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Pyrido Annelation Reaction by a Tandem Aza Wittig/Electrocyclic Ring-Closure Strategy: Preparation of Pyrazolo[4,3-c]- and Pyrazolo[3,4-c]pyridine Derivatives.

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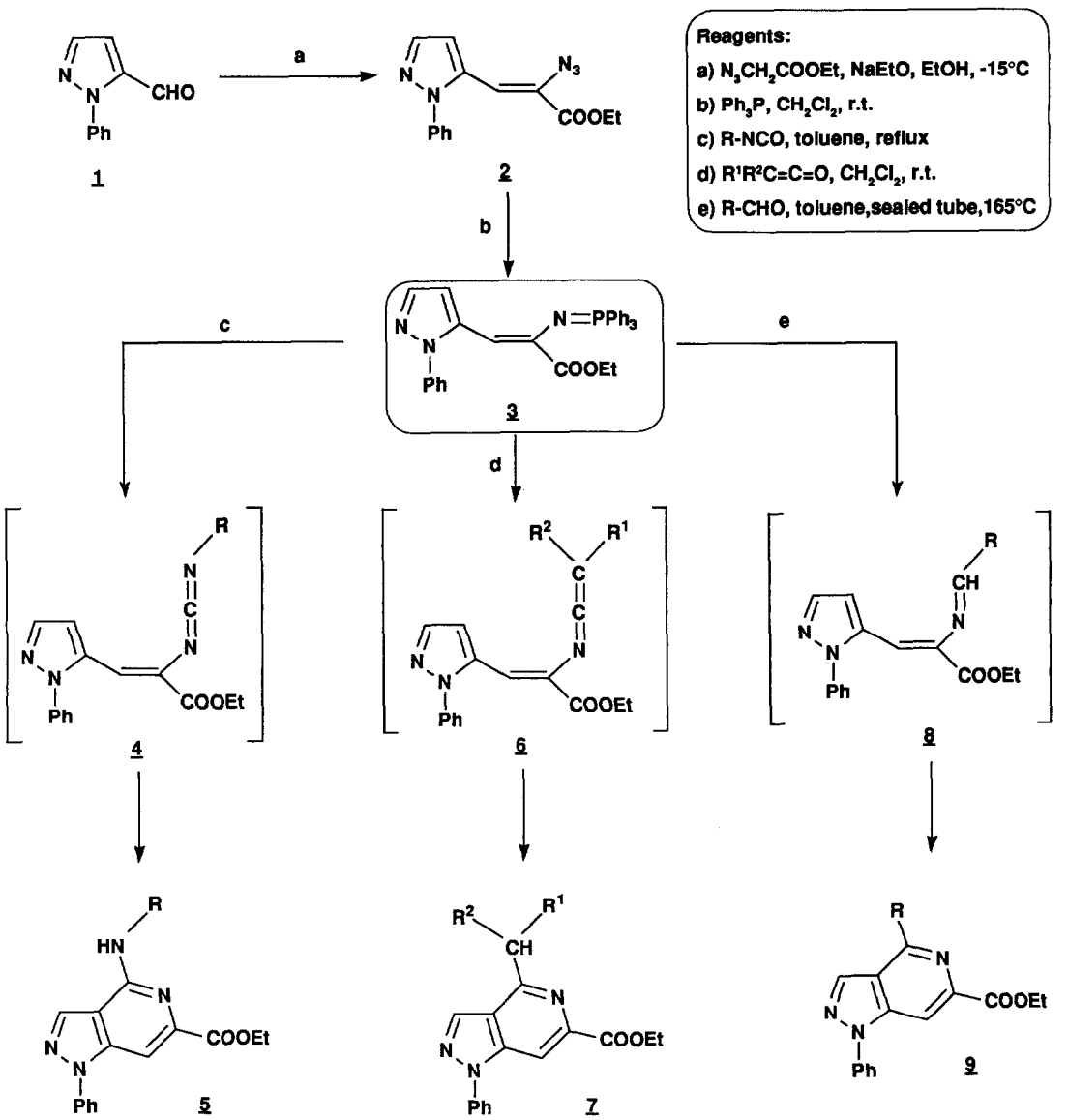
Abstract.- *The aza Wittig-type reaction of iminophosphorane* **3**, *prepared from 5-formyl-1-phenylpyrazole by sequential treatment with ethyl azidoacetate and triphenylphosphine, with isocyanates, ketenes, aldehydes and carbon disulfide leads to the functionalized pyrazolo[4,3-c]pyridines* **5**, **7**, **9** *and* **11** *respectively. Iminophosphorane* **15**, *prepared from 4-formyl-1-phenylpyrazole, undergoes pyrido annelation by reaction with ketenes to give the isomeric pyrazolo[3,4-c]pyridines* **22** *in modest yields.*

Pyrazolo pyridines have continued to attract interest because of their biological activity and structural relationship to indoles and azaindoles and several methods have been adopted for the synthesis of this ring system and have been comprehensively reviewed[1]. However, the synthesis of pyrazolo[4,3-c]pyridines has been achieved in only a limited number of ways, mostly involving the use either of 4-hydrazinopyridines or pyrazoles containing carboxylic acid functions at positions 4 and 5 as starting materials. The generality of these methods are impaired by the availability of the starting materials.

We have been interested recently in exploiting the unique reactivities afforded by the iminophosphorane function in developing efficient strategies for the preparation of polyheterocycles. In this context, we have found that the tandem aza Wittig/electrocyclization strategy has shown to be an useful protocol for the preparation of fused indoles[2], fused uracils[3] and pyrazolo[3,4-b]pyridines[4]. We report herein a new and apparently general method for the preparation of some derivatives of the pyrazolo[4,3-c]pyridine ring system. Our approach is centered on the aza Wittig-type reaction of the iminophosphorane derived from the ethyl α-azido-β-(5-pyrazolyl)acrylate with isocyanates, ketenes and aldehydes followed by heterocyclization by electrocyclic ring-closure of the resulting aza Wittig product: carbodiimide, ketenimine or aldimine respectively.

Results.- The 5-formyl-1-phenylpyrazole **1** was prepared by a previously reported procedure[5]. The aldehyde **1** was condensed with ethyl azidoacetate in the presence of sodium ethoxide at -15°C to give **2** as crystalline solid in 48% yield. The preparation of the key intermediate iminophosphorane **3** was accomplished, in near quantitative yield, by Staudinger reaction of **2** with triphenylphosphine in dry dichloromethane at room temperature. The i.r.

spectrum of iminophosphorane **3** shows a carbonyl absortion at 1699 cm^{-1} and the ^1H n.m.r. spectrum displays among others signals , a doublet at δ 6.71 ppm ($^4J_{PH}$ 7.1 Hz) corresponding to the β-proton. In the ^{13}C n.m.r. spectrum the carbonylic carbon atom appears as a doublet at δ 166,86 ppm ($^3J_{PC}$ 7.2 Hz), the quaternary carbon atom C_α appears as a doublet at δ 137.69 ppm ($^2J_{PC}$ 6.3 Hz) and the C_β appears as a doublet at δ 103.18 ppm ($^3J_{PC}$ 20.5 Hz), in addition the chemical shifts of all carbons atoms of the pyrazole ring are in good agreement with the literature values[5]. The ^{31}P n.m.r. spectrum only shows a signal at δ 9.64 ppm and the mass spectrum shows the expected molecular ion peak as the base peak.



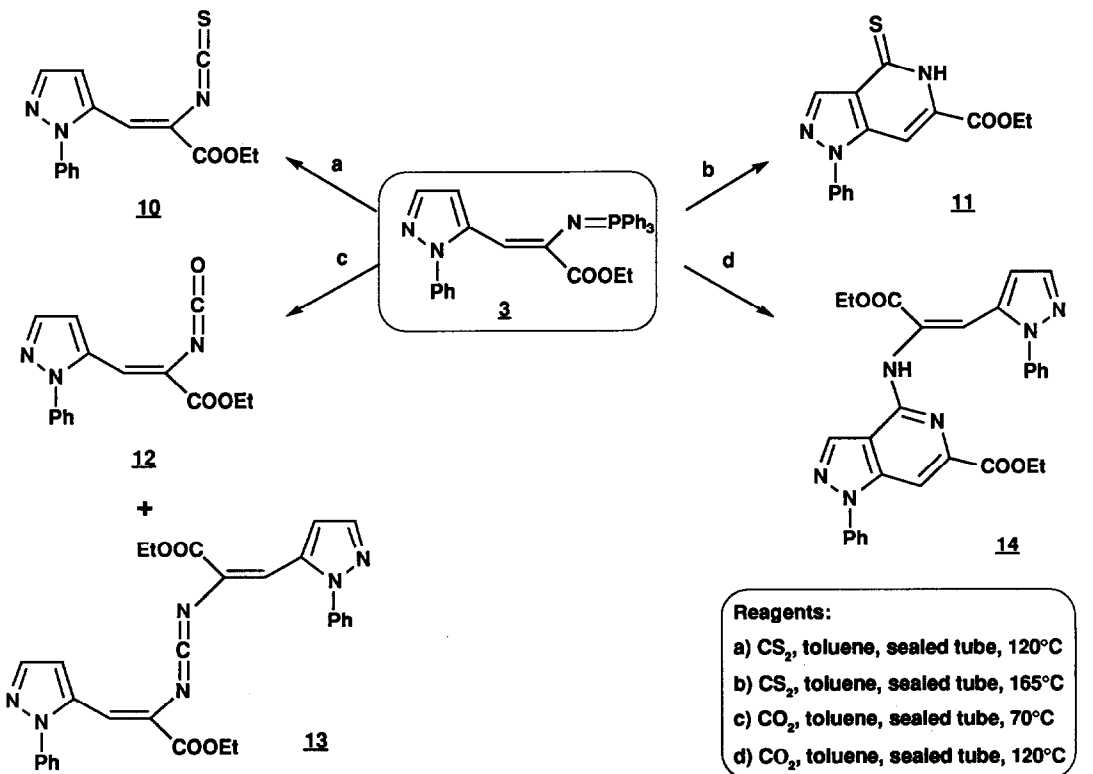
Scheme 1

Aza Wittig-type reaction of iminophosphorane **3** with isocyanates in dry toluene at room temperature led to the corresponding carbodiimides **4** (as evidenced by i.r.) which underwent cyclization in toluene solution at reflux temperature to give 4-amino-6-ethoxycarbonyl-1-phenyl-1H-pyrazolo[4,3-c]pyridines **5** in 60-89% yields. In the same way, iminophosphorane **3** reacts with ketenes in dry dichoromethane at room temperature to give the pyrazolo[4,3-c]pyridines **7a** and **7b** in excellent yields. Preparation of compound **7c** was achieved by reaction with isobutyryl chloride at 0°C in the presence of triethylamine followed by heating in dry toluene at reflux temperature.

We believe that the conversions **3**→ **5** and **3**→**7** involve initial aza Wittig-type reaction to give the intermediate heterocumulene **4** or **6** which undergoes electrocyclic ring-closure followed by [1,3] proton shift to give **5** or **7**.

On the other hand, iminophosphorane **3** also reacted with aliphatic and aromatic aldehydes in toluene at reflux temperature to give directly the corresponding 4-alkyl(aryl)-6-ethoxycarbonyl-1-phenyl-1H-pyrazolo[4,3-c]pyridines **9** in moderate yields (37-51%). These results suggest that the process involves initial aza Wittig reaction to give the unsaturated aldimine **8** which subsequently undergoes electrocyclic ring-closure; further dehydrogenation under the reaction conditions[6] leads to the pyrazolo pyridines **9** (Scheme 1).

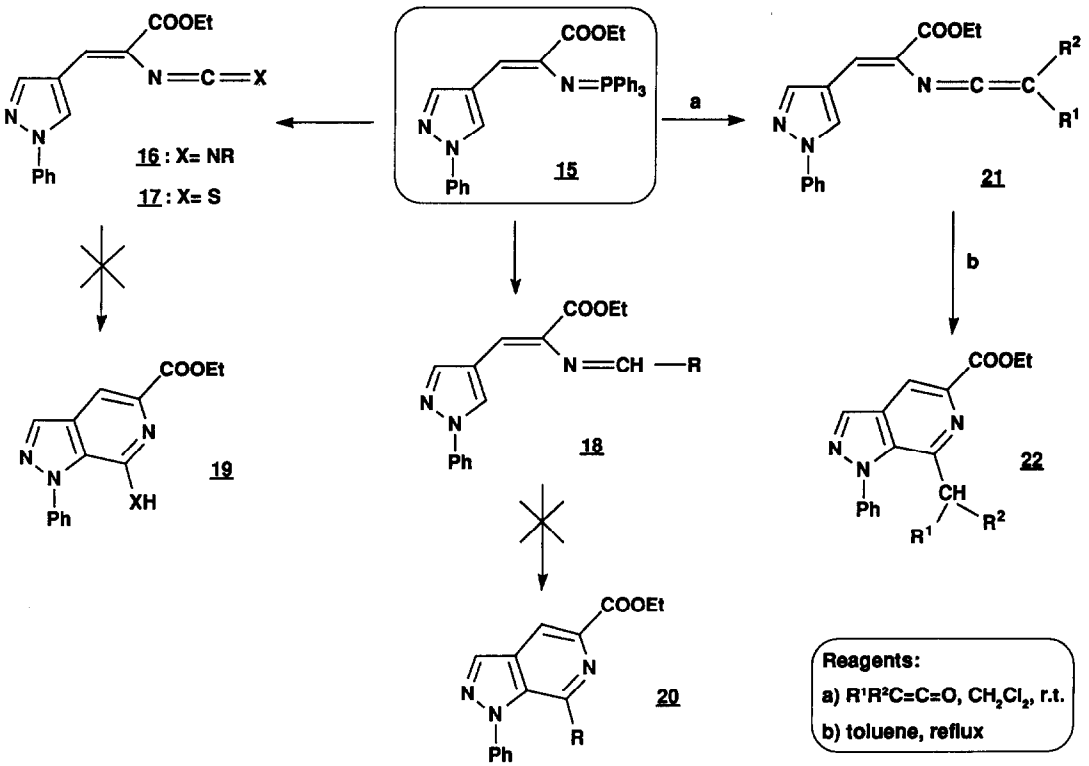
Reaction of iminophosphorane **3** with carbon disulfide in toluene in a glass sealed tube at 120°C resulted in the formation of the isothiocyanate **10**, however, when the reaction was carried out at 165°C for 30h resulted in the formation of the pyrazolo[4,3-c]pyridine-4-thione **11** directly in 95% yield. Similarly, the reaction of **3** with carbon dioxide at 70°C led to a mixture of isocyanate **12** as major product and carbodiimide **13**, presumably formed through an aza Wittig reaction between the starting iminophosphorane **3** and the isocyanate **12**. When the reaction was carried out at 120°C for 10h compound **14** was obtained in moderate yield (40%) (Scheme 2).



Scheme 2

The structure **14** is derivable from mass and i.r. spectral data and from n.m.r. absorptions as summarized in the Experimental Section. The assignment is consistent with ^{1}H and ^{13}C n.m.r. evidence as there are two sets of signals for the two ethoxycarbonyl moieties.

On the other hand, iminophosphorane **15**, readily available from 4-formyl-1-phenylpyrazole by sequential treatment with ethyl azidoacetate and triphenylphosphine, reacted with isocyanates at room temperature to give **16**, with carbon disulfide to give **17**, and with aldehydes to give the corresponding aldimines **18**. Heterocumulenes **16**, and **17** and aldimines **18**, proved to be recalcitrant to cyclization under the thermal conditions above described (165°C for 48h). They failed to form the isomeric pyrazolo[3,4-c]pyridines **19** and **20**. However, iminophosphorane **15** reacted with ketenes in dry dichloromethane at room temperature to give the corresponding ketenimines **21** which by heating in dry toluene were converted into the corresponding pyrazolo[3,4-c]pyridines **22** in moderate yields (Scheme 3).



Scheme 3

The different reactivity showed in electrocyclic ring-closure proccesses for the aza Wittig products of the iminophosphorane **3** derived from 5-formyl-1-phenylpyrazole with respect to iminophosphorane **15** derived from the 4-formyl-1-phenylpyrazole is in accord with the previously reported[5,7] results on the reactivity of 1-phenyl-5-vinylpyrazole and 1-phenyl-4-vinylpyrazole towards electron deficient dienophiles in Diels-Alder reactions.

In summary, the present study demonstrates that tandem aza Wittig/electrocyclic ring-closure strategy affords a new and general entry to a variety of fused pyrazoles. Because of their simplicity, the experimental one-pot

procedure, easy access of the starting materials, the good yields in the iminophosphorane preparation as well as in the cyclization step the investigated reactions provide a method for the preparation of different pyrazolo[4,3-c]pyridines bearing an amino group, an alkyl (aryl) group, or an sulfur atom in the 4 position, which compares favourably with other approaches to this system.

EXPERIMENTAL

All melting points were determined on a Kofler hot-plate melting point apparatus and are uncorrected. IR spectra were obtained as Nujol emulsions on a Nicolet-5DX spectrophotometer. NMR spectra were recorded on a Bruker AC-200 (200 MHz). Mass spectra were recorded on a Hewlett-Packard 5993C spectrometer. Microanalyses were performed on a Perkin-Elmer 240C instrument.

Ethyl α-acido-β[(1-phenyl)-5-pyrazolyl] acrylate 2.

To a well-stirred solution containing sodium (0.69 g, 30 mmol) in dry ethanol (20 ml), a solution of ethyl azidoacetate (3.87 g, 30 mmol) and 5-formyl-1-phenylpyrazole **1** (1.29 g, 7.5 mmol) in the same solvent (15 ml) was added dropwise at -15°C under nitrogen. The reaction mixture was stirred at this temperature for 1h then was allowed to warm to room temperature and was then stirred for 7h. After this it was poured into aqueous 30% ammonium chloride (35 ml) and the precipitated solid was collected by filtration air-dried and chromatographed on silica gel column, eluting with n-hexane/ethyl acetate (3:1) to afford **2** (48%), m.p. 116°C, as colourless prims. (Found: C, 59.58; H, 4.72; N, 24.64. $C_{14}H_{13}N_5O_2$ requires: C, 59.36; H, 4.63; N, 24.72); i.r. (Nujol) 2135, 2114, and 1713 cm^{-1}; ^1H n.r.m. δ ($CDCl_3$): 1.29 (t, 3H, J = 7 Hz), 4.29 (q, 2H, J = 7 Hz) , 6.80 (s, 1H) , 7.20 (d, 1H, J = 1.9 Hz), 7.40-7.49 (m, 5H), 7.73 (d, 1H, J = 1.9 Hz); ^{13}C n.m.r. δ ($CDCl_3$): 13.91 (CH_3), 62.31 (CH_2), 109.87, 111.10, 125.67, 126.19 (q), 128.32, 129.15, 135.58 (q), 138.92 (q), 140.32, 162.62 (C=O); m/z (%): 283 (M^+, 5), 77 (100).

Ethyl β-[(1-phenyl)-5-pyrazolyl]-α-(triphenylphosphoranylidenamino)acrylate 3.

To a solution of triphenylphosphine (0.74 g, 2.8 mmol) in dry dichloromethane (15 ml) was added dropwise at 0°C the azide **2** (0.8 g, 2.8 mmol). The mixture was stirred at room temperature for 4h and then the solvent was removed under reduced pressure. The crude product was chromatographed on silica gel column, eluting with ethyl acetate/n-hexane (2:1) to give **3** (99%), m.p. 164-166°C, as colourless prisms. (Found: C, 74.02; H, 5.69; N, 5.28. $C_{32}H_{28}N_3O_2P$ requires: C, 74.26; H, 5.45; N, 5.41); i.r. (Nujol) 1699, 1211, and 1111 cm^{-1}; 1H n.m.r. δ ($CDCl_3$): 0.85 (t, 3H, J = 7 Hz), 3.75 (q, 2H, J = 7 Hz), 6.71 (d, 1H, J = 7.1 Hz), 7.39 (m, 13H), 7.56 (d, 2H, J = 7.6 Hz), 7.65 (d, 1H, J = 1.6 Hz), 7.72 (m, 6H); ^{13}C n.m.r. δ ($CDCl_3$): 13.69 (CH_3-$CH_2$0), 60.63 (CH_3-CH_2O), 103.18 (C_β, $^3J_{P\text{-}C}$ = 20.5 Hz), 107.31 (C_4), 125.56, 127.12, 128.12 ($^3J_{P\text{-}C}$ = 12.2 Hz), 128.70, 131.02 ($^4J_{P\text{-}C}$ = 2.7 Hz), 132.18 ($^2J_{P\text{-}C}$ = 9.7 Hz), 132.29 ($^1J_{P\text{-}C}$ = 103.5 Hz), 137.69 (C_α, $^2J_{P\text{-}C}$ = 6.3 Hz), 139.95 (C_3), 140.14, 140.49 (C_5), 166.86 (C=O, $^3J_{P\text{-}C}$ = 7.2 Hz; ^{31}P n.m.r. δ 9.64 ppm; m/z (%): 517 (M^+, 100).

General Procedure for the Preparation of 4-alkyl(aryl)amino-6-ethoxycarbonyl-1-phenyl-1H-pyrazolo[4,3-c]pyridines 5.

To a solution of the iminophosphorane **3** (0.6 g, 1.2 mmol) in dry toluene (15 ml) was added the appropriate isocyanate (1.2 mmol). the reaction mixture was stirred at room temperature for 3h and then heated at reflux temperature for 6h (aromatic isocyanates) or 15h (alkyl isocyanates). After cooling, the solution was concentrated to dryness and the residual material was slurried with cold ethanol (15 ml), the solid formed was recrystallized from

ethanol to give **5**.

5a: 4-Methylamino, (60%), m.p. 175-176°C, as yellow prisms. (Found: C, 64.62; H, 5.30; N, 18.74. $C_{16}H_{16}N_4O_2$ requires: C, 64.85; H, 5.44; N, 18.91; i.r. (Nujol) 3403, 1690, and 1252 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.41 (t, 3H, J = 7.1 Hz, CH_3-CH_2), 3.22 (d, 3H, J = 5.0 Hz, CH_3-NH), 4.44 (q, 2H, J =7.1 Hz, CH_3-CH_2), 5.49 (q, 1H, J = 4.7 Hz, NH), 7.39 (t, 1H, J = 7.3 Hz, H_p), 7.54 (t, 2H, J = 7.7 Hz, H_m), 7.68 (d, 2H, J = 7.8 Hz, H_o), 7.76 (s, 1H, H_7), 8.28 (s, 1H, H_3); ^{13}C n.m.r. δ ($CDCl_3$): 14.16 (CH_3-CH_2), 28.71 (CH_3-N), 61.50 (CH_2), 98.75 (C_7), 110,81 (C_{3a}), 122.86 (C_o), 127.41 (C_p), 129.43 (C_m), 133.82 (C_3), 139.05 (C_i), 143.42 (C_{7a}), 143.60 (C_6), 153.61 (C_4), 166.18 (C=O); m/z (%): 296 (M^+, 100).

5b: 4-Benzylamino, (86%), m.p. 228-229°C as colourless prisms. (Found: C, 71.19; H, 5.27; N, 14.83. $C_{22}H_{20}N_4O_2$ requires : C, 70.95; H, 5.41; N, 15.04); i.r. (Nujol) 3380, 1721, and 1238 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.42 (t, 3H, J = 7.1 Hz, CH_3-CH_2), 4.42 (q, 2H, J = 7.1 Hz, CH_3-CH_2), 4.88 (d, 2H, J = 5.6 Hz, CH_2-NH), 5.64 (t, 1H, J = 5.6 Hz, NH), 7.35 (m, 6H), 7.54 (t, 2H, J = 7.6 Hz), 7.67 (d, 2H, J = 7.8 Hz), 7.80 (s, 1H, H_3), 8.13 (s, 1H, H_7); ^{13}C n.m.r. δ ($CDCl_3$): 14.30 (CH_3-CH_2), 46.09 (CH_2-NH), 61.59 (CH_2O), 99.50 (H_7), 110.75 (C_{3a}), 123.03, 127.50, 127.59, 128.07, 128.65, 129.58, 133.51 (C_3), 138.65 (q), 139.19 (q), 143.75 (C_{7a}), 143.77 (C_6), 152.55 (C_4), 166.19 (C=O); m/z (%): 372 (M^+, 100).

5c : 4-Phenylamino, (82%), m.p. 192-193°C, as pale yellow prisms.(Found: C, 70.16; H, 4.92; N, 15.78. $C_{21}H_{18}N_40_2$ requires: C, 70.38; H, 5.06; N, 15.63); i.r. (Nujol) 3368, 1690, and 1258 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.44 (t, 3H, J = 7.1 Hz, CH_3-CH_2), 4.45 (q, 2H, J = 7.1 Hz, CH_3-CH_2), 7.15 (t, 1H, J = 7.2 Hz), 7.37 (m, 3H), 7.52 (t, 2H, J = 7.6 Hz), 7.66 (m, 4H), 7.83 (s, 1H, NH), 7.91 (s, 1H, H_3), 7.94 (s, 1H, H_7); ^{13}C n.m.r δ ($CDCl_3$): 14.20 (CH_3-CH_2O), 61.72 (CH_3-CH_2O), 100.68 (C_7), 111.26 (C_{3a}), 122.30 (Phenyl-NH C_m), 122.99 (Phenyl C_m), 124.34 (Phenyl-NH C_p), 127.61 (Phenyl C_p), 129.10 (Phenyl-NH C_m) 129.51 (Phenyl C_m), 134.45 (C_3), 138.90 (Phenyl C_i), 139.54 (Phenyl-NH C_i), 143.10 (C_6), 143.83 (C_{7a}), 150.55 (C_4), 165.09 (C=O); m/z (%): 358 (M^+, 5), 77 (100).

5d: 4-(p-Tolyl)amino, (88%), m.p. 202-203°C, as pale yellow prisms. (Found: C, 71.19; H, 5.32; N, 14.87. $C_{22}H_{20}N_4O_2$ requires: C, 70.95; H, 5.41; N, 15.04); i.r. (Nujol) 3372, 1688, and 1256 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.43 (t, 3H, J = 7.1 Hz, CH_3-CH_2), 2.35 (s, 3H, CH_3Ar), 4.45 (q, 2H, J = 7.1 Hz, CH_3-CH_2), 7.17 (d, 2H, J = 8.3 Hz), 7.38 (t, 1H, J = 7.2 Hz), 7.51 (m, 4H), 7.55 (s, 1H, NH), 7.65 (d, 2H, J = 8 Hz), 7.70 (s, 1H, H_3), 7.90 (s, 1H, H_7);^{13}C n.m.r. δ ($CDCl_3$): 14.19 (CH_3-CH_2), 20.82 (CH_3Ar), 61.66 (CH_3-CH_2O), 100.27 (C_7), 110.96 (C_{3a}), 122.93 (phenyl C_o), 123.33 (aryl C_o), 127.50 (phenyl C_p), 129.45 (phenyl C_m), 129.70 (aryl C_m), 134.61 (q, aryl C_p), 134.69 (C_3), 136.79 (aryl C_i), 138.93 (phenyl C_i), 143.21 (C_6), 143.89 (C_{7a}), 151.23 (C_4), 165.94 (C=O); m/z (%): 372 (M^+, 13), 91 (100).

5e: 4-(p-Methoxyphenyl)amino, (89%) m.p. 196-197°C, as pale yellow prisms. (Found: C, 67.85; H, 5.32; N, 14.27. $C_{22}H_{20}N_4O_3$ requires; C, 68.03.95; H,5.19; N, 14.42); i.r. (Nujol) 3395, 1711, and 1246 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.48 (t, 3H, J = 7.1 Hz, CH_3-CH_2), 3.82 (s, 3H,CH_3OAr), 4.45 (q, 2H, J = 7.1 Hz, CH_3-CH_2O), 6.93 (d, 2H, J = 8.9 Hz, aryl H_m), 7.39 (t, 1H, J = 7.3 Hz, phenyl H_p), 7.46 (s, 1H, H_3), 7.48 (d, 2H, J = 8.9 Hz, aryl H_o), 7.53 (t, 2H J = 7.5 Hz, phenyl H_m), 7.63 (s, 1H, NH), 7.65 (d, 2H, J = 7.9 Hz, Phenyl H_o), 7.88 (s, 1H, H_7); ^{13}C n.m.r. δ ($CDCl_3$): 14.21 (CH_3-CH_2), 55.40 (CH_3OAr), 61.68 (CH_3-CH_2O), 100.01 (C_7), 110.67 (C_{3a}), 114.49 (aryl C_m), 122.98 (phenyl C_o), 126.21 (aryl C_o), 127.52 (phenyl C_p), 129.47 (phenyl C_m), 132.19 (aryl C_i), 134.82 (C_3), 138.96 (phenyl C_i), 143.24 (C_6), 144.03 (C_{7a}), 152.07 (C_4), 157.55 (aryl C_p), 165.90 (C=O); m/z (%): 388 (M^+, 28), 77 (100).

5f: 4-(p-Fluorophenyl)amino, (87%), 238-239°C, as colourless prims. (Found: C, 66.83; H, 4.31; N, 15.07. $C_{21}H_{17}FN_4O_2$ requires: C, 67.01; H, 4.55; N, 14.89); i.r. (Nujol) 3372, 1688, and 1258 cm^{-1}; ^{1}H.n.m.r. δ (DMSO-d_6): 1.36 (t, 3H, J = 7.1 Hz, CH_3-CH_2), 4.31 (q, 2H, J = 7.1 Hz, CH_3-CH_2O), 7.04 (t, 2H, J = 8.7 Hz, aryl H_m), 7.39 (t, 1H, J = 7.0 Hz, phenyl H_p), 7.55 (t, 2H, J = 7.6 Hz, phenyl H_m), 7.66 (d, 2H, J = 7.8 Hz, phenyl H_o), 7.71 (s, 1H, H_3), 8.12 (dd, 2H, J = 8.8, 5.0 Hz, aryl H_o), 8.68 (s, 1H, H_7), 9.54 (s, 1H, NH); ^{13}C n.m.r. δ (DMSO-d_6): 13.90 (CH_3-CH_2), 60.68 (CH_3-CH_2), 99.65 (C_7), 111.45 (C_{3a}), 114.49 (aryl C_m, J = 21.9 Hz), 120.57 (aryl C_o, J = 7.1 Hz), 122.40 (phenyl C_o), 127.18 (phenyl C_p), 129.33 (phenyl C_m), 134.46 (C_3), 136.90 (aryl C_i, J = 2.3 Hz), 138.69 (phenyl C_i), 142.45 (C_6), 142.62 (C_{7a}), 148.87 (C_4), 157.19 (aryl C_p, J = 239.6 Hz), 165.02 (C=O); m/z (%): 376 (M^+, 26), 77(100).

Preparation of 4-Alkyl-6-ethoxycarbonyl-1-phenyl-1H-pyrazolo[4,3-c]pyridines 7.

Method A: To a solution of iminophosphorane **3** (0.4 g, 0.8 mmol) in dry dichloromethane (20 ml) was added the corresponding ketene (0.8 mmol). The reaction mixture was stirred at room temperature until starting iminophosphorane was consumed (6h for diphenylketene and 35h for ethylphenylketene). The solution was concentrated to dryness and the residual material was washed with ether (10 ml) and recrystallized from ethanol to give **7a** and **7b**.

Method B: To a solution of isobutyryl chloride (0.10 g, 0.97 mmol) in dry ether (5 ml) was added dropwise at 0°C a solution of triethylamine (0.098 g, 0.97 mmol) in dry toluene (5 ml). The mixture was allowed to warm to room temperature and stirred for 30 min, the solution of iminophosphorane **3** (0.2 g, 0.39 mmol) in dry toluene (15 ml) was added. The resultant solution was heated at reflux temperature for 24h. After cooling, the solvent was removed and the residual material was slurried with cold ethanol (15 ml) and the separated solid was collected by filtration and recrystallized from ethanol gave **7c**.

7a: $R^1 = C_6H_5$, $R^2 = C_2H_5$, (67%), m.p. 118-120°C, as colourless prisms. (Found: C, 74.53; H, 6.19; N, 11.08. $C_{24}H_{23}N_3O_2$ requires: C, 74.78; H, 6.01; N, 10.10); i.r. (Nujol) 1732, 1213, and 1123 cm^{-1}; ^{1}H n.m.r. δ ($CDCl_3$): 0.97 (t, 3H, J = 7.1 Hz, CH_3-CH_2), 1.46 (t, 3H, J = 7.1 Hz, CH_3-CH_2O), 2.37 (ddq, 1H, J = 7.1, 7.1, 13.6 Hz), 2.53 (ddq, 1H, J = 7.1, 7.1, 13.6 Hz), 4.46 (m, 1H), 4.50 (q, 2H, J = 7.1 Hz, CH_3-CH_2O), 7.35 (m, 8H), 7.65 (d, 2H, J = 7.8 Hz), 8.14 (s, 1H, H_3), 8.29 (s, 1H, H_7); ^{13}C n.m.r δ ($CDCl_3$): 12.49 (CH_3), 14.31 (CH_3), 27.57 (CH_2), 53.85 (CH), 61.70 (CH_2O), 106.09 (C_7), 122.43 (C_{3a}), 122.96, 127.68, 127.71, 128.38, 128.47, 129.66, 134.90 (C_3), 138.92 (q), 142.27 (C_{7a}), 142.65 (q), 143.68 (C_6), 159.99 (C_4), 165.93 (C=O); m/z (%): 385 ($M^{+\cdot}$ 14), 357 (100).

7b: $R^1 = R^2 = C_6H_5$, (90%), m.p. 170-172°C, as colourless prisms. (Found: C, 77.28; H, 5.51; N, 9.52. $C_{28}H_{23}N_3O_2$ requires: C, 77.58; H, 5.35; N, 9.69); i.r. (Nujol) 1711, 1300, and 1229 cm^{-1}; ^{1}H n.m.r δ ($CDCl_3$): 1.36 (t, 3H, J = 7.1 Hz), 4.41 (q, 2H, J = 7.1 Hz), 6.15 (s, 1H, CH), 7.23 (m, 12H), 7.36 (t, 1H, J = 7.1 Hz), 7.50 (t, 2H, J = 7.7 Hz), 7.62 (d, 2H, J= 7.8 Hz), 7.64 (s, 1H, H_3), 8.31 (s, 1H, H_7); ^{13}C n.m.r. δ ($CDCl_3$): 14.25 (CH_3), 58.60 (CH), 61.82 (CH_2), 106.46 (C_7), 122.95 (C_{3a}), 122.97, 126.88, 127.78, 128.45, 129.40, 129.67, 135.47 (C_3), 138.78 (q), 141.48 (q), 142.64 (C_{7a}), 143.71 (C_6), 159.23 (C_4), 165.70 (C=O); m/z (%): 433 (M^+, 83), 432 (100).

7c: $R^1 = R^2 = CH_3$, (84%), m.p. 137-138°C, as colourless prisms. (Found: C, 69.73; H, 5.92; N, 13.38. $C_{18}H_{19}N_3O_2$ requires: C, 69.88; H, 6.19; N, 13.58); i.r. (Nujol) 1736, 1238, 1213, and 766 cm^{-1}; ^{1}H n.m.r. δ ($CDCl_3$): 1.45 (t, 3H, J = 7.1 Hz, CH_3-CH_2O), 1.54 (d, 6H, J = 7.0 Hz, 2xCH_3), 3.63 (m, 1H, J = 7.0 Hz, $(CH_3)_2$CH), 4.49 (q, 2H, J = 7.1 Hz, CH_3-CH_2O), 7.44 (t, 1H, J = 7.0 Hz, H_p), 7.59 (t, 2H, J = 7.7 Hz, H_m), 7.72 (d, 2H, J = 7.8 Hz, H_o), 8.32 (s, 1H, H_3), 8.44 (s, 1H, H_7); ^{13}C n.m.r. δ ($CDCl_3$): 14.25 (CH_3), 21.95 (2xCH_3), 35.85 ((CH_3)$_2$CH), 61.78 (CH_3-

CH_2O), 106.04 (C_7), 121.16 (C_{3a}), 122.93 (C_o), 127.71 (C_p), 129.64 (C_m), 134.81 (C_3), 138.87 (C_i), 142.27 (C_{7a}), 143.53 (C_6), 163.68 (C_4), 165.84 (C=O); m/z (%):309 (M^+, 66), 294 (100).

General Procedure for the Preparation of 4-Substituted 1H-pyrazolo[4,3-c]pyridines 9.

A mixture of iminophosphorane **3** (0.2 g, 0.39 mmol) and the appropriate aldehyde (0.39 mmol) in dry toluene (10 ml) was heated in a glass sealed tube at 165°C for 48h. After cooling, the solvent was removed and the resulting solid was recrystallized from ethanol to give **9**.

9a: R= CH_3 (37%), m.p. 185-187°C, as white prisms. (Found: C, 68.19; H, 5.57; N, 14.79. $C_{16}H_{15}N_3O_2$ requires: C, 68.31; H, 5.37; N, 14.94); i.r. (Nujol) 1705, 1501, 1240, and 768 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.46 (t, 3H, J = 7.1 Hz, C*H*$_3$-CH_2O), 2.96 (s, 3H, CH_3), 4.50 (q, 2H, J = 7.1 Hz, CH_3-C*H*$_2$O), 7.45 (t, 1H, J = 7.2 Hz, H_p), 7.60 (t, 2H, J = 7.7 Hz, H_m), 7.73 (d, 2H, J = 7.9 Hz, H_o), 8.35 (s, 1H, H_3), 8.38 (s, 1H, H_7); ^{13}C n.m.r. δ ($CDCl_3$):14.34 (*C*H_3-CH_2O), 22.47 (CH_3), 62.08 (CH_3-*C*H_2O), 106.15 (C_7), 122.92 (C_o), 123.20 (C_{3a}), 127.84 (C_p), 129.75 (C_m), 135.18 (C_3), 138.98 (C_i), 141.78 (C_{7a}), 143.79 (C_6), 155.04 (C_4), 165.81 (C=O); m/z (%): 281 (M_+, 5), 209 (100).

9b: R = C_6H_5 , (41%), m.p. 171-172°C, as pale yellow prisms. (Found: C, 73.21; H, 5.22; N, 12.08. $C_{21}H_{17}N_3O_2$ requires: C, 73.43; H, 4.99; N, 12.24); i.r. (Nujol) 1707, 1244, and 750 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.47 (t, 3H, J = 7.1 Hz), 4.52 (q, 2H, J = 7.1 Hz), 7.46 (t, 1H, J = 7.2 Hz), 7.59 (m, 5H), 7.75 (d, 2H, J = 7.8 Hz), 8.13 (dd, 2H, J = 7.6, 1.7 Hz), 8.43 (s, 1H, H_3), 8.55 (s, 1H, H_7); ^{13}C n.m.r. δ ($CDCl_3$): 14.31 (*C*H_3-CH_2), 61.99(CH_3-*C*H_2O), 106.34 (C_7), 121.34 (C_{3a}), 123.14, 127.94, 128.92, 128.96, 129.76, 129.95, 135.88 (C_3), 138.29 (q), 138.86 (q), 143.01 (C_{7a}), 143.79 (C_6), 154.57 (C_4), 165.84 (C=O); m/z (%): 343 (M^+, 32), 271 (100).

9c: R = 4-$H_3C.C_6H_4$, (51%), m.p. 169-170°C, as white prisms. (Found: C, 73.75; H, 5.16; N, 11.92. $C_{22}H_{19}N_3O_2$ requires: C, 73.93; H, 5.36; N, 11.76); i.r. (Nujol) 1709, 1246, and 772 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.47 (t, 3H, J = 7.1 Hz), 2.46 (s, 3H), 4.51 (q, 2H, J = 7.1 Hz), 7.38 (d, 2H, J = 8.1 Hz), 7.45 (t, 1H, J = 7.3 Hz), 7.59 (t, 2H, J = 7.7 Hz), 7.74 (d, 2H, J = 7.8 Hz), 8.03 (d, 2H, J = 8.1 Hz), 8.39 (s, 1H, H_3) 8.54 (s, 1H, H_7); ^{13}C n.m.r. δ ($CDCl_3$): 14.27 (*C*H_3-CH_2O), 21.33 (CH_3Ar), 61.89 (CH_3-*C*H_2O), 106.02 (C_7), 121.15 (C_{3a}), 123.06 (phenyl C_o), 127.82 (phenyl C_p), 128.82 (aryl C_o), 129.56 (aryl C_m), 129.68 (phenyl C_m), 135.50 (aryl C_i), 135.90 (C_3), 138.84 (phenyl C_i), 140.08 (aryl C_p), 142.94 (C_{7a}), 144.03 (C_6), 154.51 (C_4), 165.84 (C=O); m/z (%): 357 (M^+, 38), 285 (100).

9d: R = 4-$CH_3O.C_6H_4$, (49%), m.p. 180-181°C, as pale yellow prisms. (Found: C, 70.56; H, 5.25; N, 11.31. $C_{22}H_{19}N_3O_3$ requires: C, 70.76; H, 5.13; N, 11.25); i.r. (Nujol) 1709, 1249, and 775 cm^{-1};^1H n.m.r. δ ($CDCl_3$): 1.47 (t, 3H, J = 7.1 Hz), 3.90 (s, 3H), 4.51 (q, 2H, J = 7.1 Hz), 7.10 (d, 2H, J = 8.7 Hz), 7.46 (t, 1H, J = 7.2 Hz), 7.60 (t, 2H, J = 7.7 Hz), 7.74 (d, 2H, J = 7.8 Hz), 8.11 (d, 2H, J = 8.7 Hz), 8.37 (s, 1H, H_3), 8.54 (s, 1H, H_7); ^{13}C n.m.r. δ ($CDCl_3$): 14.30 (*C*H_3-CH_2O), 55.37 (CH_3OAr), 61.92 (CH_3-*C*H_2O), 105.75 (C_7), 114.33 (aryl C_m), 120.92 (C_{3a}), 123.12 (phenyl C_o), 127.87 (phenyl C_p), 129.72 (phenyl C_m), 130.37 (aryl C_o), 130.96 (aryl C_i), 135.90 (C_3), 138.88 (phenyl C_i), 143.02 (C_{7a}), 144.01 (C_6), 154.12 (C_4), 161.20 (aryl C_p), 165.90 (C=O); m/z (%): 373 (M^+, 50), 301 (100).

9e: R = 4-$Cl.C_6H_4$, (51%), m.p. 203-205°C, as white prisms.(Found: C, 66.55; H, 4.39; N, 11.33. $C_{21}H_{16}ClN_3O_2$ requires: C, 66.77; H, 4.27; N, 11.12); i.r. (Nujol) 1703. 1304, 1246, and 774 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.47 (t, 3H, J = 7.1 Hz), 4.52 (q, 2H, J = 7.1 Hz), 7.47 (t, 1H, J = 7.1 Hz), 7.59 (m, 4H), 7.74 (d, 2H, J = 7.8 Hz),

8.07 (d, 2H, J = 8.4 Hz), 8.42 (s, 1H, H_3), 8.50 (s, 1H, H_7); ^{13}C n.m.r. δ ($CDCl_3$): 14.30 (CH_3-CH_2O), 62.04 (CH_3-CH_2O), 106.54 (C_7), 121.10 (C_{3a}), 123.14 (phenyl C_o), 128.04 (phenyl C_p), 129.15 (aryl C_o), 129.78 (phenyl C_m), 130.18 (aryl C_m), 135.47 (C_3), 136.19 (aryl C_i), 136.68 (aryl C_p), 138.73 (phenyl C_i), 143.01 (C_{7a}), 144.05 (C_6), 153.13 (C_4), 165.64 (C=O); m/z (%): 379 (M^++2, 6), 377 (M^+, 18), 307 (32), 305 (100).

Reaction of Iminophosphorane 3 with Carbon Disulfide: Preparation of 6-Ethoxycarbonyl-1-phenyl-1H-pyrazolo[4,3-c]pyridine-4-thione 11.

A mixture of iminophosphorane **3** (0.2 g, 0.39 mmol) and carbon disulfide (0.088 g, 1.16 mmol) in dry toluene was heated in a glass sealed tube at 120°C for 10h. After cooling, the solvent was removed and the residual material was chromatographed on a silica gel column, eluting with n-hexane/ethyl acetate (1:1) to give the isothiocyanate **10** (0.08 g, 73%) as viscous oil. (Found: C, 60.03; H, 4.53; N, 13.85. $C_{15}H_{13}N_3O_2S$ requires: C, 60.19; H, 4.38; N, 14.04); i.r. (Nujol) 2029, 1728, 1240, and 1105 cm^{-1}; m/z (%): 299 (M^+, 100).

When the reaction was carried out at 165°C for 28h, compound **11** was isolated in 95% yield, m.p. 164-166°C as yellow prisms. (Found: C, 60.28; H, 4.43; N, 13.91. $C_{15}H_{13}N_3O_2S$ requires: C, 60.19; H, 4.38; N, 14.04); i.r. (Nujol) 3254, 1719, 1373, and 758 cm^{-1}; ^{1}H n.m.r. δ ($CDCl_3$): 1.44 (t, 3H, J = 7.1 Hz), 4.49 (q, 2H, J = 7.1 Hz), 7.56 (m , 6H), 8.55 (s, 1H), 10.67 (br s, 1H, NH); ^{13}C n.m.r. δ ($CDCl_3$): 14.03 (CH_3-CH_2O), 63.35 (CH_3-CH_2O), 101.16 (C_7), 123.37 (C_o), 127.50 (C_{3a}), 128.61 (C_p), 129.72 (C_m), 132.55 (C_6), 137.34 (C_{7a}), 138.00 (C_i), 140.48 (C_3), 160.12 (C=O), 176.66 (C=S); m/z (%): 299 (M^+, 60), 225 (100).

Reaction of Iminophosphorane 3 with Carbon Dioxide.

A mixture of iminophosphorane **3** (0.2 g, 0.39 mmol) and excess of solid carbon dioxide in dry toluene (10 ml) was heated in a sealed tube at 120°C for 10h. After cooling, the solvent was removed under reduced pressure and the crude product was chromatographed on a silica gel column, eluting with n-hexane/ethyl acetate (1:1) and further recrystallized from ethanol to give **14**: (0,08 g, 40%), m.p. 212-213°C, as white crystals. (Found: C, 66.40; H, 4.91; N, 15.89. $C_{29}H_{26}N_6O_4$ requires: C, 66.66; H, 5.02; N, 16.08);i.r. (Nujol) 3329, 1713, 1377, and 1242cm^{-1} ; ^{1}H n.m.r. δ ($CDCl_3$): 1.17 (t, 3H, J = 7.1 Hz), 1.32 (t, 3H, J = 7.1 Hz), 4.22 (q, 2H, J = 7.1 Hz), 4.33 (q, 2H, J = 7.1 Hz), 6.65 (d, 1H, J = 2.1 Hz), 7.19 (s, 1H), 7.41 (t, 1H, J = 7.3 Hz), 7.54 (m, 8H), 7.65 (d, 2H, J = 7.7 Hz), 7.93 (s, 1H), 8.25 (s, 1H); ^{13}C n.m.r δ ($CDCl_3$): 13.93 (CH_3-CH_2O), 14.17 (CH_3-CH_2O), 61.61 (CH_3-CH_2O), 61.85 (CH_3-CH_2O), 101,46 (C_7), 108.49, 112.02 (q), 115.37, 123.01, 125.47, 127.76, 128.21, 129.15, 129.57, 133.38, 136.39 (q), 138.84 (q), 139.08 (q), 140.30, 142.99 (q), 143.69 (q), 149.01 (q), 165.24 (C=O), 165.48 (C=O); m/z (%): 522 (M^+, 45), 448 (100).

Preparation of iminophosphorane 15.

Reaction of 4-formyl-1-phenyl-1H-pyrazole **8** with ethyl azidoacetate under the reaction conditions described for the preparation of **2** leads to ethyl α-azido-β[(1-phenyl)-4-pyrazolyl]acrylate (77%), m.p. 98-99°C, as colourless prisms. (Found: C, 59.22; H, 4.38; N, 24.86. $C_{14}H_{13}N_5O_2$ requires: C, 59.36; H, 4.63; N, 24.72); i.r. (Nujol) 2131, 2106, and 1711 cm^{-1}; ^{1}H n.m.r δ ($CDCl_3$): 1.37 (t, 3H, J = 7.1 Hz), 4.33 (q, 2H, J = 7.1 Hz), 6.85 (s, 1H, H_β), 7.29 (t, 1H, J = 6.9 Hz, H_p), 7.44 (t, 2H, J = 7.7 Hz, H_m), 7.70 (d, 2H, J = 8.1 Hz, H_o), 7.95 (s, 1H, H_3), 8.41 (s, 1H, H_5); ^{13}C n.m.r δ ($CDCl_3$): 14.10 (CH_3-CH_2O), 61.90 (CH_3-CH_2O), 116.08 (C_β), 117.44 (C_α), 119.15 (C_o), 123.75 (C_4), 126.90 (C_p), 127.67 (C_5), 129.37 (C_m), 139.46 (C_i), 142.49 (C_3), 163.08 (C=O); m/z (%): 283 (M^+, 5), 182 (100).

Reaction of Ethyl α-azido-β[(1-phenyl)-4-pyrazolyl]acrylate with triphenylphosphine under the conditions described for the preparation of **3** led lo the iminophosphorane **15** (99%), m.p. 154-156°C, as white crystals.(Found: C, 74.07; H, 5.63; N, 5.32. $C_{32}H_{28}N_3O_2P$ requires: C, 74.26; H, 5.45; N, 5.41); i.r. (Nujol) 1696, 1238, and 1215

cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 0.99 (t, 3H, J = 7.1 Hz), 3.87 (q, 2H, J = 7.1 Hz), 6.81 (d, 1H, $^4J_{P-H}$ = 7.1 Hz, H_β), 7.38 (m, 14H), 7.71 (m, 6H), 7.87 (s, 1H, H_3), 8.79 (s, 1H, H_5); ^{13}C n.m.r. δ ($CDCl_3$): 13.96 (CH_3-CH_2O), 60.47 (CH_3-CH_2O), 108.79 (C_β, $^3J_{P-C}$ = 20.6 Hz), 118.25, 121.64 (C_4), 125.47 (C_5), 126.30, 128.20 ($^3J_{P-C}$ = 12.1 Hz), 128.97, 130.89 ($^4J_{P-C}$ = 2.5 Hz), 132.21 ($^2J_{P-C}$ = 9.5 Hz), 132.84 ($^1J_{P-C}$ = 102.8 Hz), 134.90 (C_α, $^2J_{P-C}$ = 7.0 Hz), 140.08, 141.92 (C_3), 167.04 (C=O, $^3J_{P-C}$ = 6.2 Hz); ^{31}P n.m.r. δ 9.33 ppm; m/z (%): 517 (M^+, 21), 183 (100).

Preparation of 7-Substituted-5-ethoxycarbonyl-1-phenyl-1H-pyrazolo[3,4-c]pyridines 22.

To a solution of iminophosphorane **15** (0.2 g, 0.39 mmol) in dry dichloromethane (10 ml) was added the appropriate ketene (0.39 mmol). The resultant solution was stirred at room temperature for 4h. Then, the solvent was removed under reduced pressure and the residue was disolved in dry toluene (10 ml), the solution was treated at reflux temperature for 24h. After cooling, the solution was concentrated to dryness and the crude product was chromatographed on a silica gel column, eluting with ethyl acetate/n-hexane (2:3) and further recrystallized from ethanol to give **22.**

22a: $R^1 = C_2H_5$; $R^2 = C_6H_5$, (25%), m.p. 155-157°C, as white prisms.(Found: C, 74.61; H, 5.85; N, 11.12. $C_{24}H_{23}N_3O_2$ requires: C, 74.78; H, 6.01; N, 10.90); i.r. (Nujol) 1711, 1502, 1252, and 1192 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 0.71 (t, 3H, J = 7.1 Hz), 1.47 (t, 3H, J = 7.1 Hz), 2.01 (m, 1H), 2.36 (m, 1H), 4.00 (t, 1H, J = 7.3 Hz), 4.49 (q, 2H, J= 7.1 Hz), 6.91 (m, 2H), 7.11 (m, 3H), 7.38 (m, 2H), 7.59 (m, 3H), 8.25 (s, 1H, H_3), 8.43 (s, 1H, H_4); ^{13}C n.m.r δ ($CDCl_3$): 12.59 (CH_3-CH_2), 14.37 (CH_3-CH_2O), 29.89 (CH_2), 49,70 (CH), 61.19 (CH_3-CH_2O), 116.33 (C_4), 126.25, 127.88, 127.97, 128.57, 129.20, 129.43 (C_{3a}), 129.65, 135.56 (C_3), 136.54 (C_{7a}), 138.50, 140.56 (C_5), 142.19, 148.46 (C_7), 165.73 (C=O); m/z (%): 385 (M^+, 17), 357 (100).

22b: $R^1 = R^2 = C_6H_5$, (39%), m.p. 140-142°C, as white prisms. (Found: C, 77.32; H, 5.58; N, 9.79. $C_{28}H_{23}N_3O_2$ requires: C, 77.58; H, 5.35; N, 9.69); i.r. (Nujol) 1713, 1595, 1260, and 1202 cm^{-1}; ^1H n.m.r. δ ($CDCl_3$): 1.42 (t, 3H, J = 7.1 Hz), 4.41 (q, 2H, J = 7.1 Hz), 5.55 (s, 1H), 7.17 (m, 10H), 7.35 (d, 2H, J = 8.1 Hz). 7.51 (t, 2H, J = 7.8 Hz), 7.57 (t, 1H, J = 6.7 Hz), 8.27 (s, 1H, H_3), 8.45 (s, 1H, H_4); ^{13}C n.m.r. δ ($CDCl_3$): 14.22 (CH_3), 53.29 (CH), 61.10 (CH_2), 116.51 (C_4), 126.44, 127.81, 127.96, 129.33, 129.74, 135.60 (C_3), 136.32 (C_{7a}), 138.44 (q), 140.31 (C_5), 141.70 (q), 146.72 (C_7), 165.57 (C=O). The C_{3a} carbon atom was not observed; m/z (%): 433 (M^+, 100).

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