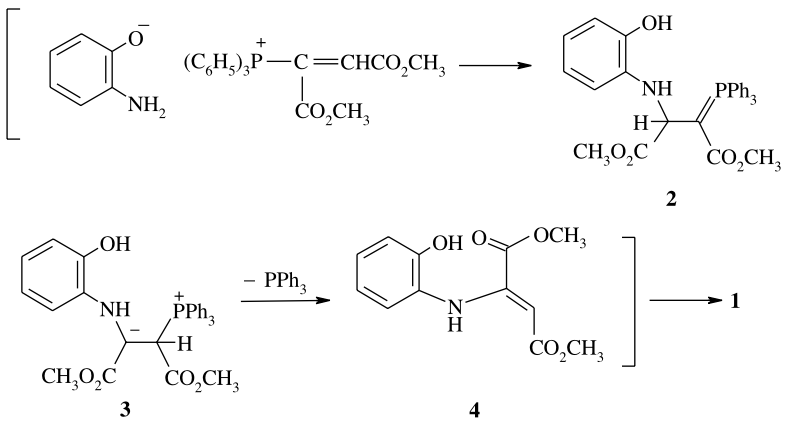
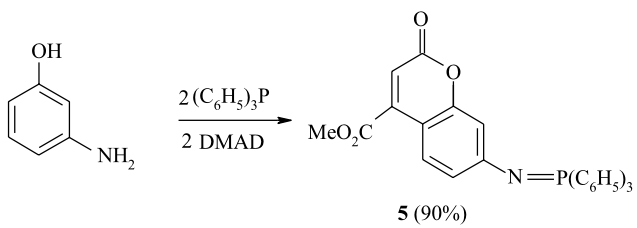


Scheme 2.



Scheme 3.

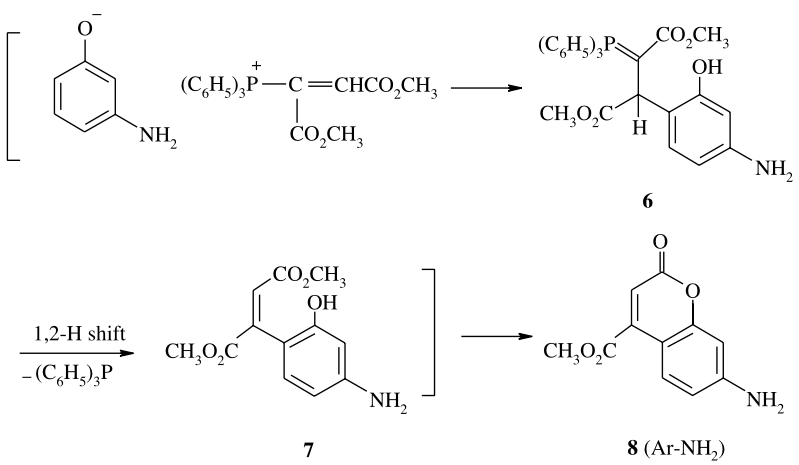
2.2. 3-Aminophenol

The reaction of 3-aminophenol with 2 equiv. of DMAD in the presence of 2 equiv. of triphenylphosphine was carried out in refluxing toluene to produce compound **5** (see Scheme 3). Structure **5** was assigned to the isolated product on the basis of its elemental analyses and IR, ^{1}H, ^{13}C, and ^{31}P NMR and mass spectral data. No other compound was obtained from the reaction mixture by column chromatography.

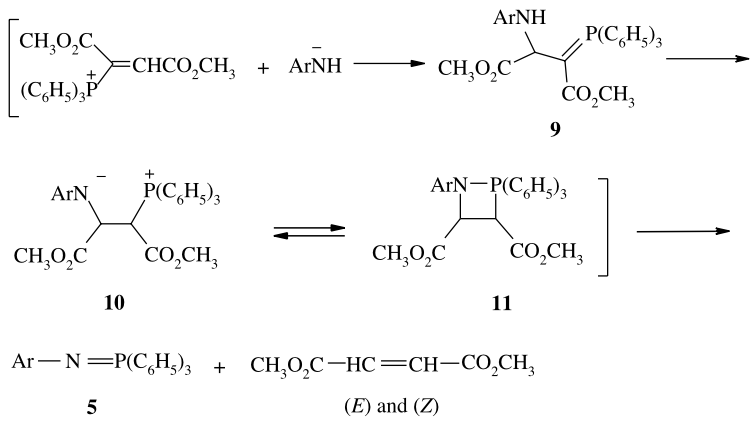
Although we have not yet established the mechanism of the formation of iminophosphorane derivative **5** in an experimental manner, a possible explanation is proposed in Schemes 4 and 5. 3-Aminophenol potentially has two acidic protons, which can protonate the 1:1 adduct of triphenylphosphine and acetylenic ester. These processes are separately shown in Schemes 4 and 5. On the basis of the well established chemistry of trivalent phosphorus nucleophiles, it is reasonable to assume that heterocyclic moiety of **5** results from the initial addition of triphenylphosphine to the acetylenic ester and subsequent protonation of the reactive 1:1 adducts, followed by electrophilic attack of the vinyltriphenylphosphonium cation on the aromatic ring at the position activated by both activating groups (Scheme 4). The coumarin moiety is presumably produced by intramolecular lactonization of the unsaturated diester **7**, which results from **6** by 1,2-hydrogen shift and elimination of triphenylphosphine (see Scheme 4). A possibility for formation of the iminophosphorane moiety is depicted in Scheme 5. The reaction, presumably proceeds through a proton shift from nitrogen to the ylidic carbon of **9**, which leads to the 1,4-diionic species **10**. This betaine intermediate can be in equilibrium with the azaphosphetane **11**. Elimination of dimethyl fumarate and dimethyl maleate from the later produces iminophosphorane derivative **5** (Scheme 5). Observation of of the signals of dimethyl fumarate and dimethyl maleate in the ^{1}H and ^{13}C NMR spectra of the crude reaction mixture supports the proposed mechanism.

2.3. 4-Aminophenol

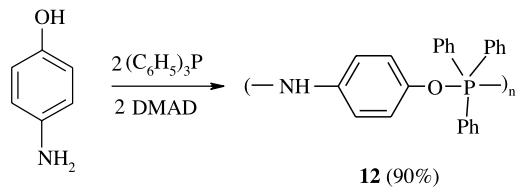
The reaction of 4-aminophenol with 2 equiv. of DMAD in the presence of 2 equiv. of triphenylphosphine was carried out in dichloromethane. A white powder was obtained from



Scheme 4.



Scheme 5.



Scheme 6.

the reaction mixture after 12 h. The product **12** (see Scheme 6) recovered unchanged after refluxing in boiling toluene for 24 h. Compound **12** is only slightly soluble in hot dimethyl sulfoxide. On the basis of its elemental analyses, IR, and ^{1}H NMR spectral data we assigned the following structure to compound **12**.

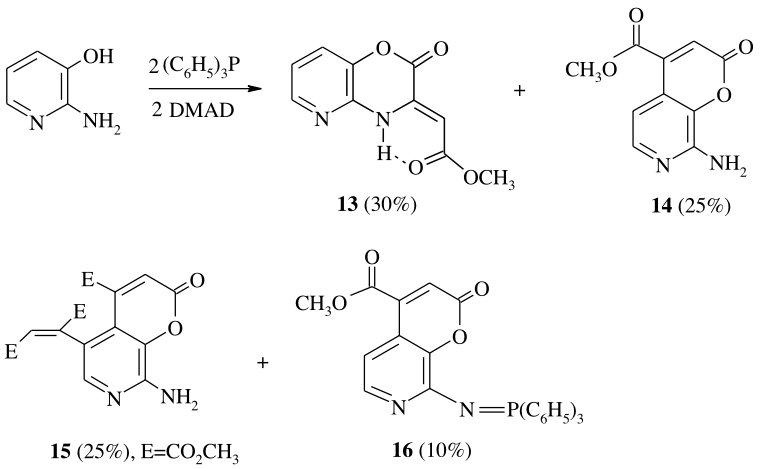
2.4. 2-Amino-3-hydroxypyridine

Under the reaction conditions given for 3-aminophenol, four products were isolated from the reaction mixture of 2-amino-3-hydroxypyridine with DMAD. These products were identified as methyl 2-[2-oxo-2*H*-pyrido[3,2-*b*][1,4]oxazin-3(4*H*)-yliden]acetate (**13**), methyl 8-amino-2-oxo-2*H*-pyrano[2,3-*c*]pyridine-4-carboxylate (**14**), dimethyl (*E*)-2-[8-amino-4-(methoxycarbonyl)-2-oxo-2*H*-pyrano[2,3-*c*]pyridin-5-yl]-2-butanedioate (**15**), and methyl 2-oxo-8-[(triphenylphosphoranylidene)amino]-2*H*-pyrano[2,3-*c*]pyridine-4-carboxylate (**16**) (see Scheme 7).

Structures **13**–**16** were assigned to the isolated products on the basis of their elemental analyses and IR, ^{1}H, ^{13}C, and ^{31}P NMR and mass spectral data. The (*E*)-configuration of the carbon–carbon double bond in **15** is based on the chemical shift of the olefinic proton.[13] Formation of compound **13** may be similar to that outlined in Scheme 2 for 1,4-benzoxazine derivative **1**. Compounds **14**, **15**, and **16** could be obtained by mechanisms similar to those mentioned in Schemes 2–5.

3. Conclusions

We have found that the reaction between triphenylphosphine and dimethyl acetylenedicarboxylate in the presence of 2-aminophenol, 3-aminophenol, 4-aminophenol and 2-amino-3-hydroxypyridine leads to vinylphosphonium salts, which undergo Michael addition with the cojugate base of the aminophenol or aminohydroxypyridine to produce highly functionalized heterocyclic systems of potential synthetic interest. The present method carries the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification. The unexpected formation of iminophosphorane derivatives **5** and **16**, requires further investigation of the present method to establish its utility and scope.



Scheme 7.

4. Experimental

Dimethyl acetylenedicarboxylate, triphenylphosphine, 2-aminophenol, 3-aminophenol, 4-aminophenol and 2-amino-3-hydroxypyridine were obtained from Fluka (Buchs, Switzerland) and were used without further purification. Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H and N were performed using a Heraeus CHN–O-Rapid analyzer. Mass spectra were recorded on a FINNIGAN-MATT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H, ^{13}C and ^{31}P NMR spectra were measured ($CDCl_3$ solution) with a Bruker DRX-500 AVANCE spectrometer at 500.1, 125.8, and 202.5 MHz, respectively. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Chromatography columns were prepared from Aldrich silica gel 70–230 mesh.

4.1. General

To a magnetically stirred solution of triphenylphosphine (1.05 g, 4 mmol) and 2-aminophenol (0.218 g, 2 mmol) in toluene (20 mL) was added dropwise a mixture of DMAD (0.568 g, 4 mmol) in toluene (4 mL) at −5°C for 10 min. The reaction mixture was then allowed to warm up to room temperature and refluxed for 12 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography using hexane–ethyl acetate (2:1) as eluent. The solvent was removed under reduced pressure and the product was recrystallized from ethyl acetate or hexane–ethyl acetate (1:2).

4.1.1. Methyl 2-[2-oxo-2*H*-1,4-benzoxazine-3(4*H*)-yliden]acetate (1). Pale yellow crystals, mp 167–168°C (from 2:1 ethyl acetate–hexane) (lit.[12] mp 170°C), yield 70%. ^{1}H NMR: δ 3.78 (3H, s, OCH_3), 5.90 (1H, s, CH), 6.98 (1H, d, J=7.7 Hz, CH), 7.00 (1H, t, J=7.5 Hz, CH), 7.11 (1H, t, J=7.5 Hz, CH), 7.12 (1H, d, J=7.5 Hz, CH), 10.64 (1H, br s, NH). ^{13}C NMR: δ 52.25 (OCH_3), 90.64, 114.83, 116.99 and 122.78 (4CH), 124.16 (C), 125.66 (CH), 138.15 and 140.00 (2C), 155.86 and 165.33 (2C=O).

4.1.2. Methyl 2-oxo-7-[(triphenylphosphoranylidene)-amino]-2*H*-chromene-4-carboxylate 5. Yellow crystals, mp 161–163°C (from ethyl acetate), yield 90%. IR (KBr) (ν_{max}, cm^{-1}): 1700 (C=O), 1591, 1568, 1489, 1346, 1244, 1122. MS, *m/z* (%): 479 (M^+, 100), 402 (10), 277 (7), 262 (15), 183 (80), 108 (25), 51 (12). Anal. Calcd for $C_{29}H_{22}NO_4P$ (479.47): C, 72.65; H, 4.62; N, 2.92. Found (%): C, 72.7; H, 4.6; N, 2.9. ^{1}H NMR: δ 3.92 (3H, s, OCH_3), 6.45 (1H, s, CH), 6.53 (1H, d, $^{4}J_{HH}$=2.2 Hz, CH), 6.85 (1H, dd, $^{3}J_{HH}$=8.9 Hz, $^{4}J_{HH}$=2.1 Hz, CH), 7.48 (6H, td, $^{3}J_{HH}$=7.7 Hz, $^{4}J_{PH}$=3 Hz, *meta* CH), 7.56 (3H, td, $^{3}J_{HH}$=7.7 Hz, $^{5}J_{PH}$=1.4 Hz, *para* CH), 7.74 (6H, dd, $^{3}J_{HH}$=7.6 Hz, $^{3}J_{PH}$=12.2 Hz, *ortho* CH), 7.81 (1H, dd, $^{3}J_{HH}$=8.9 Hz, $^{4}J_{HH}$=0.8 Hz, CH). ^{13}C NMR: δ 52.78 (OCH_3), 106.85 (C), 108.66 (d, $^{3}J_{PC}$=16.9 Hz, CH), 111.32 (CH), 122.41 (d, $^{3}J_{PC}$=21.8 Hz, CH), 126.53 (d, $^{4}J_{PC}$=1.8 Hz, CH), 128.98 (d, $^{3}J_{PC}$=12.3 Hz, C^{m}), 129.23 (d, $^{1}J_{PC}$=100.2 Hz, C^{ipso}), 132.37 (d, $^{4}J_{PC}$=2.5 Hz, C^{p}), 132.57 (d, $^{2}J_{PC}$=9.7 Hz, C^{o}), 143.14 (C), 156.32 (d, $^{2}J_{PC}$=2.5 Hz, C–N), 157.58 (d, $^{4}J_{PC}$=1.2 Hz, C–O), 161.83 and 165.27 (2C=O). ^{31}P NMR: δ 7.54 ($Ph_3P^+-N^-$).

4.1.3. Poly(4-aminophenoxytriphenylphosphorane) 12. White powder, mp 200–203°C (melted and decomposed), yield 90%. IR (KBr) (ν_{max}, cm^{-1}): 3195 (NH), 1710, 1571, 1483, 1427, 1316, 1234, 1099, 826. Anal. Calcd for $(C_{24}H_{20}NOP)_n$ $(369.40)_n$: C, 78.04; H, 5.46; N, 3.79. Found (%): C, 78.1; H, 5.5; N, 3.8. ^{1}H NMR: δ 6.05 (2H, d, J=9.0 Hz, 2CH), 6.55 (2H, d, J=9.0 Hz, 2CH), 7.4–7.7 (15H, m, $3C_6H_5$), 8.51 (1H, br, NH). ^{31}P NMR: δ 22.04.

4.1.4. Methyl 2-[2-oxo-2*H*-pyrido[3,2-*b*][1,4]oxazine-3(4*H*)-yliden]acetate 13. Pale yellow crystals, mp 117–119°C (from ethyl acetate), yield 30%. IR (KBr) (ν_{max}, cm^{-1}): 3185 (NH), 1747, 1668 and 1615 (C=O). MS, *m/z* (%): 220 (M^+, 82), 188 (44), 160 (100), 93 (53), 65 (25). Anal. Calcd for $C_{10}H_8N_2O_4$ (220.18): C, 54.55; H, 3.66; N, 12.72. Found (%): C, 54.5; H, 3.6; N, 12.7. ^{1}H NMR: δ 3.78 (3H, s, OCH_3), 5.97 (1H, s, CH), 6.97 (1H, dd, J=7.9, 4.8 Hz, CH), 7.38, (1H, d, J=7.9 Hz, CH), 8.07 (1H, d, J=4.8 Hz, CH), 10.76 (1H, br s, NH). ^{13}C NMR: δ 51.66 (OCH_3), 94.00, 118.29 and 123.95 (3CH), 135.70, 137.33 and 138.04 (3C), 144.74 (CH), 154.98 and 168.99 (2C=O).

4.1.5. Methyl 8-amino-2-oxo-2*H*-pyrano[2,3-*c*]pyridine-4-carboxylate 14. Pale orange crystals, mp 220°C (dec) (from ethyl acetate), yield 25%. IR (KBr) (ν_{max}, cm^{-1}): 3450 and 3255 (NH), 1731, 1705 and 1626 (C=O). MS, *m/z* (%): 220 (M^+, 100), 192 (28), 161 (25), 133 (20), 105 (30), 63 (32). Anal. Calcd for $C_{10}H_8N_2O_4$ (220.18): C, 54.55; H, 3.66; N, 12.72. Found (%): C, 54.6; H, 3.7; N, 12.7. ^{1}H NMR: δ 3.98 (3H, s, OCH_3), 6.00 (2H, br, NH_2), 7.07 (1H, s, CH), 7.31 (1H, d, J=5.5 Hz, CH), 7.90 (1H, d, J=5.5 Hz, CH). ^{13}C NMR: δ 52.66 (OCH_3), 107.85 (CH), 120.29 (C), 123.20 and 123.27 (2CH), 141.65, 142.56 and 149.50 (3C), 158.19 and 163.62 (2C=O).

4.1.6. Dimethyl (*E*)-2-[8-amino-4-(methoxycarbonyl)-2-oxo-2*H*-pyrano[2,3-*c*]pyridin-5-yl]-2-butanedioate 15. Yellow crystals, mp 161–163°C (from ethyl acetate), yield 25%. IR (KBr) (ν_{max}, cm^{-1}): 3500 and 3475 (NH), 1726 (C=O). MS, *m/z* (%): 362 (M^+, 82), 331 (74), 303 (49), 271 (100), 244 (55), 216 (30), 185 (20), 157 (18), 129 (20), 103 (12), 87 (40), 75 (38), 59 (80). Anal. Calcd for $C_{16}H_{14}N_2O_8$ (362.30): C, 53.04; H, 3.89; N, 7.73. Found (%): C, 53.1; H, 3.9; N, 7.7. ^{1}H NMR: δ 3.80, 3.98 and 3.99 (9H, 3s, $3OCH_3$), 5.21 (2H, br, NH_2), 6.86 (1H, s, CH), 7.18 (1H, s, CH), 7.67 (1H, s, CH). ^{13}C NMR: δ 52.12, 52.78 and 53.43 ($3OCH_3$), 109.07 and 119.12 (2CH), 120.87 (C), 124.22 (CH), 137.73, 140.68, 144.04, 146.77 and 147.77 (5C), 157.93, 162.93, 165.54 and 167.91 (4C=O).

4.1.7. Methyl 2-oxo-8-[(triphenylphosphoranylidene)-amino]-2*H*-pyrano[2,3-*c*]pyridine-4-carboxylate 16. Pale red crystals, mp 204–206°C (from hexane–ethyl acetate 1:2), yield 10%. IR (KBr) (ν_{max}, cm^{-1}): 1714 (C=O), 1570, 1452, 1421, 1350, 1115, 1010. MS, *m/z* (%): 481 (M^++1, 49), 393 (40), 277 (75), 262 (70), 199 (20), 183 (100), 152 (28), 108 (45), 77 (50). Anal. Calcd for $C_{28}H_{21}N_2O_4P$ (480.46): C, 70.00; H, 4.41; N, 5.83. Found (%): C, 70.1; H, 4.4; N, 5.8. ^{1}H NMR: δ 3.97 (3H, s, OCH_3), 7.07 (1H, s, CH), 7.20 (1H, br d, J=7.5 Hz, CH), 7.45 (6H, td, $^{3}J_{HH}$=7.7 Hz, $^{4}J_{PH}$=2.8 Hz, *meta* CH), 7.53 (3H, td, $^{3}J_{HH}$=7.7 Hz, $^{5}J_{PH}$=1.4 Hz, *para* CH), 7.71 (1H, br d, J=7.5 Hz, CH), 7.90 (6H, dd, $^{3}J_{HH}$=7.5 Hz, $^{3}J_{PH}$=12.2 Hz,

ortho CH), 7.81 (1H, dd, $^{3}J_{HH}$=8.9 Hz, $^{4}J_{HH}$=0.8 Hz, CH). ^{13}C NMR: δ 53.07 (OCH_3), 106.90 (CH), 122.05 (d, $^{4}J_{PC}$=4.5 Hz, C), 123.65 (CH), 128.42 (d, $^{3}J_{PC}$=12.2 Hz, C^{m}), 129.29 (d, $^{1}J_{PC}$=101.9 Hz, C^{ipso}), 131.84 (d, $^{4}J_{PC}$=2.6 Hz, C^{p}), 133.22 (d, $^{2}J_{PC}$=9.9 Hz, C^{o}), 142.87 (CH), 143.50 (C), 148.25 (d, $^{3}J_{PC}$=23.5 Hz, C), 154.08 (d, $^{2}J_{PC}$=6.1 Hz, C), 158.45 and 162.52 (2C=O). ^{31}P NMR: δ 15.77 ($Ph_3P^{+}-N^{-}$).

Acknowledgments

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