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PREPARATION OF FUSED [1,3,5]BENZOTRIAZEPINES BY A TANDEM AZA WITTIG/CARBODIIMIDE-MEDIATED ANNELATION REACTION.

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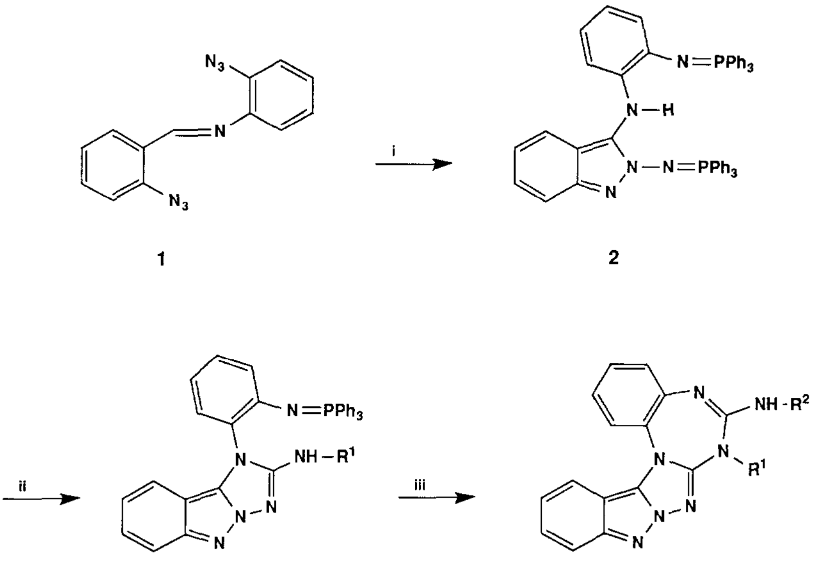
Abstract.–*AzaWittig type reaction of bis(iminophosphorane)* **2**, *available from the diazide* **1** *and triphenylphosphine, with one mole of isothiocyanate leads to the iminophosphoranes* **3** *derived from the [1,2,4]triazolo[2,3-b]indazole ring, which by treatment with a second mol of isothiocyanate afforded pentacyclic [1,3,5]benzotriazepines* **4**. *Direct conversion of* **2** *to* **4** *was achieved using two moles of isothiocyanate.*

Iminophosphorane-mediated synthesis of heterocyclic ring systems have developed remarkably in recent years, which is obviously linked to the rapid progress in the preparation of functionalized iminophosphoranes. While relevant examples involving iminophosphoranes have been reported[1], the chemistry of the bis(iminophosphoranes) have been much less investigated; it has only been briefly mentioned[2] that bis(iminophosphoranes) derived from *o*-phenylenediamine reacts with diethyl acetylenedicarboxylate to give a quinoxaline derivative. Bis(iminophosphoranes) are valuable building blocks, they can compose a reaction system in which the two iminophosphorane units can react either with a reagent having two functionalities or with two separate reagents bearing the same functionality, in this case the bis(iminophosphorane) serves as a conjunctive substrate, combining two reagents. It is expected that the utility of the bis(iminophosphoranes) could be enhaNced if the two iminophosphorane moieties show different reactivity towards the same functionality. In this context, we report here the preparation and reactivity of the bis(iminophosphorane) **2** in aza-Wittig type reactions, thus providing an efficient and general route to fused [1,3,5]benzotriazepines.

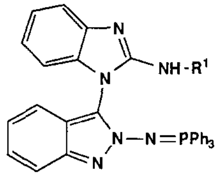
The starting diazide **1** was readily prepared in 70% yield by condensation of the *o*-azidobenzaldehyde with *o*-azidoaniline in ethanol in the presence of acetic acid. When a dichloromethane solution of **1** was treated with triphenylphosphine (TPP) at 0°C for 7h the bis(iminophosphorane) **2** was obtained in almost pure form[3]. The ^{31}P n.m.r. spectrum clearly indicates the presence of two different iminophosphorane groups; it shows two signals at δ 4.53 ppm and δ 17.58 ppm respectively which are in good agreement with the previously reported values for N-aryl iminophosphorane[4] and iminophosphoranes derived from N-amino heterocycles[5]. In the ^{13}C n.m.r. spectrum the chemical shifts of all carbon atoms of the indazole ring are in good agreement with the literature values[6]; it worth noting that the C_3 carbon atom appears as a doublet at δ 129.54 ppm ($^3J_{P\text{-}C}$ = 10.7 Hz) and in the phenylamino residue the two ortho-carbon atoms to the iminophosphorane group appear as two doublets at δ 119.40 ppm ($^3J_{P\text{-}C}$ = 9.5 Hz) and δ 138.07 ppm ($^3J_{P\text{-}C}$ = 20.6 Hz) respectively. The formation of **2** shows the different behaviour of the two azide groups in compound **1** towards TPP in the Staudinger reaction; the azido group belonging to the *o*-azidobenzaldehyde fragment reacts to give a phosphazide as intermediate which clearly undergoes cyclization by nucleophilic attack of the central nitrogen atom of the phosphazide moiety on the carbon atom of the azomethine group leading to a zwitterionic intermediate and further transformation of this will lead to the 2H-indazole ring[7], whereas the azido group belonging to the *o*-azidoaniline fragment react in a "normal" fashion to give the iminophosphorane function with nitrogen evolution.

Compound **2** reacts with alkyl and aryl isothiocyanates at room temperature to give the iminophosphoranes **3** derived from the 1H-1,2,4-triazolo[2,3-*b*]indazole[8]. The ^{31}P n.m.r spectra only show a signal around δ 10 ppm (δ



	R¹	R²	Yield (%)
3a	4-F-C_6H_4		63
3b	4-CH_3-C_6H_4		82
3c	4-CH_3O-C_6H_4		76
3d	C_2H_5		43
3e	C_6H_5-CH_2		53
4a	4-CH_3O-C_6H_4	C_2H_5	52
4b	4-CH_3O-C_6H_4	4-CH_3O-C_6H_4	55
4c	C_2H_5	C_2H_5	70
4d	C_2H_5	4-CH_3O-C_6H_4	50

i: TPP/CH_2Cl_2, 0°C
ii: R^1-NCS/CH_2Cl_2, r.t.
iii: R^2-NCS/toluene, reflux



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10.43 for **3b** and δ 8.83 ppm for **3e**), while the ^{13}C n.m.r. spectra clearly show that three carbon atoms (two quaternaries and one CH) belonging to the phenyl group are coupled with the phosphorus atom of the iminophosphorane moiety, in addition coupling of the C_{3a} carbon atom of the indazole ring with the phosphorus atom was not observed. These data confirm the proposed structure **3** and rule out the alternative structure **5**.

Compound **3** reacts with a second mol of isothiocyanate in toluene solution at reflux temperature to give the previously unreported benzotriazepines[9] **4** (50-70%). Compounds **4** can also be directly obtained from **2** by treatment with two moles of the corresponding isothiocyanate in toluene solution at reflux temperature. The ^1H n.m.r. spectra suggested the exocyclic NH of **4**; e.g. for **4c** one methylene signal appeared as a complex multiplet. In the ^{13}C n.m.r. spectra the [1,2,4]triazolo[2,3-*b*]indazole ring carbon atoms display similar chemical shifts to the observed in compound **3**, and the new quaternary carbon atom C_6 appears in the range δ 145.69-153.68 ppm.The mass spectra show the expected molecular ion peaks in high intensity other peaks appear at m/z (M^+-R^1NCNR^2) and m/z 156 (indazole ring), very informative peaks are also found at m/z (R^1NCNR^2) and m/z (R^2NHCN). Both conversion **2** → **3** and **3** → **4** involve a tandem aza-Wittig/carbodiimide-mediated annelation strategy. The formation of iminophosphoranes **3** from **2** shows the preferential reactivity of the N-iminophosphorane with respect to the C-iminophosphorane in aza-Wittig type reactions towards isothiocyanates.

The present study demonstrate that the tandem aza-Wittig-carbodiimide-mediated annelation strategy afford a new entry to a variety of fused [1,3,5]benzotriazepines. Because of their simplicity, easy accessibility of starting materials, mild reaction conditions, the good yields in the iminophosphorane preparation as well as in the cyclization steps and straighforward product isolation[10] the investigated reactions provide a method for the preparation of different [1,3,5]benzotriazepines which compares favourably with other approaches to this ring system.

ACKNOWLEDGEMENTS:

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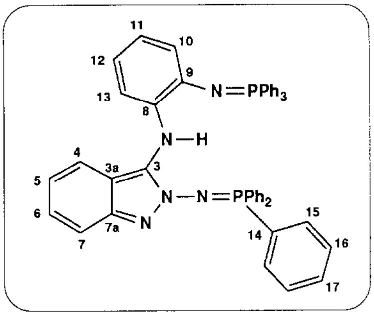
2. E.M. Briggs, G.M. Brown, W.T. Dawson, J. Jiricny, *J. Chem. Soc. Chem. Commun.*, **1975**, 641.
3. A solution of TPP (10 mmol) in dry dichloromethane (20 ml) was added dropwise under nitrogen to a well-stirred solution of the diazide **1** (1.31 g, 5 mmol) in the same solvent (30 ml) at 0°C. After the stirring was continueded for 1h at the same temperature, the mixture was slowly warmed to room temperature for 7h, and then the solvent was removed under reduced pressure. The resultant crude product was chromatographed on a silica gel column, eluting with ethyl acetate/hexane (3:1) to give **2** in 80% yield, m.p. 189-190°C as yellow prisms. ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 111.91 (C_{13}), 112.74 (C_{3a}), 115.51 (C_7), 116.89 (C_{12}), 117.88 (C_{11}), 118.17 (C_5), 119.40 ($^3J_{P\text{-}C}$ = 9.5 Hz, C_{10}), 120.19 (C_4), 123.13 (C_6), 128.21 ($^3J_{P\text{-}C}$ = 12.0 Hz, C_{16}), 128.55 ($^3J_{P\text{-}C}$ = 11.8 Hz, C'_{16}), 128.63 ($^1J_{P\text{-}C}$ = 97.6 Hz, C_{14}), 129.54 ($^3J_{P\text{-}C}$ = 10.7 Hz, C_3), 130.90 ($^1J_{P\text{-}C}$ = 99.1 Hz, C'_{14}), 131.63 ($^4J_{P\text{-}C}$ = 2.7 Hz, C_{17}), 131.72 ($^4J_{P\text{-}C}$ = 2.8 Hz, C'_{17}), 132.59 ($^2J_{P\text{-}C}$ = 9.8 Hz, C_{15}), 133.26 ($^2J_{P\text{-}C}$ = 9.5 Hz, C'_{15}), 137.54 (C_9), 138.07 ($^3J_{P\text{-}C}$ = 20.6 Hz, C_8), 142.97 (C_{7a}). Values assigned by decoupling methods and 2D ^1H–^{13}C correlation techniques. m/z (%) 759 (M^+, 5), 183 (100).



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5. P. Molina, M. Alajarín, M.J. Pérez de Vega, A. López, *Heterocycles*, **1989**, *29*, 1607.
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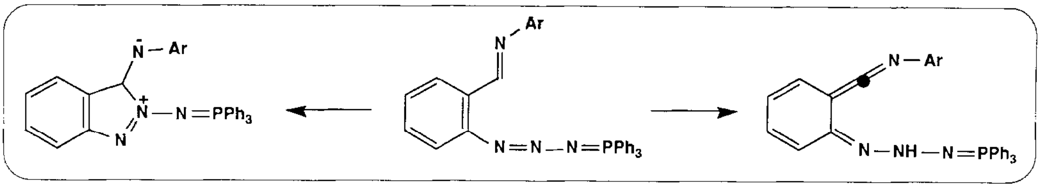
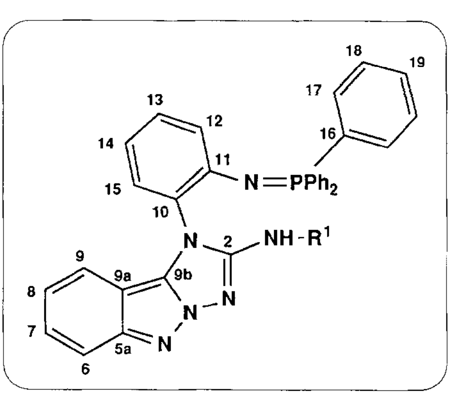
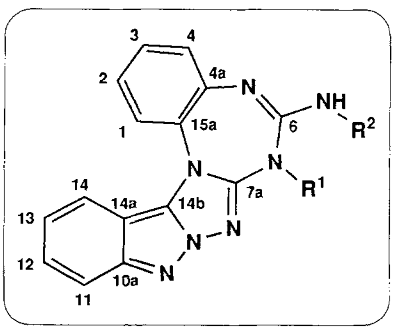
7. P. Molina, A. Arques, M.V. Vinader, *Tetrahedron Lett.*, **1989**, 6237. Another pausible pathway would involve the conversion of the phosphazide to a ketenimine through [1,5] sigmatropic proton shift which cyclizes by nucleophilic attack of the amino group on the central *sp* hybridized carbon atom of the ketenimine to give the 2H-indazole ring.



8. Typical Procedure: To a solution of bis(iminophosphorane) **2** (0.5 g, 0.66 mmol) in dry dichloromethane (15 ml) was added dropwise the appropriate isothiocyanate (0.66 mmol) and the reaction mixture was stirred at room temperature for 7h. The solvent was removed under reduced pressure and the residual material was chromatographed on a silica gel column, eluting with dichloromethane/ethyl acetate (3:1) to afford **3** as crystalline solids. Compound **3a**: 63% yield; m.p. 203-204°C. ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 103.29 (C_{9a}), 115.22 ($^{2}J_{F\text{-}C}$ = 22.5 Hz, C_m), 116.24 (C_6), 117.33 (C_9), 117.52 (C_8), 118.83 ($^{3}J_{F\text{-}C}$ = 7.7 Hz, C_o), 119.03 (C_{14}), 123.77 ($^{3}J_{P\text{-}C}$ = 11.4 Hz, C_{12}), 124.49 (C_7), 125.89 (C_{15}), 128.45 ($^{3}J_{P\text{-}C}$ = 19.2 Hz, C_{10}), 128.87 ($^{1}J_{P\text{-}C}$ = 100.7 Hz, C_{16}), 128.93 (C_{9b}), 129.13 (C_{13}), 129.85 ($^{3}J_{P\text{-}C}$ = 12.3 Hz, C_{18}), 132.23 ($^{2}J_{P\text{-}C}$ = 10.0 Hz, C_{17}), 132.48 ($^{4}J_{P\text{-}C}$ = 2.8 Hz, C_{19}), 135.62 ($^{4}J_{F\text{-}C}$ = 2.4, C_i), 144.62 ($^{2}J_{P\text{-}C}$ = 1.0 Hz, C_{11}), 148.74 (C_{5a}), 150.43 (C_2), 157.67 ($^{1}J_{F\text{-}C}$ = 240.1 Hz, C_p). m/z (%): 618 (M^+, 5), 183 (100).
   Compound **3d**: 43% yield; m.p. 241-242 °C. ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 14.35 (CH_3), 38.24 (CH_2), 103.50 (C_{9a}), 116.16 (C_6), 117.10 (C_8), 117.28 (C_9), 118.48 (C_{14}), 123.41 ($^{3}J_{P\text{-}C}$ = 9.9 Hz, C_{12}), 124.01 (C_7), 125.97 (C_{15}), 128.60 ($^{3}J_{P\text{-}C}$ = 19.0 Hz, C_{10}), 128.79 (C_{13}), 128.91 ($^{3}J_{P\text{-}C}$ = 12.2 Hz, C_{18}), 129.37 ($^{1}J_{P\text{-}C}$ = 100.5 Hz, C_{16}), 129.60 (C_{9b}), 132.24 ($^{2}J_{P\text{-}C}$ = 10.0 Hz, C_{17}), 132.33 ($^{4}J_{P\text{-}C}$ = 2.8 Hz, C_{19}), 145.04 ($^{2}J_{P\text{-}C}$ = 1.0 Hz, C_{11}), 148.42 (C_{5a}), 154.81 (C_2). m/z (%): 552 (M^+, 12), 183 (100).



9. Typical Procedure: To a solution of **3** (0.5 mmol) in dry toluene (25 ml), was added the appropriate isothiocyanate (0.5 mmol) and the reaction mixture was stirred at room temperature for 24h. After cooling, the solvent was removed and the residue was chromatographed on a silica gel column, eluting with dichloromethane/ethyl acetate (3:1) to give **4**. Compound **4a**: 52% yield; m.p. 253-254°C. ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 1.16 (t, 3H, ^{3}J = 7.2 Hz), 3.43 (q, 2H, ^{3}J = 7.2 Hz), 3.78 (s, 3H), 4.75 (br. s, 1H, NH), 6.88 (d, 2H, ^{3}J = 8.9 Hz), 7.06 (t, 1H, ^{3}J= 7.7 Hz), 7.18-7.39 (m, 4H), 7.57 (d, 2H, ^{3}J = 8.9 Hz), 7.68-7.77 (m, 3H); ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 14.25 (CH_3), 37.90 (CH_2), 55.53 (CH_3O), 103.26 (C_{14a}), 114.63 (C_m), 116.87 (C_{11}), 117.79 (C_{14}), 118.98 (C_{13}), 120.42, 123.78 (C_{12}), 125.75, 126.18 (C_o), 127.03 (q), 127.25 (q), 128.02, 128.19, 131.48 (C_i), 140.19 (q), 149.51 (C_{10a}), 150.18 (C_6), 150.65 (C_{7a}), 158.50 (C_p); m/z (%) 423 (M^+, 83), 90 (100).
   Compound **4c**: 70% yield; m.p. 260-261°C. ^{1}H n.m.r. (200 MHz, $CDCl_3$) δ 1.28 (t, 3H, ^{3}J = 6.9 Hz), 1.38 (t, 3H, ^{3}J = 7.1 Hz), 3.51-3.56 (m, 2H), 3.79 (q, 2H, ^{3}J = 7.1 Hz), 5.41 (br. s, 1H, NH), 7.01 (t, 1H, ^{3}J = 7.6 Hz), 7.16-7.41 (m, 4H), 7.64-7.77 (m, 3H); ^{13}C n.m.r. (50 MHz, $CDCl_3$) δ 13.50 (CH_3), 14.48 (CH_3), 37.76 (CH_2), 43.02 (CH_2), 103.50 (C_{14a}), 116.58 (C_{11}), 117.82 (C_{14}), 119.02 (C_{13}), 119.73, 123.50 (C_{12}), 125.70, 127.29 (q), 127.59 (q), 127.75, 127.96, 140.41 (q), 149.16 (C_{10a}), 151.11 (C_{7a}), 153.68 (C_6); m/z: (%) 345 (M^+, 54), 90 (100).



10. Satisfactory ^{1}H, ^{13}C n.m.r., mass spectra and elemental analyses were obtained for all new compounds.

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