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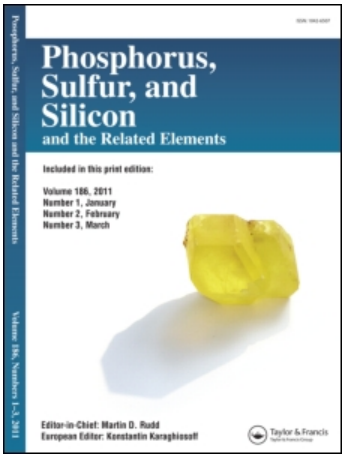

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STUDIES ON PHOSPHONIUM YLIDES-XIV. THE BEHAVIOUR OF 5-(4-PYRIDYL)-2-THIONO-1,3,4-OXADIAZOLE TOWARDS WITTIG REAGENTS

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(Received July 23, 1990)

Wittig reagents (**Ia–c**) react with 5-(4-pyridyl)-2-thiono-1,3,4-oxadiazole (**II**) yielding the new adducts (**IIIa–d**). Structural reasoning for compounds **III** was based on compatible analytical and spectral data (IR, ^{1}H NMR, ^{31}P NMR, and MS). The mechanism that accounts for formation of adducts **III** is discussed.

Key words: Wittig reagents (**I**); 5-(4-Pyridyl)-2-thiono-1,3,4-oxadiazole (**II**); Cyano-5-(4-pyridyl)-β-cyano-α-(triphenylphosphoranylidene)-2-propyl-1,3,4-oxadiazole (**IIIa**); Benzoyl-5-(4-pyridyl)-β-benzoyl-2-propene-1,3,4-oxadiazole (**IIIb**); Methyl-5-(4-pyridyl)-2-carboxyethylene-1,3,4-oxadiazole (**IIIc**); and 5-(4-Pyridyl)-2-propyl-1,3,4-oxadiazole (**IIId**).

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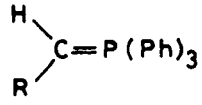
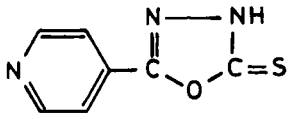
INTRODUCTION

The antibacterial, fungicidal, and pharmacological characteristics[1–3] inherent in substituted 1,3,4-oxa- and thiadiazole derivatives enhanced the synthesis of new compounds incorporating such important nuclei that may possibly lead to further biological activity. This investigation deals with the reaction of Wittig reagents (**I**) with 5-(4-pyridyl)-2-thiono-1,3,4-oxadiazole (**II**).



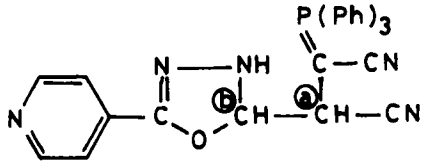
I **a**, R = CN
b, R = COPh
c, R = $COOCH_3$



II

RESULTS AND DISCUSSION

We have found that when oxadiazole derivative **II** was treated with one equivalent of cyanomethylenetriphenylphosphorane (**Ia**) in boiling toluene for 6 hours, cyano-5-(4-pyridyl)-β-cyano-α-(triphenylphosphoranylidene)-2-propyl-1,3,4-oxadiazole (**IIIa**), triphenylphosphine sulfide and some unchanged oxadiazole (**II**) were isolated. Carrying out the reaction using two moles of phosphonium ylide (**Ia**) instead of one, lead to the formation of adduct **IIIa** in good yields. The structure of the new product **IIIa** is assignable from its analysis, IR, ^{1}H, ^{31}P NMR and mass spectral data. Elemental and mass spectral analyses (by Field Ionization Method) for compound **IIIa** corresponded to an empirical formula of $C_{29}H_{22}N_5OP$. Its IR



III a

spectrum, in KBr, revealed the presence of NH absorption band at 3010 cm^{-1}. On the other hand, the C=S band present around 1260 cm^{-1} in the spectrum of **II** was absent in the IR spectrum of **IIIa**. Moreover, the IR spectrum of IIIa exhibits strong absorption bands at 1680 and 1505 cm^{-1} characteristic for the $\rangle C{=}P$ group absorption[4] and at 1400 cm^{-1} denoting the $\rangle P{-}C{-}$ (phenyl) absorption.[5] Adduct **IIIa** possesses ylid-phosphorane structure since it exhibits a positive shift in its ^{31}P NMR (δ = +29.736, vs. 85% H_3PO_4) and absorbs in the region characteristic for this class of compounds.[6]

^1H NMR spectrum of cyano-5-(4-pyridyl)-β-cyano-α-(triphenylphosphoranylidene)-2-propyl-1,3,4-oxadiazole (**IIIa**) showed signals centered at δ = 3.3 (*dd* with ^3J HP = 12 Hz, J HH = 7.15 Hz) and at δ = 4.2 (*d* with J HH = 7.15 Hz) corresponding to the exocyclic methine protons ⓐ and ⓑ, respectively. The exchangeable (D_2O) proton (NH) appears as a broad singlet at 8.53 ppm. The four methylene protons of the pyridyl ring appeared as two doublets centered at δ = 7.9 and 8.3 ppm with coupling constant value of 6.05 Hz.[7] The spectrum also revealed a complex pattern due to the aromatic protons (15 H) in the region 7.44–7.78 ppm. The mass spectrum of **IIIa** showed the molecular ion peak at m/e 487.

The mechanism proposed to account for the formation of adduct **IIIa** is shown in "Scheme 1." Adduct **IIIa** can be obtained via thiocarbonyl olefination by one mole of Wittig reagent (**Ia**) to give the intermediate (A) followed by Michaelis addition of a second phosphorane molecule to afford the stable ylid-phosphorane adduct **IIIa** possible via migration of the α-proton to the electron rich center of the molecule.

Similarly, the reaction of benzoylmethylenetriphenylphosphorane (**Ib**) with 5-(4-pyridyl)-2-thiono-1,3,4-oxadiazole (**II**) proceeds in boiling toluene to give chromatographically pure adduct assigned structure **IIIb**. Triphenylphosphine and triphenylphosphine sulfide were also isolated from the reaction medium. Compound **IIIb** is equally obtained irrespective whether one or two mole equivalents of the Wittig reagent **Ib** were used. Reasons for structure **IIIb** were: (a) Correct elemental analysis, (b) IR spectrum of benzoyl-5-(4-pyridyl)-β-benzoyl-2-propene-1,3,4-oxadiazole (**IIIb**) shows bands at 1620 (C=N), 3010 (NH), and at 1660, 1665 cm^{-1} for the two CO—Ph groups. The ^1H NMR spectrum of **IIIb** shows two singlet at 6.8 and 7 ppm corresponding to the two methine protons ⓐ and ⓑ, respectively.

The four methylene protons of the pyridyl ring appeared as two doublets centered at δ = 7.9 and 8.3 ppm with J HH = 6 Hz. The aromatic protons together with the NH proton appeared as multiplet at 7.3–7.6 ppm (*m*, 10 H + NH). Moreover, the mass spectrum of **IIIb** shows the ion peak at m/e 383 (M^+, 3%), m/e 278 (M^+

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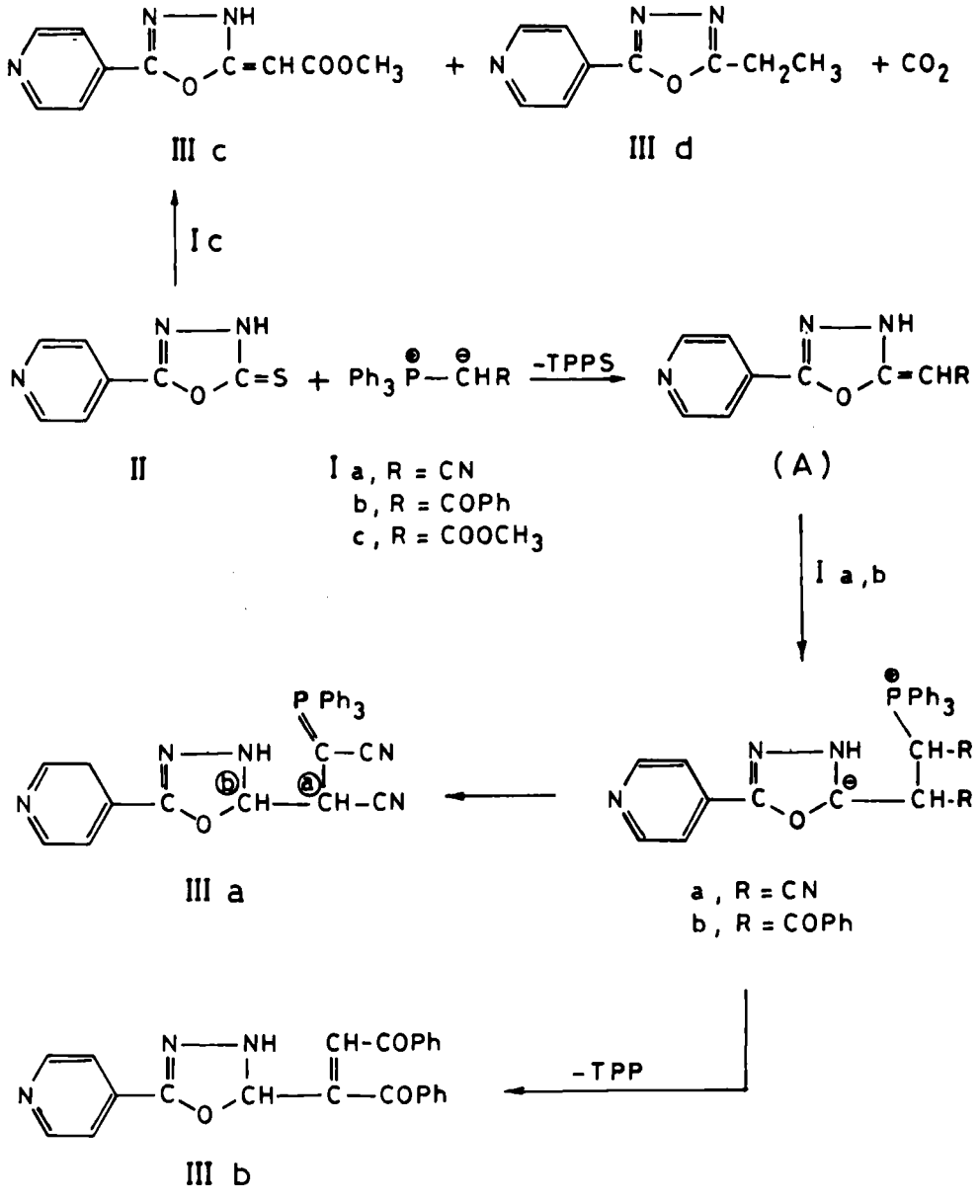

Scheme (1)

—CO Ph, 35%), m/e 173 (M^+ – 2 CO Ph, 75%) and m/e 148 ($C_7H_5N_3O$, 95%) base peak.

It could be demonstrated that the formation of adduct **IIIb** can be explained by initial nucleophilic attack by the carbanion center in the ylide **Ib** on the reactive thiocarbonyl-carbon to give the olefinic compound (A) which adds a second molecule of the ylide **Ib** by Michaelis addition followed by expulsion of triphenylphosphine to yield the final product **IIIb** "cf. Scheme I."

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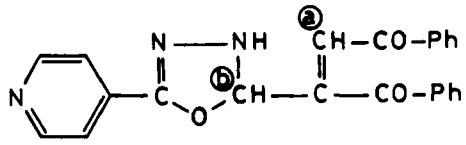
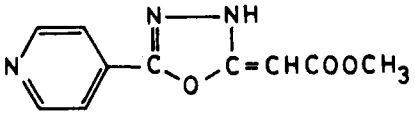
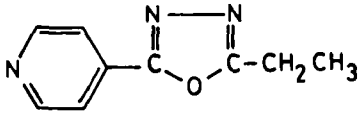


III b

When oxadiazole derivative (**II**) was allowed to react with carbmethoxymethylenetriphenylphosphorane (**Ic**) in boiling toluene in 1:1 mole ratio, two colourless products assigned structures **IIIc** and **IIId** were obtained accompanied with the formation of triphenylphosphine sulfide and evolution of carbon dioxide. Under similar conditions, however, compounds **IIIc** and **IIId** were obtained when two mole equivalents of phosphorane **Ic** were used. On the basis of IR, ^{1}H NMR, MS, and elemental analyses, the structure of compounds **IIIc** and **IIId** were deduced (cf. Experimental).



III c



III d

In the ^{1}H NMR spectrum of **IIIc**, signals appeared at δ = 2.95 (3H, OCH_3, *s*), 5.6 (1H, =C<u>H</u>COOCH$_3$, *s*). The four protons of the pyridyl ring appeared as two doublets at δ = 7.85, 8.85 ppm with coupling constant value of 6.05 Hz. The exchangeable (D_2O) NH proton appeared as singlet at δ = 8.9 ppm. The ^{1}H NMR spectrum of the other product **IIId** showed signals at δ = 1.5 (3H, ethyl-CH_3, *t*) and at 3.35 (2H, ethyl-CH_2, *q*).

A possible explanation for the course of the reaction of carbmethoxymethylenetriphenylphosphorane (**Ic**) with **II** is shown in "Scheme I."

The findings of the present investigation are of particular interest since they represent a novel application of the Wittig reaction. Moreover, a new method for the preparation of 5-(4-pyridyl)-2-propyl-1,3,4-oxadiazole (**IIId**) by the utilization of Wittig reagent **Ic** is developed.

EXPERIMENTAL

All melting points are uncorrected. The toluene used was dried over Na. Cyanomethylene-,[8] benzoylmethylene-,[9] and methoxymethylene[10]-triphenylphosphoranes, were prepared according to established procedures. The IR spectra were recorded in KBr, with Perkin-Elmer Infracord Model 137 and Beckman Infracord Model 4220. The ^{1}H NMR spectra were taken in $CDCl_3$ on JNM-GX-400 FA Jeol, Tokio, Spectrophotometer. The ^{31}P NMR spectrum was recorded in $CDCl_3$ (vs. H_3PO_4 as external standard) on JNM-PS-100 Fa Jeol Spectrometer. The mass spectra were run at 70 eV on Kratos MS equipment and/or Varian MAT 311 A Spectrometer.

Cyano-5-(4-pyridyl)-β-cyano-α-(triphenylphosphoranylidene)-2-propyl-1,3,4-oxadiazole (**IIIa**): A mixture of 0.01 mole of oxadiazole (**II**)[11] and 0.02 mole of ylide (**Ia**) was heated in 25 ml of dry toluene under reflux for 6 hr. After cooling to room temperature, the reaction mixture was evaporated on a rotavapor under reduced pressure and the residue was treated with pet-ether (b.p. 40–60°C). The colourless precipitated material was filtered off, crystallized from pet-ether (40–60°C) to give **IIIa** as colourless crystals in 90% yield, mp. 55°. Anal. Calcd. for $C_{29}H_{22}N_5OP$ (487.55) C, 71.44; H, 4.55; N, 14.37; P, 6.35. Found: C, 71.50; H, 4.60; N, 14.35; P, 6.30% Mol. Wt (MS) = 487.
Triphenylphosphine sulfide was also isolated from the residual substance (mp. and mixed mp.).

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Benzoyl-5-(4-pyridyl)-β-benzoyl-2-propene-1,3,4-oxadiazole (**IIIb**): A mixture of 0.01 mole of diazole (**II**) and 0.02 mole of ylide (**Ib**) was heated in 25 ml of dry toluene for 6 hr. The reaction mixture was evaporated under reduced pressure and the residue applied to silica gel column using methylene chloride/pet-ether (3:1) as eluent. Adduct IIIb was separated in 75% yield as colourless crystals, mp. 132°. Anal. Calcd. for $C_{23}H_{17}N_3O_3$ (383.437) C, 72.04; H, 4.47; N, 10.96. Found: C, 72.10; H, 4.50; N, 10.9%. Mol. Wt. (MS) = 383.

Triphenylphosphine and triphenylphosphine sulfide were also isolated (mp. and mixed mp.).

Reaction of carbmethoxymethylenetriphenylphosphorane (**Ic**) with 5-(4-pyridyl)-2-thiono-1,3,4-oxadiazole (**II**):

To a suspension of oxadiazole (**II**) (0.18 g, 0.001 mol) in dry toluene (20 ml), was added ylide (1c) (0.33 g, 0.001 mol) in toluene (10 ml) and the reaction mixture was heated under reflux for 6 hr. until no more of the starting materials could be detected (TLC). After cooling to room temperature, the reaction mixture was evaporated under reduced pressure and applied to silica gel column using (acetone/pet-ether 40–60) (3:7) as eluent.

Adduct **IIIc** is separated as colourless crystals mp. 82° in 45% yield. Anal. Calcd. for $C_{10}H_9N_3O_3$ (219.23) C, 54.78; H, 4.14; N, 19.18. Found: C, 54.80; H, 4.20; N, 19.20% Mol. Wt. (MS) = 219.

IR: bands at 1610 (C=N), 3015 (NH), 1690 (C=O, ester).

MS: 219 (M^+), 188 (M^+ —OCH_3), 160 (M^+ —$COOCH_3$).

Similarly, 5-(4-pyridyl)-2-propyl-1,3,4-oxadiazole (**IIId**) was separated in 45% yield from pet-ether (40–60°) as colourless crystals mp. 75°. Anal. Calcd. for $C_9H_9N_3O$ (176.219) C, 61.69; H, 5.18; N, 23.99. Found: C, 61.70; H, 5.20; N, 23.9% Mol. Wt. (MS) = 175.

IR: bands at 1610 (C=N), 1620 (C=N), MS m/e (relative Intensity %) 175 (20), 146 (65), 78 (90) %.

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