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Amidine function in constructing novel types of phosphorus-containing heterocycles

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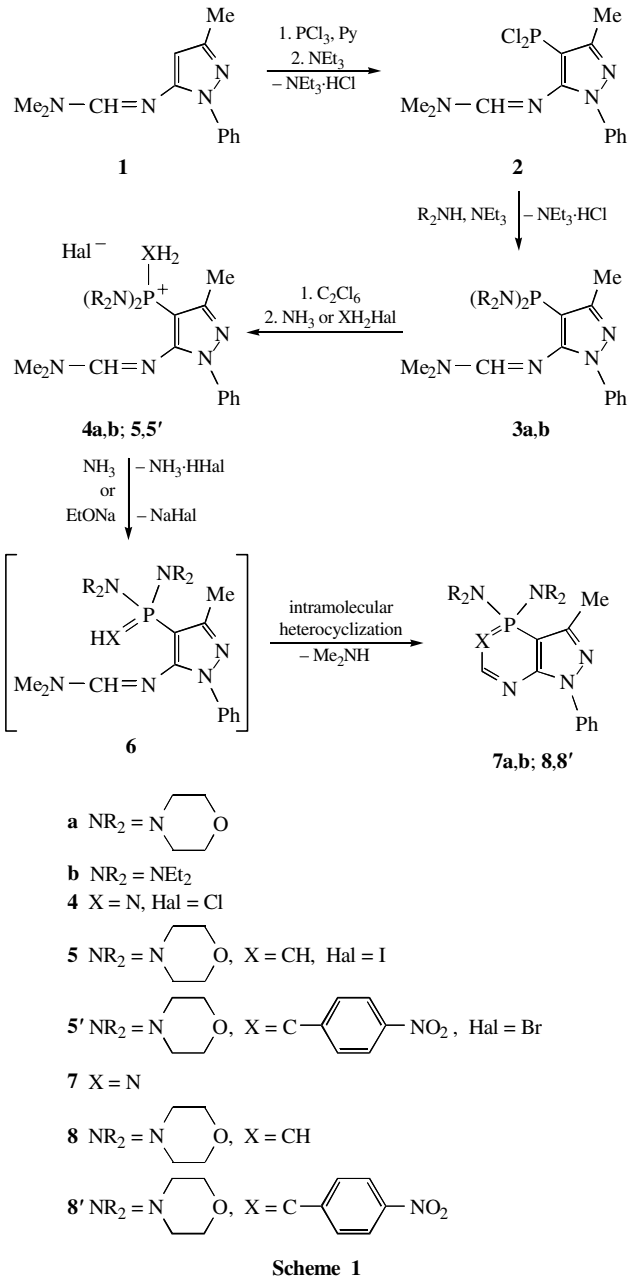
Novel pyrazolo[5,4-*b*]azaphosphinine and pyrazolo[4,5-*e*]diazaphosphinine ring systems have been synthesised from 4-phosphorylated 5-formamidinopyrazoles.

We have previously found that the amidine substituent (–N=CH–NMe_2) is a convenient protecting group in electrophilic reactions involving trivalent phosphorus halides, in which classical acetamide protection is not suitable. In this way, it was possible to introduce phosphorus substituents into the 4-position of thiazole and thiadiazole amidines. Subsequent removal of the amidine protecting group was found to lead to promising phosphorylated amino heterocycles.[1]

Here we report the use of the amidine substituent in heterocyclization reactions. Initially, the amidine group provides protection and activation ($\sigma^\circ = -0.25$)[2] for the introduction of a dihalophosphine moiety into the neighbouring position in the ring system. Next, an appropriate transformation of the phosphorus-containing moiety can result in an intramolecular nucleophilic substitution reaction to produce a phosphorus-containing heterocycle.

A dichlorophosphino moiety was successfully introduced into the 4-position of the pyrazole ring using N^1,N^1-dimethyl-N^2-5-pyrazolylformamidine **1** as the model system (Scheme 1). Note that **1** is considerably more reactive towards phosphorylation than other pyrazoles.[3] This fact illustrates the strong electron-donating properties of the amidine substituent. Dichlorophosphine **2** was then transformed into bis(dialkylamino)phosphines **3a**,**b** under mild conditions. Imidophosphonic diamide **6** (X = N), which was prepared from **3** by chlorination with hexachloroethane followed by reaction with NH_3, undergoes cyclization *in situ* to give the novel pyrazolo[4,5-*e*]diazaphosphinine ring system† of **7a**,**b**.

Dimorpholinophosphine **3a** was transformed into phosphonium salts **5** and **5′** by the action of methyl iodide and *p*-nitrobenzyl bromide, respectively. Reactions of salts **5** and **5′** give phosphorus ylides **6** (X = HC or 4-$NO_2C_6H_4C$), which undergo intramolecular nucleophilic substitution *in situ* to form pyrazolo-



Scheme 1

[5,4-*b*]azaphosphinines **8** and **8′**. The formation of the ylides from the salts is a rate-limiting step in the overall transformation. This results in a considerable decrease in the reaction rate when the methylphosphonium salt is used in the heterocyclization in place of the *p*-nitrobenzylphosphonium salt. Although the -C–H proton in methylphosphonium salt **5** exhibits low acidity, nevertheless, the steady-state concentration of non-stabilised methylide **6** (X = CH) produced by EtONa is sufficient to perform the heterocyclization.‡

† *4-[5-(3-Methyl-1,3-diazabut-1-enyl)-3-methyl-1-phenyl]pyrazolyldichlorophosphine* **2**. To a solution of 2.28 g of **1** (0.01 mol) in pyridine (23 ml), 1.31 ml of PCl_3 (0.015 mol) was added with cooling (0 °C) and stirring. The reaction mixture was allowed to stand for 1.5 h. Next, 2.8 ml of NEt_3 (0.02 mol) was added with cooling and stirring; after standing for 5 min, the salts were filtered off, and the reaction mixture was evaporated to dryness *in vacuo*. The product was crystallised from dry octane.

4-[5-(3-Methyl-1,3-diazabut-1-enyl)-3-methyl-1-phenyl]pyrazolyldimorpholinophosphine **3a** and *4-[5-(3-methyl-1,3-diazabut-1-enyl)-3-methyl-1-phenyl]pyrazolyl[bis(diethylamino)phosphine]* **3b**. A secondary amine (morpholine or diethylamine) (0.021 mol) was added to a mixture of **2** (0.01 mol) and NEt_3 (0.03 mol) in 30 ml of benzene with cooling and stirring. The reaction mixture was allowed to stand for 2 h. The salts formed were filtered off, and the reaction mixture was evaporated to dryness *in vacuo*. Product **3a** was crystallised from dry octane, and **3b** was extracted with dry hexane.

3-Methyl-4,4-bis(1-morpholino)-1-phenylpyrazolo[4,5-e]-1,3,4λ⁵-diazaphosphinine **7a** and *3-methyl-4,4-bis(diethylamino)-1-phenylpyrazolo-[4,5-e]-1,3,4λ⁵-diazaphosphinine* **7b**. Amide **3a** or **3b** (0.01 mol) was dissolved in dry benzene (30 ml); next, C_2Cl_6 (0.01 mol) in 10 ml of benzene was added with cooling and stirring. The reaction mixture was allowed to stand overnight and then evaporated to dryness in a vacuum. The residue was dissolved in CH_2Cl_2, the solution was saturated with gaseous NH_3 during 4 h and then allowed to stand for 24 h. The salts were filtered off, and the reaction mixture was evaporated to dryness. Compound **7a** was recrystallised from octane and isopropanol. Compound **7b** was recrystallised from hexane.

The ease of the cyclizations is caused by a significant polarization of P=XH bonds in both phosphazocompounds (X = N) and ylides (X = CR). An electron-rich nitrogen or carbon atom attacks the spatially adjacent electron-deficient carbon atom in the amidine group resulting in the replacement of a dimethylamino group and the formation of a heterocyclic ring.§

Nucleophilic substitution at a formamidine carbon atom is a promising approach which can be used in constructing heterocycles.[4] However, most of the systems containing active functional groups in the position adjacent to the amidine substituent are difficult to obtain. Only *o*-formylamidines can be easily prepared from the corresponding amines by reactions with an excess of the Vilsmaier reagent.[5]

We found that C-phosphorylation of N^1,N^1-dimethyl-N^2-hetarylformamidines can proceed at the heterocyclic moiety, in contrast to N^1,N^1-dimethyl-N^2-arylformamidines in which the formamidine carbon is the site of attack.[6] Thus, systems containing phosphorus and amidine groups at neighbouring positions can be produced. Appropriate modification of the phosphorus-containing substituent provides means for achieving subsequent cyclization. This strategy is promising for the synthesis of a wide range of phosphorus-containing heterocycles.

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‡ *4-[5-(3-Methyl-1,3-diazabut-1-enyl)-3-methyl-1-phenyl]pyrazolyldimorpholinomethylphosphonium iodide* **5** and *4-[5-(3-methyl-1,3-diazabut-1-enyl)-3-methyl-1-phenyl]pyrazolyldimorpholino-p-nitrobenzylphosphonium bromide* **5′**. Dimorpholinophosphine **3a** (0.01 mol) was dissolved in 25 ml of benzene, and a benzene solution (15 ml) of MeI (0.01 mol) or *p*-nitrobenzyl bromide (0.01 mol) was added. The reaction mixture was allowed to stand for 4 days. The product was filtered and recrystallised from isopropanol.

3-Methyl-4,4-bis(1-morpholino)-1-phenylpyrazolo[5,4-b]-1,4λ⁵-azaphosphinine **8** and *3-methyl-4,4-bis(1-morpholino)-5-(4-nitrophenyl)-1-phenylpyrazolo[5,4-b]-1,4λ⁵-azaphosphinine* **8′**. A mixture of **5** or **5′** (0.01 mol) and EtOH (10 ml) was added to EtONa (0.015 mol) in EtOH (20 ml). The reaction mixture was stirred for 12 (**5**) or 2 days (**5′**). Compound **8** was isolated by evaporating the reaction mixture to dryness, washing with water and recrystallization from ethanol. Compound **8′** was isolated by filtration, washing with water and then with dry diethyl ether.

§ ^{31}P, ^{13}C and ^{1}H NMR spectra were measured on a Varian VXR-300 instrument (131.313, 63.6 and 300 MHz, respectively) using TMS as an internal standard (^{13}C and ^{1}H) or 85% H_3PO_4 as an external standard (^{31}P). Elemental analysis data correspond to the calculated values to within 0.25%.

2: yield 88%, mp 88–89 °C. ^{1}H NMR (C_6D_6) δ: 8.04 (d, 2H, Ph, *o*-H, *J* 7.8 Hz), 7.17 (2H, Ph, *m*-H), 7.10 (d, 1H, NCHN, J_{PH} 6.9 Hz), 6.99 (t, 1H, Ph, *p*-H, *J* 7.5 Hz), 2.77 (s, 3H, MeHet), 2.27, 1.92 (6H, Me_2N). ^{13}C NMR (C_6D_6) δ: 156.97 (NCHN, J_{CP} 11.6 Hz), 156.93 (Het, 5-C, J_{CP} 36.7 Hz), 153.15 (Het, 3-C, J_{CP} 11.6 Hz), 140.76 (Ph, N–C), 129.24 (Ph, *m*-C), 126.97 (Ph, *p*-C), 124.29 (Ph, *o*-C), 105.43 (Het, 4-C, J_{CP} 57.2 Hz), 39.84, 34.57 (NMe_2), 15.52 (*Me*Het, J_{CP} 4.5 Hz). ^{31}P NMR (C_6D_6) δ: 148.04 (d, J_{PH} 6.9 Hz).

3a: yield 90%, mp 102–103 °C. ^{31}P NMR (pyridine) δ: 88.42.

3b: yield 81%, oil. ^{31}P NMR (pyridine) δ: 87.53.

5: yield 79%, mp 188–189 °C. ^{31}P NMR (EtOH) δ: 48.78.

5′: yield 77%, mp 160–162 °C. ^{31}P NMR (acetone) δ: 46.14 (br. m).

7a: yield 84%, mp 134–135 °C. ^{1}H NMR ($CDCl_3$) δ: 8.01 (d, 1H, NCHN, J_{PH} 46.2 Hz), 7.96 (d, 2H, Ph, *o*-H, *J* 8.1 Hz), 7.47 (t, 2H, Ph, *m*-H), 7.29 (t, 1H, Ph, *p*-H, *J* 7.2 Hz), 3.71 (8H, CH_2N), 3.15 (s, 8H, CH_2O), 2.42 (s, 3H, MeHet). ^{13}C NMR ($CDCl_3$) δ: 160.13 (Het, 5-C, J_{CP} 6.9 Hz), 157.36 (NCHN, J_{CP} 15.4 Hz), 145.69 (Het, 3-C, J_{CP} 1.1 Hz), 139.17 (Ph, N–C), 128.85 (Ph, *m*-C), 126.34 (Ph, *p*-C), 122.99 (Ph, *o*-C), 82.80 (Het, 4-C, J_{CP} 142.79 Hz), 66.97 (CH_2N, J_{CP} 10.6 Hz), 44.39 (CH_2O), 15.11 (*Me*Het, J_{CP} 2 Hz). ^{31}P NMR ($CHCl_3$) δ: 26.55 (d, J_{PH} 46.2 Hz). MS, *m*/*z*: 400 [M$^+$].

7b: yield 77%, mp 76–77 °C. ^{1}H NMR ($CDCl_3$) δ: 8.01 (d, 1H, NCHN, J_{PH} 45.9 Hz), 8.00 (d, 2H, Ph, *o*-H, *J* 8.4 Hz), 7.45 (t, 2H, Ph, *m*-H), 7.25 (t, 1H, Ph, *p*-H, *J* 7.5 Hz), 3.13 (m, 8H, NCH_2Me), 2.41 (s, 3H, MeHet), 1.08 (t, 12H, NCH_2Me, *J* 6.9 Hz). ^{31}P NMR (CH_2Cl_2) δ: 28.61 (m). MS, *m*/*z*: 372 [M$^+$].

8: yield 74%, mp 246–247 °C. ^{1}H NMR ($CDCl_3$) δ: 8.34 (dd, 1H, HCCP, J_{PH} 5.1 Hz, J_{HH} 9.9 Hz), 7.76–7.58 (m, 4H, Ph, *o*-H, *m*-H), 7.50 (t, 1H, Ph, *p*-H, *J* 7.2 Hz), 5.38 (dd, 1H, HCP, J_{PH} 38 Hz, J_{HH} 9.9 Hz), 3.74 (8H, CH_2N), 3.19 (s, 8H, CH_2O), 2.48 (s, 3H, MeHet). ^{13}C NMR (CD_3OD) δ: 150.45 (Het, 5-C, J_{CP} 7.6 Hz), 147.54 (PCH*C*HN, J_{CP} 12 Hz), 145.73 (Het, 3-C, J_{CP} 1.1 Hz), 138.06 (Ph, N–C), 131.48 (Ph, *m*-C), 131.15 (Ph, *p*-C), 126.78 (Ph, *o*-C), 85.23 (Het, 4-C, J_{CP} 113.4 Hz), 80.58 (P*C*HCHN, J_{CP} 96.86 Hz), 68.01 (CH_2N, J_{CP} 7 Hz), 46.40 (CH_2O), 15.12 (*Me*Het, J_{CP} 1 Hz). ^{31}P NMR ($CHCl_3$) δ: 29.89 (dm, J_{PCH} 38 Hz). MS, *m*/*z*: 399 [M$^+$].

8′: yield 72%, mp 241–243 °C. ^{1}H NMR ($CDCl_3$) δ: 8.26 (d, 2H, *o*-NO_2–H, *J* 12.3 Hz), 8.19 (d, 2H, *m*-NO_2–H), 8.03 (HCCP, J_{PH} 5.1 Hz), 7.60–7.40 (4H, Ph, *o*-H, *m*-H), 7.30 (t, 1H, Ph, *p*-H, *J* 7.2 Hz), 3.61 (8H, CH_2N), 3.11 (s, 8H, CH_2O), 2.97 (s, 3H, MeHet). ^{31}P NMR (CH_2Cl_2) δ: 30.32 (br. m).