Amidine function in constructing novel types of phosphorus-containing heterocycles

Gennady V. Oshovsky,* Alexander M. Pinchuk and Andrei A. Tolmachev

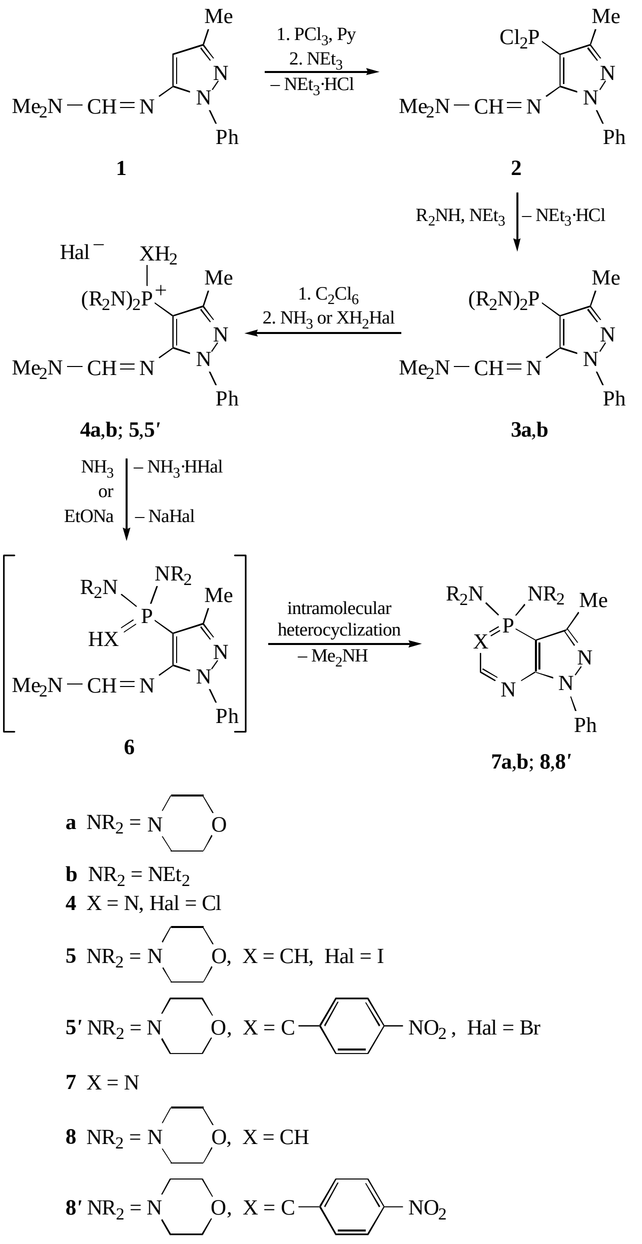
Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 253660 Kiev, Ukraine.
Fax: +7 044 573 2643; e-mail: oshovsky@carrier.kiev.ua

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 ($\sigma° = -0.25$)[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**.



Scheme 1

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[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 α-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.

G. V. Oshovsky is grateful to the International Science Educational Program (ISEP) of the International Science Foundation and to the International Renaissance Foundation for partial financial support of this work (grant nos. PSU073017 and PSU083047).

References

1 (*a*) G. V. Oshovsky, A. A. Tolmachev, A. A. Yurchenko, A. S. Merkulov and A. M. Pinchuk, *Izv. Akad. Nauk, Ser. Khim.*, 1999, 1353 (in Russian); (*b*) A. A. Tolmachev, G. V. Oshovsky, A. S. Merkulov and A. M. Pinchuk, *Khim. Geterotsikl. Soedin.*, 1996, 1288 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1996, 1109]; (*c*) G. V. Oshovsky, A. A. Tolmachev, A. S. Merkulov and A. M. Pinchuk, *Khim. Geterotsikl. Soedin.*, 1997, 1422 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1997, 1242].

2 E. D. Raczynska and M. Drapala, *J. Chem. Res. (S)*, 1993, 54.

3 A. A. Tolmachev, A. I. Sviridon, A. N. Kostyuk and A. M. Pinchuk, *Heteroatom Chemistry*, 1995, **6**, 449.

4 (*a*) V. G. Granik, *Usp. Khim.*, 1983, **52**, 669 (*Russ. Chem. Rev.*, 1983, **52**, 377); (*b*) O. L. Acevedo, S. H. Krawczyk and L. B. Townsend, *J. Heterocycl. Chem.*, 1985, **22**, 349; (*c*) R. Troschuetz, *Arch. Pharm.*, 1991, **324**, 485; (*d*) E. N. Dozorova, A. V. Kadushkin, G. A. Bogdanova, N. P. Solov'eva and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 1991, 754 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1991, 590]; (*e*) A. V. Komkov, A. M. Sakharov, V. S. Bogdanov and V. A. Dorokhov, *Izv. Akad. Nauk., Ser. Khim.*, 1995, 1324 (*Russ. Chem. Bull.*, 1995, **44**, 1278).

5 (*a*) O. Meth-Cohn and B. Norine, *Synthesis*, 1980, 133; (*b*) V. S. Velezheva, S. V. Simakov, V. N. Dymov and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, 1980, 851 (in Russian).

6 (*a*) G. V. Oshovsky, A. M. Pinchuk, A. N. Chernega, I. I. Pervak and A. A. Tolmachev, *Mendeleev Commun.*, 1999, 38; (*b*) A. A. Tolmachev, A. S. Merkulov, G. V. Oshovsky and A. B. Rozhenko, *Zh. Obshch. Khim.*, 1996, **66**, 1930 [*J. Gen. Chem.* (*Engl. Transl.*), 1996, **66**, 1877]; (*c*) A. A. Tolmachev, A. S. Merkulov and G. V. Oshovsky, *Khim. Geterotsikl. Soedin.*, 1997, 1000 [*Chem. Heterocycl. Compd.* (*Engl. Transl.*), 1997, 877].

Received: 9th February 1999; Com. 99/1440

[‡] *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]-1,4λ^5-azaphosphinine **8** and *3-methyl-4,4-bis(1-morpholino)-5-(4-nitrophenyl)-1-phenylpyrazolo[5,4-b]-1,4λ^5-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).