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Iminophosphorane-Mediated Synthesis of Functionalized Indoles and 1,3-Benzodiazepines

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Abstract.-*Aza Wittig-type reaction of bis(iminophosphorane) **2** with aromatic isocyanates leads to either indoles **5** or pyrimido[4,5-b]indoles **6**, whereas with aliphatic isocyanates and acyl chlorides afforded pyrrolo[2,3-b]indoles **7** and 1,3-benzodiazepines **10** respectively.*

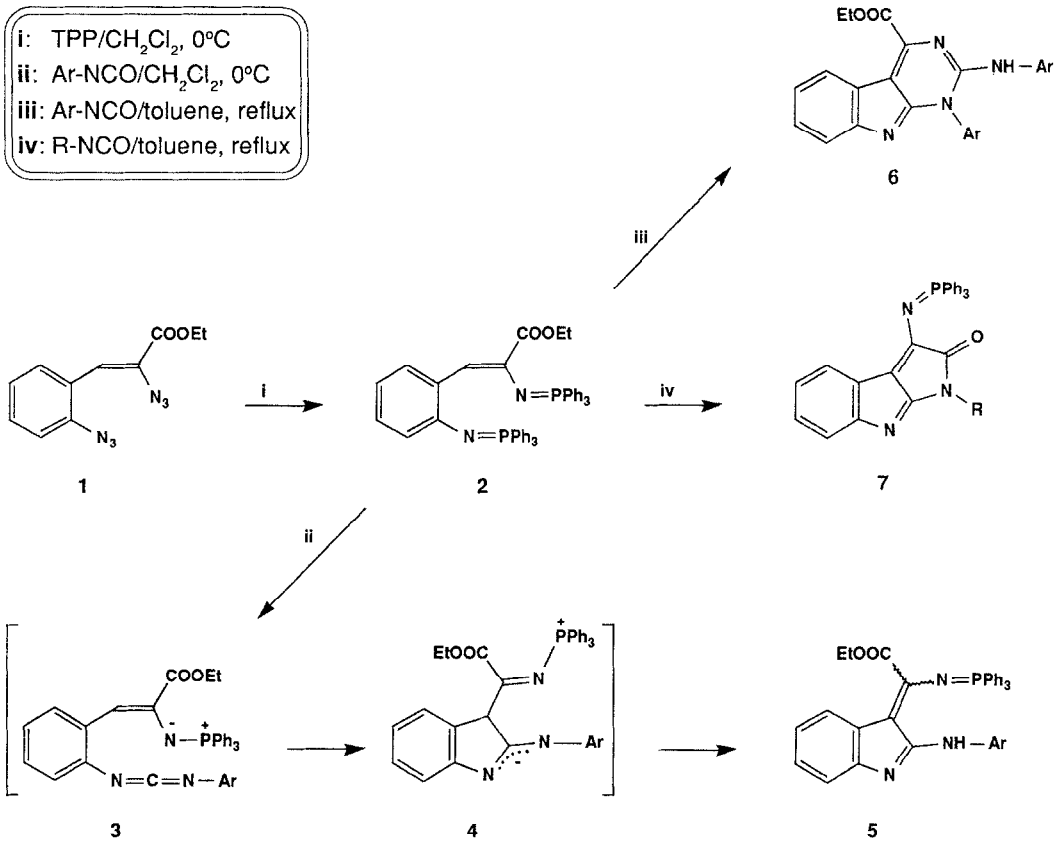
The indole skeleton is a fundamental unit of numerous biologically active alkaloids. As such, the chemistry of indole has been widely investigated[1] and the indole-based alkaloids have been the target of countless synthetic efforts. In recent years, a variety of functionalized iminophosphoranes have become available, and the versatility of these iminophosphoranes in organic synthesis has been well-recognized[2]. One of the important goals achieved in the iminophosphorane chemistry is the formation of functionalized heterocumulenes which exhibit a rich chemistry of unusual synthetic promise. Heterocyclization reactions of such functionalized heterocumulene systems e.g. electrocyclic ring-closure[3], intramolecular Diels-Alder cycloaddition[4] and intramolecular heterocumulene-promoted amination[5], provide an attractive entry to a variety of carbocycles and heterocycles.

In this context, we have recently reported[6] a new synthesis of α-carbolines and quinindolines from *o*-butadienyl diarylcarbodiimides, based on a tandem intramolecular Diels-Alder cycloaddition/oxidative aromatization process. We report here the preparation and reactivity of the bis(iminophosphorane) **2**, bearing two chemically different iminophosphorane groups, in aza Wittig-type reactions, thus providing routes to fused indoles and 1,3-benzodiazepines.

The starting diazide **1** was prepared in 68% yield by condensation of *o*-azidobenzaldehyde[7] with ethyl azidoacetate; Staudinger reaction between the diazide **1** and triphenylphosphine in dry dichloromethane at 0°C led to the bis(iminophosphorane) **2** (88%, m.p. 199-200°C).

Compound **2** reacts with aromatic isocyanates in dry dichloromethane at 0°C to give monoiminophosphoranes **5** (36-60%) derived from the indole ring[8]. The conversion **2**→**5** can be rationalized in terms of an initial aza Wittig-type reaction between the iminophosphorane group linked to the aromatic ring and the isocyanate to give a carbodiimide **3** as highly reactive intermediate which undergo cyclization by nucleophilic attack of the β-carbon atom at the chain side in ortho-position leading to the zwitterionic intermediate **4**. Further transformations of **4** will lead to the indoles **5**. As it has been previously reported[9], this conversion also shows that an aryl iminophosphorane group is more reactive than a β-styryliminophosphorane one in aza Wittig-type reactions towards isocyanates.

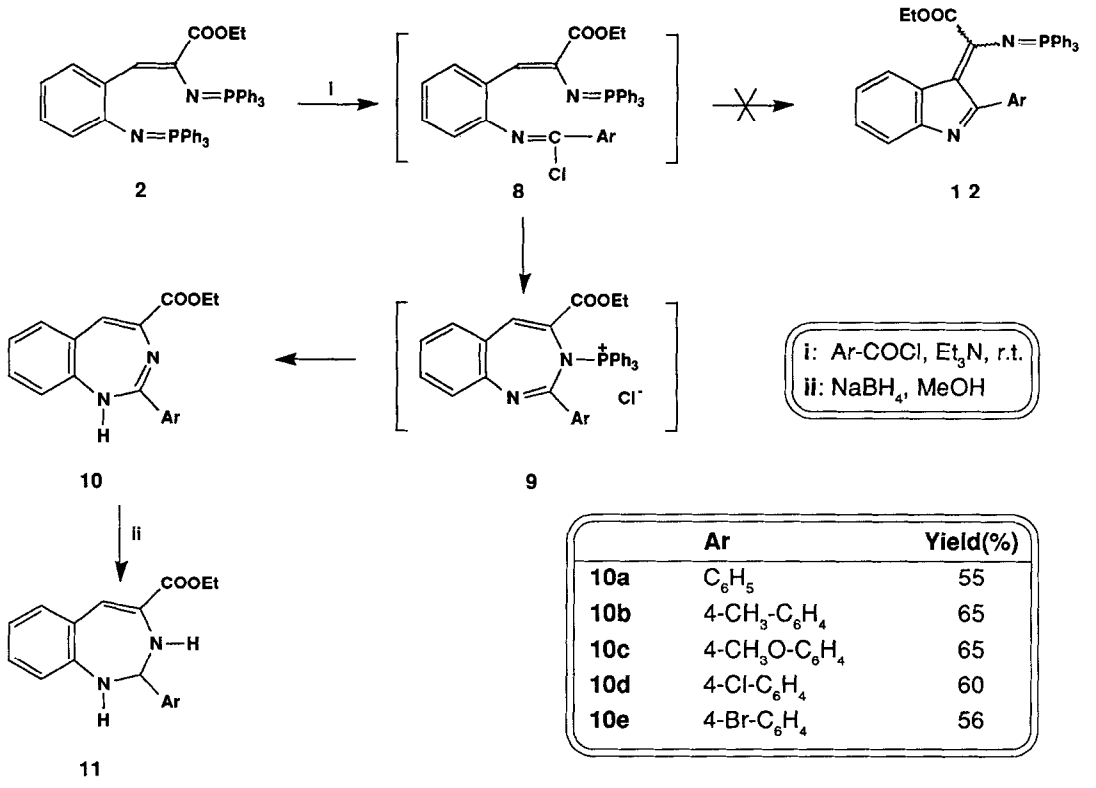
When the reaction of **2** with aromatic isocyanates was carried out in toluene at reflux temperature pyrimido[4,5-



b]indoles **6** were isolated[10]. This conversion involves initial formation of **5** followed by an aza Wittig reaction with a second mol of isocyanate to give a carbodiimide, pyrimido-annelation occurs by intramolecular amination by nucleophilic attack of the exocyclic amino group on the central carbon atom of the carbodiimide moiety.

Compound **2** also reacted with aliphatic isocyanates in toluene at reflux temperature to afford pyrrolo[2,3-*b*]indole derivatives[11] **7**. The conversion **2**→**7** can be understood by initial formation of an intermediate type **5** followed by intramolecular acylation of the exocyclic amino group. The different reactivity showed by the two iminophosphorane moieties in compound **2** allows, by changing the nature of the isocyanate, that the reaction may be driven towards the production of pyrimido-indoles **6** or pyrrolo-indoles **7**.

Finally, bis(iminophosphorane) **2** reacts with acyl chlorides in dry dichloromethane in the presence of triethylamine at room temperature to give 1,3-benzodiazepines **10** in good yields, with no evidence of indole **12** formation. Presumably, the formation of **10** involves initial formation of an imidoyl chloride **8** as intermediate which cleanly undergoes cyclization by nucleophilic attack of the nitrogen atom of the iminophosphorane portion followed by P-N bond cleavage to give **10**. Compounds **10** were characterized on the basis of their spectroscopic data and mass spectrometry[12]. In addition, reduction with sodium borohydride leads to the dehydro derivatives **11**. In the ^{1}H n.m.r. spectra the H-2 appears at δ 5.18 ppm as a triplet and the two N-H protons appear at δ 5.92 and 6.87 ppm



	Ar	Yield(%)
10a	C_6H_5	55
10b	4-CH_3-C_6H_4	65
10c	4-CH_3O-C_6H_4	65
10d	4-Cl-C_6H_4	60
10e	4-Br-C_6H_4	56

respectively as doublets. In the ^{13}C n.m.r. spectra the C-2 appears at δ 69.66 ppm.

In conclusion the results reported herein reveals that bis(iminophosphorane) **2** can be used as valuable building blocks for the preparation of functionalized indoles and 1,3-benzodiazepines[13]. In aza Wittig-type reactions the two iminophosphorane groups show different reactivity towards isocyanates and acyl chlorides. Due to the easy access of the starting materials, good yields, mild reaction conditions and due to the simplicity of the experimental one-pot procedure, these synthetic approaches compare favourably with other synthetic methods.

Acknowledgements:

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8. Typical Procedure: To a solution of bis(iminophosphorane) **2** (0.5 g, 0.6 mmol) in dry dichlorometane (20 ml) was added dropwise at 0°C *p*-tolyl isocyanate (0.11 g, 0.8 mmol) and the reaction mixture was stirred at 0°C for 1h. The solvent was removed under reduced pressure and the residual material was slurried with ether (60 ml). The formed solid was separated by filtration and recrystallized from ethanol to afford **5** (Ar = 4-CH_3-C_6H_4) (50 %, m.p. 225-226°C). ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 0.95 (t, 3H, ^{3}J= 7.1 Hz), 2.26 (s, 3H), 3.41 (q, 2H, ^{3}J= 7.1 Hz), 6.79 (td, 1H, ^{3}J= 7.9, ^{4}J= 0.7 Hz), 6.96-7.05 (m, 5H), 7.35 (d, 1H, ^{3}J= 7.6 Hz), 7.52-7.79 (m, 16H), 10.62 (s, 1H, NH); ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 13.23 (CH_3), 20.68 (CH_3), 61.13 (CH_2), 112.50 (C_3, $^3J_{P-C}$= 20.7 Hz), 116.69 (C_7), 118.15 (C_4), 118.91, 119.57 (C_5), 125.10 (C_6), 126.72 (C_{3a}, $^3J_{P-C}$= 2.1 Hz), 127.54 (C_i, $^1J_{P-C}$= 102.6 Hz), 128.96 (C_m, $^3J_{P-C}$= 12.6 Hz), 129.17, 130.60 (q), 132.85 (C_o, $^2J_{P-C}$= 10.2 Hz), 132.91 (C_p, $^4J_{P-C}$= 2.8 Hz), 138.30 (q), 145.90 (C_α, $^2J_{P-C}$= 3.9 Hz), 153.94 (C_{7a}), 161.80 (C_2, $^4J_{P-C}$= 1.1 Hz), 165.56 (C=O, $^3J_{P-C}$= 9.9 Hz); ^{31}P n.m.r. δ 17.03 ppm; m/z (%) 581(M^+, 3).
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10. Compound **6** (Ar= 4-CH_3-C_6H_4).^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 1.55 (t, 3H, ^{3}J= 7.1 Hz), 2.32 (s, 3H), 2.51 (s, 3H), 4.58 (q, 2H, ^{3}J= 7.1 Hz), 6.46 (s, 1H, NH), 7.10-7.44 (m, 3H), 7.49-7.64 (m, 8H), 8.54 (d, 1H, ^{3}J= 7.7 Hz); ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 14.25 (CH_3), 20.79 (CH_3), 21.46 (CH_3), 61.99 (CH_2), 117.28 (q), 118.61, 120.38, 121.36, 122.54 (q), 124.77, 127.79, 128.27, 129.41, 131.45 (q), 132.07, 134.00 (q), 134.92 (q), 141.41 (q), 142.03 (q), 146.05 (q), 154.22 (q), 157.77 (q), 165.33 (q); m/z (%) 436 (M^+, 42).
11. Compound **7** (R= CH_3) (40 %, m.p. 103-104°C). ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 3.05 (s, 3H), 6.80 (td, 1H, ^{3}J= 7.4, ^{4}J= 0.7 Hz), 6.98-7.04 (m, 2H), 7.24 (d, 1H, ^{3}J= 7.3 Hz), 7.48-7.58 (m, 9H), 7.76 (ddd, 6H, $^3J_{P-H}$= 12.1, ^{3}J= 7.7, ^{4}J= 1.6 Hz); ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 25.82 (CH_3), 118.73, 121.12, 122.82, 125.69, 126.35 (q), 128.79 (C_m, ^{3}J= 12.6 Hz), 129.18 (C_i, ^{1}J= 103.2 Hz), 132.40 (C_p, ^{4}J= 2.9 Hz), 132.84 (C_o, ^{2}J= 10.2 Hz), 132.99 (q), 143.75 (q), 159.61 (q), 171.18 (q, J= 14.4 Hz), 173.71 (q); m/z (%) 459 (M^+, 50).
12. Compound **10** (Ar= 4-CH_3O-C_6H_4). ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 1.37 (t, 3H, ^{3}J= 7.3 Hz), 3.83 (s, 3H), 4.31 (q, 2H, ^{3}J= 7.3 Hz), 6.53 (s, 1H, H-5), 6.59 (s, 1H, NH), 6.79 (d, 1H, ^{3}J= 7.3 Hz, H-6), 6.89-6.93 (m, 4H, H-7 + H-9 + 2 x H_m), 7.13 (td, 1H, ^{3}J= 7.8, ^{4}J= 1.4 Hz, H-8), 7.84 (d, 2H, ^{3}J= 8.7 Hz, 2 x H_o); ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 14.31 (CH_3), 55.47 (CH_3O), 62.20 (CH_2), 113.95 (C_m), 121.93 (C_5), 125.29 (C_7), 128.34 (C_i), 129.09 (C_9), 129.59 (C_o), 130.20 (C_4), 130.53 (C_8), 131.48 (C_6), 133.66 (C_{5a}), 149.79 (C_{9a}), 159.32 (C_2), 162.23 (C_p), 163.57 (C=O); m/z (%) 322 (M^+, 100).
13. Satisfactory ^{1}H, ^{13}C n.m.r. (values assigned by decoupling methods and 2D ^{1}H-^{13}C correlation techniques), mass spectra and elemental analyses were obtained for all new compounds.

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