Heteroatom Chemistry
Volume 13, Number 1, 2002

Synthesis and Properties of 4,5-Dihydrobenzo[*e*]imidazo[2,1-*c*][1,4,2]diazaphosphinine Derivatives

Vladimir V. Ivanov, Alexandr A. Yurchenko, Alexander N. Chernega, Alexandr M. Pinchuk, and Andrej A. Tolmachev

Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kiev-94, 02094, Ukraine

Received 10 March 2001; revised 3 July 2001

ABSTRACT: *A number of 4,5-dihydrobenzo[e]imidazo[2,1-c][1,4,2]diazaphosphinine derivatives were prepared by the direct phosphorylation of 1-(4-Chlorophenylcarboxamido)-2-(1*H*-1-imidazolyl)-5-trifluoromethylbenzene in basic medium with phosphorus(III) bromide and dibromophenylphosphine. The tricyclic compounds* **6a, 6b**, *and* **9** *having a trivalent phosphorus atom undergo the diazaphosphinine ring opening upon treatment with secondary amines in the presence of sulfur.* © 2002 John Wiley & Sons, Inc. Heteroatom Chem 13:84–92, 2002; DOI 10.1002/hc.10000

INTRODUCTION

The direct C-phosphorylation with phosphorus(III) halides in basic medium has proved to be an efficient and convenient method for the introduction of a variety of phosphorus functions in the electron-rich aromatic [1] and heteroaromatic [2] compounds. When applied to functionalized pyrroles [3] and pyrazoles [4], this reaction has afforded a number of novel phosphorus-containing fused heterocycles. These heterocyclizations inevitably require two nucleophilic centers, one of them being an endocyclic carbon atom.

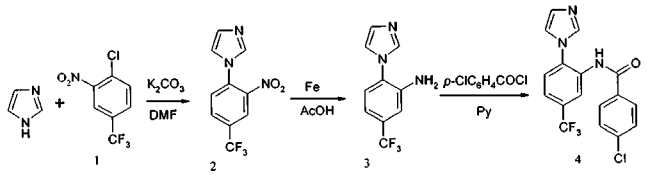
Correspondence to: Vladimir V. Ivanov; e-mail: vovch1@yahoo.com.

1,3-Azoles are reacted with phosphorus(III) and phosphorus(V) halides to yield the products of meso-phosphorylation [5]. This reaction was shown to follow the so-called "ylide" mechanism [5b] and can be formally regarded as a phosphorylation of the carbon atom with inverse reactivity. Herein, we report on the first example of an annelation of a phosphorus-containing heterocycle to a 1,3-azole nucleus by the direct phosphorylation with phosphorus(III) bromides, which resulted in the construction of the novel fused heterocyclic system starting from the amide **4**.

RESULTS AND DISCUSSION

The synthesis of the starting material was carried out according to Scheme 1. Imidazole was arylated with 1-chloro-2-nitro-4-trifluoromethylbenzene (**1**) in DMF in the presence of K_2CO_3. Reduction of the nitro group in **2** using the Fe/AcOH system afforded the *o*-imidazolylaniline (**3**). Acylation of the latter with *p*-chlorobenzoyl chloride in pyridine gave rise to the amide **4**.

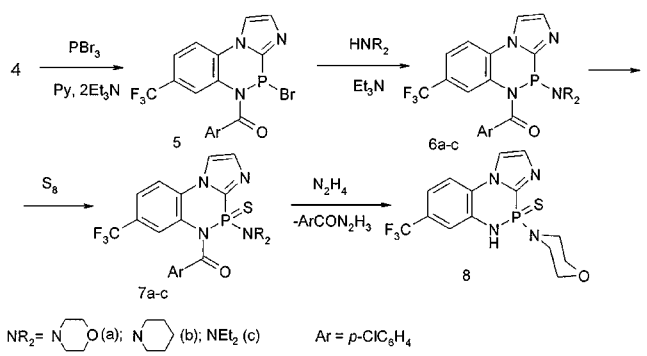
The amide **4** was reacted with phosphorus(III) bromide to yield the tricyclic compound **5** ($\delta\ ^{31}P =$ 43.7 ppm in pyridine) (Scheme 2). The reaction can be carried out in a low-polar solvent (toluene) in the presence of two equivalents of triethylamine as well as in the pyridine medium. However, in the latter case, the reaction appeared to proceed more smoothly in the presence of triethylamine. Significantly, this condition, in contrast to the



SCHEME 1

phosphorylation of *N*-alkylimidazoles [5b], is not obligatory. This fact can be explained by decreased basicity of the imidazole moiety in the amide **4** resulting in increased acidity of the 2-C—H bond in an intermediate imidazolium salt formed by N-phosphorylation with any of P—Br species present in the reaction mixture. The structure of **5** was confirmed by ^{31}P and ^{1}H NMR spectra (Table 1) as well as by chemical transformations. Compound **5** was prepared in toluene or pyridine and used in these reactions without isolation.

The bromine atom in **5** can easily be substituted by a secondary amino group upon treatment with the corresponding amine. The resulting cyclic phosphamides **6a–c** possess δ ^{31}P values of about 33 ppm in pyridine solutions. One of these compounds (**6a**) was isolated and additionally characterized by its ^{1}H NMR spectrum (Table 1). The phosphamides **6a–c** as well as the other derivatives of benzo[*e*]imidazo[2,1-*c*][1,4,2]diazaphosphinine having a phosphorus(III) atom are air-sensitive compounds. Sulfur was added to the reaction mixtures in order to convert **6a–c** into the air-stable phosphorus(V) derivatives **7a–c**. It was found that the sulfur addition takes place slowly. For example, this reaction in the case of **6a** is complete after 9 h of heating of the reaction mixture at 85°C. However, some acceleration can be achieved by increasing the basicity of the reaction medium via addition of triethylamine. This phenomenon was used in the synthesis of **7c**. The ^{31}P NMR, IR, physical, and elemental analysis data



SCHEME 2

of the compounds **7a–c**, as well as other prepared compounds, are summarized in Table 2.

The structure of **7a** was proved by X-ray analysis. The perspective view of molecule **7a** is shown in Fig. 1 [6], selected geometrical parameters being given in Table 3. The P(1)C(1)N(2)C(4)C(5)N(3) six-membered central heterocycle has the conformation of a *half-boat* [7]: the C(1), N(2), C(4), C(5), and N(3) atoms are roughly coplanar (deviations from the least-squares plane do not exceed 0.13 Å), whereas the P(1) atom is out of this plane by 0.58 Å; the "edge" P(1)C(1)N(3) forms with the "bottom" C(1)N(2)C(4)C(5)N(3) a dihedral angle of 25°. Torsion angles in this ring are as follows: P(1)—C(1)—N(2)—C(4) −2.8°, C(1)—N(2)—C(4)—C(5) 17.9°, N(2)—C(4)—C(5)—N(3) 2.3°, C(4)—C(5)—N(3)—P(1) −37.0°, C(5)—N(3)—P(1)—C(1) 42.0°, N(3)—P(1)—C(1)—N(2) −23.2°. The C(1)N(1)C(2)C(3)N(2) and C(4)–C(9) rings are approximately coplanar to the best least-squares plane of the central heterocycle, the corresponding dihedral angles being only 12.4° and 13.6°. Bond lengths and angles of **7a** are unexceptional [8,9].

The rotation of the morpholine moiety in **7a** around the P—N bond is sterically hindered by the adjacent acyl substituent. As a consequence, the protons of four methylene groups in the morpholine ring become diastereotopic and are observed in the ^{1}H NMR spectrum as four 2H-multiplets. On the contrary, in the ^{1}H NMR spectrum of **8**, prepared by hydrazinolysis of **7a**, these protons are observed as two 4H-multiplets.

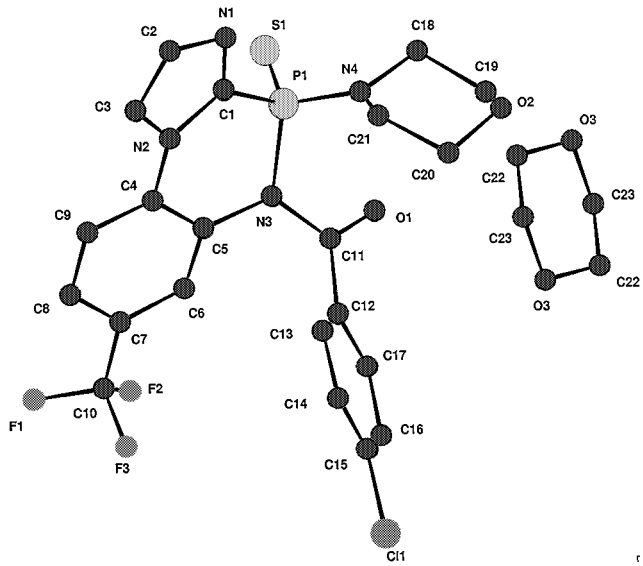


FIGURE 1 Perspective view and labeling scheme for molecule **7a** (hydrogen atoms are omitted for clarity).

TABLE 1 The ^{1}H NMR Data of **5, 6a, 7a–c, 8–10** [δ (ppm) and J (Hz) values]

							p-ClC_6H_4CO		
	Solvent	*H-1 (m, 1H)*	*H-2 (m, 1H)*	*H-6 (d, 1H)*	*H-8 (dd, 1H)*	*H-9 (d, 1H)*	*o-H (d, 2H)*	*m-H (d, 2H)*	*Other Signals*
5	CD_3CN	7.55	8.28	7.69	7.79, 8.4	8.07, 8.4	7.58, 8.1	7.44, 8.1	
6a	C_6D_6	7.01	7.44	7.67,1.2	7.07, 8.4, 1.2	6.73, 8.4	6.98, 8.4	6.84, 8.4	3.07 (m, 2H, NCH_2), 2.96 (m, 2H, NCH_2), 2.44 (m, 4H, OCH_2)
7a	$CDCl_3$	7.52	7.69	7.17	7.56, 9.0	7.61–7.64	7.64–7.66	7.41, 8.7	2.92 (m, 2H, NCH_2), 3.41 (m, 2H, NCH_2), 3.67 (m, 2H, OCH_2), 3.81 (m, 2H, OCH_2)
7b	DMSO-d_6	7.66	8.46	7.36	7.72, 8.7	8.17, 8.7	7.65, 8.4	7.46, 8.4	1.42 (m, 2H, CH_2), 1.53(m, 2H, CH_2), 1.64 (m, 2H, CH_2), 3.03 (m, 2H, NCH_2), 3.27 (m, 2H, NCH_2)
7c	$CDCl_3$	7.52	7.68	7.06	7.49–7.52	7.60, 8.1	7.56, 8.8	7.35, 8.8	1.18 (t, J =7.2 Hz, 6H, CH_3), 3.16 (m, 2H, NCH_2), 3.45 (m, 2H, NCH_2)
8	DMSO-d_6	7.53	8.43	7.54	7.44, 8.7	8.13, 8.7			3.18 (m, 4H, NCH_2), 3.54 (m, 4H, OCH_2), 9.43 (s, 1H, NH)
9	C_6D_6	7.11	7.73	7.40	6.84–6.88	7.08–7.12	7.12–7.15	6.83, 8.7	6.49 (m, 1H, *p*-H Ph), 6.73 (m, 2H, *o*-H Ph), 6.97 (m, 2H, *m*-H Ph)
10	acetone-d_6	7.45	8.36	7.47	7.80, 8.4	8.24, 8.4	7.69, 8.7	7.39, 8.7	7.53 (dt, 7.5 Hz, 4.2 Hz, 2H, *m*-H Ph), 7.65 (m, 1H, *p*-H Ph), 8.11 (dd, $J_{P,H}$ = 16.5, 7.2 Hz, 1H, *o*-H Ph)

TABLE 2 The Data of **7a–c, 8, 10, 12a–e**

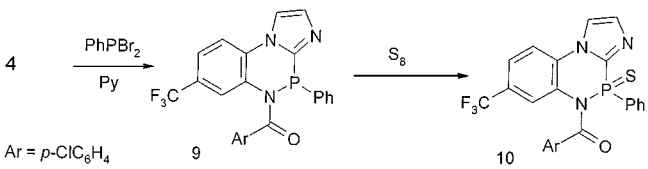
					Found% (Calcd %)		
	Yield (%)	*mp (°C)*	*Formula*	*δ ^{31}P (ppm), solvent*	*N*	*P*	*IR (KBr, cm^{-1})*
7a	59	193–194[a]	$C_{21}H_{17}ClF_3N_4O_2PS{\cdot}1/2\ C_4H_8O_2$	45.1, CD_3CN	10.32 (10.06)	5.38 (5.56)	1700 (C=O)
7b	48	220–221[b]	$C_{22}H_{19}ClF_3N_4OPS$	45.0, DMSO-d_6	11.08 (10.97)	5.78 (6.06)	1695 (C=O)
7c	61	218–219[b]	$C_{21}H_{19}ClF_3N_4OPS$	45.7, $CDCl_3$	11.32 (11.23)	6.15 (6.21)	1677 (C=O)
8	86	269–270[c]	$C_{14}H_{14}F_3N_4OPS$	38.8, DMSO-d_6	15.27 (14.97)	8.61 (8.27)	3750 (NH), 1630, 1610
10	32	212–215[d]	$C_{23}H_{14}ClF_3N_3OPS$	40.4, acetone-d_6	8.44 (8.34)	6.86 (6.15)	1690 (C=O)
12a	53	189[b]	$C_{25}H_{26}ClF_3N_5O_3PS$	55.0, CD_3CN	11.23 (11.67)	5.04 (5.16)	3450 (NH), 1690 (C=O)
12b	12	148–149[e]	$C_{27}H_{30}ClF_3N_5OPS$	55.8, acetone-d_6	11.95 (11.75)	5.16 (5.20)	3415 (NH), 1698 (C=O)
12c	32	153–154[e]	$C_{26}H_{28}ClF_3N_5O_2PS$	55.4, acetone-d_6	11.88 (11.71)	5.11 (5.18)	3425 (NH), 1700 (C=O)
12d	50	163–164[b]	$C_{27}H_{23}ClF_3N_4O_2PS$	50.4 (m), DMSO-d_6	9.38 (9.48)	5.09 (5.24)	3290 (NH), 1698 (C=O)
12e	59	146–147[e]	$C_{28}H_{25}ClF_3N_4OPS$	50.2 (m), DMSO-d_6	9.52 (9.51)	5.39 (5.26)	3455 (NH), 1700 (C=O)

[a]Recrystallized from *i*-PrOH. Analytical sample was prepared as dioxanate (**7a**/dioxane 2:1) by slow evaporation of the dioxane solution upon standing.
[b]Recrystallized from a toluene–heptane mixture.
[c]Recrystallized from EtOH/H_2O (1:1).
[d]Recrystallized from toluene.
[e]Recrystallized from heptane.

TABLE 3 Selected Bond Lengths Åand Angles (deg) in **7a**

Bond lengths	
S(1)—P(1)	1.918(2)
P(1)—N(3)	1.736(4)
P(1)—N(4)	1.622(4)
P(1)—C(1)	1.799(4)
O(1)—C(11)	1.205(5)
N(1)—C(1)	1.316(5)
N(1)—C(2)	1.370(6)
N(2)—C(1)	1.375(5)
N(2)—C(3)	1.391(5)
N(2)—C(4)	1.412(5)
N(3)—C(5)	1.437(5)
N(3)—C(11)	1.421(5)
C(2)—C(3)	1.348(6)
C(11)—C(12)	1.493(6)
Bond angles	
S(1)—P(1)—N(3)	116.00(15)
S(1)—P(1)—N(4)	115.89(16)
N(3)—P(1)—N(4)	106.41(19)
S(1)—P(1)—C(1)	116.72(16)
N(3)—P(1)—C(1)	95.61(19)
N(4)—P(1)—C(1)	103.7(2)
C(1)—N(1)—C(2)	104.9(3)
C(1)—N(2)—C(3)	106.3(3)
C(1)—N(2)—C(4)	125.5(3)
P(1)—N(3)—C(5)	121.4(3)
P(1)—C(1)—N(2)	122.5(3)
N(1)—C(1)—N(2)	111.7(4)
N(1)—C(2)—C(3)	112.0(3)
N(2)—C(3)—C(2)	105.1(4)
N(3)—C(5)—C(4)	120.7(4)
N(2)—C(4)—C(5)	119.4(3)

The amide **4** was treated with $PhPBr_2$ to furnish the tricyclic compound **9** (δ $^{31}P = 5.5$ ppm in pyridine) (Scheme 3). Again, as in the case of PBr_3, the reaction can be carried out in pyridine as well as in toluene in the presence of triethylamine. The structure of **9** was also confirmed by ^1H NMR spectroscopy and by chemical transformations. Compound **9** was prepared in toluene or pyridine and used in these reactions without isolation. ^{31}P NMR-monitoring of the reaction mixture revealed the formation of an intermediate, $\delta = 110.7$ ppm, which is probably a product of the amide function phosphorylation.



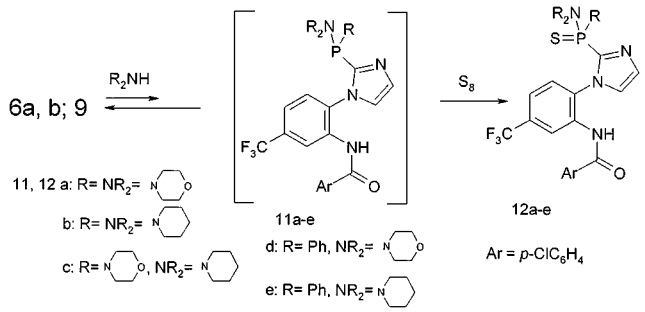
SCHEME 3

Sulfur addition to **9** afforded the air-stable compound **10**. This reaction occurs as slowly as in case of the phosphamides **6a–c**.

Sulfur addition to **6a** in the presence of morpholine in the reaction mixture gave a product of the oxidative endocyclic P—N bond cleavage (**12a**, Scheme 4, Table 4). It was deduced that the P—N bond cleavage occurs in the phosphorus(III) derivative **6a** because **7a** does not react with morpholine either in pyridine solution or under reflux in MeCN. Morpholine addition to a pyridine solution of **6a** resulted in emergence in the ^{31}P NMR spectrum of a signal at $\delta = 72.5$ ppm. This signal can be attributed to **11a** since its δ value is close to that (75.7 ppm) of 1-methyl-1*H*-2-imidazolyl(dimorpholino)phosphane [5b]. The resonance peak of **11a** has a static low intensity. Thus, an equilibrium between **6a** and **11a** probably exists. The phosphorus atom of **11a** is more nucleophilic than that of **6a** because it is no longer in conjugation with the heterocyclic system. This explains the relative swiftness of the described transformation, in which sulfur preferably reacts with **11a** to shift the equilibrium toward the opening of the diazaphosphinine ring.

The competing process of sulfur addition to **6** became significant when an analogous transformation of **6b** in the presence of piperidine was attempted and dominated in the case of the reaction of **6c** with Et_2NH that did not allow preparation of **12c**. The observed increase in the percentage in the formation of the phosphorus(V) derivatives of type **7** is probably connected with the growth of basicity of the amine precursors as well as by the earlier found acceleration of sulfur addition by increasing the medium basicity.

The property of the phosphamide **6a** to undergo the diazaphosphinine ring opening upon treatment with a secondary amine enables the synthesis of the mixed amide **12c**. This transformation can also be carried out as the treatment of the phosphamide **6b**



SCHEME 4

TABLE 4 The ^{1}H NMR Data of **12a–e** [δ (ppm) and J (Hz) values]

		Imidazole		*Arene*			*p-ClC$_6$H$_4$CO*		
	Solvent	*H-4 (m, 1H)*	*H-5 (m, 1H)*	*H-6 (d, 1H)*	*H-4 (dd, 1H)*	*H-3 (d, 1H)*	*o-H (d, 2H)*	*m*-H *(d, 2H)*	*Other Signals*
12a	$CDCl_3$	7.32	7.08	8.37, 1.6	7.58, 8.7, 1.6	7.34, 8.7	7.67, 8.4	7.40, 8.4	8.27 (bs, 1H, CONH); 3.76 (m, 4H, OCH_2); 3.57 (m, 4H, OCH_2); 3.26 (m, 4H, NCH_2); 3.04 (m, 4H, NCH_2)
12b	acetone-d_6	7.73	7.34	7.44	7.72–7.78	8.55, 6.9	7.76, 8.4	7.55, 8.4	8.59 (s, 1H, CONH); 3.09 (bs, 8H, NCH_2); 1.54 (m, 12H, CH_2)
12c	acetone-d_6	7.73	7.35	7.48	7.72–7.75	8.53–8.55	7.72–7.75	7.54, 8.7	8.53–8.55 (bs, 1H, CONH); 3.60 (bs, 4H, OCH_2); 3.08 (bs, 8H, NCH_2); 1.51 (m, 6H, CH_2)
12d	DMSO-d_6	7.67	7.38	8.14					9.65 (s, 1H, CONH); 7.81, 7.62, 7.61, 7.56, 7.46 (bs, 11H, the other aromatic protons); 3.39 (bs, 4H, OCH_2); 3.02 (bs, 2H, NCH_2); 2.86 (m, 2H, NCH_2)
12e	DMSO-d_6	7.63	7.35	8.16					9.57 (s, 1H, CONH); 7.82, 7.56, 7.45, (bs, 11H, the other aromatic protons); 2.96 (m, 2H, NCH_2); 2.78 (m, 2H, NCH_2); 1.39 (m, 2H, CH_2); 1.27 (m, 2H, CH_2)

with morpholine in the presence of sulfur. However, in this case, the greater affinity of **6b** for sulfur leads to a far inferior yield of **12c**.

Similarly, addition of morpholine to the pyridine solution of the phenylphosphine **9** gave an equilibrium mixture of the starting **9** and the product of the diazaphosphinine ring cleavage (**11d**, δ ^{31}P = 36.9 ppm). The equilibrium is shifted toward the formation of the cleaved product upon addition of sulfur. The composition of thus prepared phosphorus(V) derivative **12d** was confirmed by elemental analysis. The ^{31}P NMR spectrum of **12d** ($CDCl_3$) exhibited two peaks at $\delta = 48.98$ and 49.50 ppm (in ~3:1 ratio), which account for the complicated ^{1}H NMR spectrum in the same solvent. The occurrence of **12d** in two spectroscopically detected isomers provides evidence for the presence of a second (after the asymmetric phosphorus atom) chiral element in the molecule of this compound. Such an element might be the axis running through the C_{Arene}–$N_{Imidazole}$ bond. This chiral axis originates from the hindered rotation around the above-mentioned bond in view of the steric obstacles caused by the bulky substituents (NHCOAr and P(S)PhNR$_2$) and/or dipole–dipole intramolecular interactions between the same groups. On the other hand, the ^{31}P NMR spectrum of **12d** in DMSO-d_6 solution showed a narrow (~1 ppm) multiplet at $\delta = 50.4$ ppm. Although the ^{1}H NMR spectrum is structurally unresolved, some assignments can still be made (Table 4). Compound **12e** was prepared analogously when **9** was treated with piperidine in the presence of sulfur. The ^{31}P NMR spectrum of **12e** in $CDCl_3$ solution exhibits two peaks at $\delta = 49.06$ and 49.60 ppm in ~2:1 ratio, whereas in DMSO-d_6, a narrow multiplet is observed at $\delta = 49.7$ ppm.

EXPERIMENTAL

All the manipulations with air-sensitive compounds were performed under an atmosphere of dry argon using standard Schlenk techniques. Solvents were purified by conventional procedures. Melting points were determined with an electrothermal capillary melting point apparatus and were not corrected.

The ^{31}P, ^{1}H, and ^{13}C NMR spectra were obtained on a Varian VXR-300 spectrometer (121, 300, and 75 MHz, respectively). Chemical shifts are reported relative to internal tetramethylsilane (^{1}H, ^{13}C) or external 85% H_3PO_4 (^{31}P).

X-ray Structure Determination of **7a**

Crystal data: $C_{21}H_{17}ClF_3N_4O_2PS\cdot 1/2C_4H_8O_2$, MW = 556.93 monoclinic, $a = 13.984(9)$ Å, $b = 10.563(9)$ Å, $c = 17.358(9)$ Å, $\beta = 98.70(5)^\circ$, $V = 2534.5$ Å^3, $Z = 4$, $d = 1.46$ g cm^{-1}, space group $P2_1/a$, $\mu = 3.43$ cm^{-1}, $F(000) = 1146$, crystal size ca. 0.16 mm × 0.28 mm × 0.38 mm. All crystallographic measurements were performed at 18°C on a CAD-4-Enraf-Nonius diffractometer operating in the ω–2θ scan mode (the ratio of the scanning rates $\omega/2\theta = 1.2$). Intensity data were collected within the range $2 < \theta < 23^\circ$ ($0 < h < 12$, $0 < k < 11$, $-19 < l < 19$) using graphite monochromated Mo Kα radiation ($\lambda = 0.71069$ Å). Intensities of 3622 reflections (3241 unique reflection, $R = 0.032$) were measured. Data were corrected for Lorentz and polarization effects, and an empirical absorption correction based on azimuthal scan data [10] was applied. The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation using the CRYSTALS program package [11]. In the refinement, 2046 reflections with $I > 3\sigma(I)$ were used. Most (ca. 80%) hydrogen atoms were located in the different Fourier maps, and the remaining H atoms were placed in calculated positions. All H atoms were included in the final refinement with fixed positional and thermal parameters. Convergence was obtained at $R = 0.043$ and $R_w = 0.045$, GOF = 1.107 (352 refined parameters; obs/variabl. 5.8; the largest and minimal peaks in the final difference map, 0.26 and −0.33 e/Å^3). The Chebushev weighting scheme [12] with parameters 0.70, 0.09, 0.56, −0.02, and 0.17 was used.

Full crystallographic details have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for this material should quote the full literature citation and the reference number CCDC 157270.

*1-(2-Nitro-4-trifluoromethylphenyl)-1*H*-imidazole (***2***)*

To a solution of imidazole (75 g, 1.1 mol) in DMF (140 ml) was added 1-chloro-2-nitro-4-trifluoromethylbenzene (**1**) (150 ml, 1.0 mol). The reaction mixture was heated to 100–105°C and freshly calcined, finely ground K_2CO_3(235 g, 1.7 mol) was added portionwise under stirring. Then the reaction mixture was stirred at 105–110°C for 1.5 h, cooled to room temperature, and poured into water (1.8 l). The precipitated crystalline solid was filtered off, washed with water, and dissolved in 0.5 l of 10% HCl. The resulting solution was treated with activated charcoal (30 g) and stirred for 40 min. The mixture was filtered and the filtrate was basified with aqueous K_2CO_3. The crystalline solid was filtered off and thoroughly washed with water to afford 193 g (75%) of the pure product. mp = 82–83°C (cyclohexane). ^{1}H NMR (DMSO-d_6): δ (ppm) 7.15 (s, 1H, H-5 imidazole), 7.50 (s, 1H, H-4 imidazole), 7.98 (d, $J = 8.4$ Hz, 1H, H-6), 8.01 (s, 1H, H-2 imidazole), 8.30 (dd, $J = 8.4$ Hz and 2.0 Hz, 1H, H-5), 8.60 (d, $J = 2.0$ Hz, 1H, H-3). IR (KBr): 3140, 3030, 1640, 1590, 1555, 1525, 1490, 1350 cm^{-1}. Anal. Calcd. for $C_{10}H_6F_3N_3O_2$: C, 46.70; H, 2.35; N, 16.34; Found: C, 46.80; H, 2.45; N, 16.29%.

*2-(1*H*-1-Imidazolyl)-5-trifluoromethylaniline(***3***)*

A mixture of the nitro compound **2** (15 g, 58.3 mmol), Fe powder (30 g, 0.537 mol), HOAc (100 ml), and *i*-PrOH (50 ml) was heated in a 0.5-l round bottom flask equipped with a cooler until a vigorous reaction took place. Then, the heating bath was removed and the mixture was allowed to boil. When boiling ceased, the reaction mixture was refluxed for 1.5 h, cooled to room temperature, and filtered under an atmosphere of argon. The filtrate was evaporated under reduced pressure. The dark-brown oily residue was dissolved in 200 ml of ethanol and treated with saturated aqueous K_2CO_3 under vigorous shaking to provide a clear solution with a Fe-containing lower layer. The solution was decanted and evaporated under reduced pressure to dryness. The solid residue was dissolved in dilute HCl. The resulting solution was treated with charcoal and stirred for 0.5 h, filtered, and basified with aqueous K_2CO_3. The crystalline solid was collected by filtration and washed with water to afford 8.3 g (63%) of the product. mp = 132°C (toluene–heptane). ^{1}H NMR ($CDCl_3$): δ (ppm) 3.99 (s, 1H, NH_2), 7.06 (d, $J = 8.1$ Hz, 1H, H-4), 7.09 (s, 1H, H-5 imidazole), 7.15 (s, 1H, H-2), 7.23 (d, $J = 8.1$ Hz, 1H, H-5), 7.27 (s, 1H, H-4 imidazole), 7.66 (s, 1H, H-2 imidazole). IR (KBr): 3390, 3228, 3170, 3133, 1650, 1540, 1495, 1456 cm^{-1}. Anal. Calcd. for $C_{10}H_8F_3N_3$: C, 52.87; H, 3.55; N, 18.50; Found: C, 52.87; H, 3.72; N, 18.47%.

*1-(4-Chlorophenylcarboxamido)-2-(1*H*-1-imidazolyl)-5-trifluoromethylbenzene (***4***)*

4-ClC_6H_4COCl (5.12 ml, 40.3 mmol) was poured into pyridine (150 ml). The aniline **3** (9.15 g, 40.3 mmol) was added to the stirred mixture at −15, . . . , −10°C. Stirring was continued for 0.5 h at −5, . . . , 0°C and then for a further 3 h at room temperature. The reaction mixture was poured into water (1.7 l). The formed crystalline solid was filtered off and washed with water to afford 11.6–11.9 g

(79–81%) of the product, which was recrystallized from either toluene or ethanol–water. mp = 201–202°C (toluene). ^{1}H NMR (DMSO-d_6): δ (ppm) 7.05 (s, 1H, H-5 imidazole), 7.48 (s, 1H, H-4 imidazole), 7.61 (d, $J = 8.4$ Hz, 2H, *m*-H COC_6H_4Cl), 7.75 (d, $J = 8.4$ Hz, 1H, H-4), 7.83 (d, $J = 8.4$ Hz, 1H, H-5), 7.86 (d, $J = 8.4$ Hz, *o*-H COC_6H_4Cl), 7.97 (s, 1H, H-2 imidazole), 8.03 (s, 1H, H-2). IR (KBr): 3355, 3144, 3054, 1667, 1630, 1602, 1549, 1510, 1486, 1443 cm^{-1}. Anal. Calcd. for $C_{17}H_{11}ClF_3N_3O$: Cl, 9.69; N, 11.49; Found: Cl, 9.67; N, 11.38%.

*5-(4-Chlorobenzoyl)-4-bromo-7-trifluoromethyl-4,5-dihydrobenzo[e]imidazo[2,1-c][1,4,2]diazaphosphinine (**5**)*

(a) Isolation Method. Phosphorus tribromide (1.0 ml, 10.5 mmol) was added to a stirred mixture of **4** (3.85 g, 10.5 mmol), Et_3N (2.94 ml, 21.1 mmol), and toluene (60 ml) at −20°C. The mixture was stirred for 1 h on a cooling bath, the temperature being allowed to rise to 0°C, and then kept overnight at room temperature. The reaction mixture was filtered, the filtrate evaporated to half of its initial volume under reduced pressure and diluted with heptane (20 ml), then again filtered and the filtrate evaporated almost to dryness. The residue was repeatedly treated with heptane to yield the crystalline solid, which was filtered off and dried in vacuum. Yield 67%. ^{31}P NMR (CD_3CN): $\delta = 31.5$ ppm.

(b) Preparation of the Pyridine Solution of **5**. Phosphorus tribromide (0.39 ml, 4.1 mmol) was added to a stirred mixture of **4** (1.5 g, 4.1 mmol), triethylamine (1.2 ml, 8.6 mmol), and pyridine (20 ml) at −30°C. The mixture was stirred for 1.5 h on a cooling bath, the temperature being allowed to rise to −5°C. The reaction was complete within 1.5 h of stirring of the reaction mixture at room temperature. ^{31}P NMR: $\delta = 43.7$ ppm.

*5-(4-Chlorobenzoyl)-4-morpholino-7-trifluoromethyl-4,5-dihydrobenzo[e]imidazo[2,1-c][1,4,2]diazaphosphinine (**6a**)*

To a stirred mixture of **4** (3.85 g, 10.5 mmol), Et_3N (2.94 ml, 21.1 mmol), and toluene (60 ml) was added phosphorus tribromide (1.0 ml, 10.5 mmol) at −20°C. The mixture was stirred for 1 h on a cooling bath, the temperature being allowed to rise to 0°C, and then kept overnight at room temperature. To the stirred reaction mixture was added Et_3N (1.5 ml, 10.8 mmol) and morpholine (0.92 ml, 10.5 mmol) at −10, . . . ,0°C. After 4 h of stirring at room temperature, the reaction mixture was worked-up as described for **5**. Yield 80%. ^{31}P NMR (benzene): $\delta = 32.7$ ppm.

*5-(4-Chlorobenzoyl)-4-morpholino-4-thioxo-7-trifluoromethyl-4,5-dihydrobenzo[e]imidazo[2,1-c][1,4,2]diazaphosphinine(**7a**) and 5-(4-Chlorobenzoyl)-4-piperidino-4-thioxo-7-trifluoromethyl-4,5-dihydrobenzo[e]imidazo[2,1-c][1,4,2]diazaphosphinine (**7b**)*

To a pyridine solution of **5**, prepared as described above and cooled below 0°C, were added Et_3N (0.6 ml, 4.3 mmol) and the corresponding secondary amine (4.1 mmol). Sulfur (140 mg, 4.4 mmol) was added to the reaction mixture after 30 min of stirring. Stirring was continued at 85°C for 9 h in the case of **7a** and for 5 h in the case of **7b**. The reaction mixture was cooled to room temperature and diluted with benzene (20 ml). The precipitate of the salts was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was triturated with toluene to give the crystalline solid in the case of **7a** and subjected to flash chromatography on silica gel using toluene/CH_2Cl_2 (1:1) as eluent followed by trituration of the product with hexane in the case of **7b**.

*5-(4-Chlorobenzoyl)-4-diethylamino-4-thioxo-7-trifluoromethyl-4,5-dihydrobenzo[e]imidazo[2,1-c][1,4,2]diazaphosphinine (**7c**)*

To a pyridine solution of **5**, preliminarily cooled below 0°C, were added Et_3N (0.6 ml, 4.3 mmol) and Et_2NH (4.1 mmol). Sulfur (140 mg, 4.4 mmol) was added to the reaction mixture after 30 min of stirring. Stirring was continued until the sulfur was completely dissolved, and then the reaction mixture was left for 3 days at room temperature and treated with Et_3N (1.14 ml, 8.2 mmol) to complete the reaction in a further 2 days. The reaction mixture was diluted with benzene (20 ml). The precipitate of the salts was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was subjected to flash chromatography on silica gel using toluene as eluent.

*4-Morpholino-4-thioxo-7-trifluoromethyl-4,5-dihydrobenzo[e]imidazo[2,1-c][1,4,2]diazaphosphinine (**8**)*

A solution of the phosphamide **7a** (0.5 g, 0.97 mmol) and $N_2H_4 \cdot H_2O$ (0.1 ml, 2.1 mmol) in *n*-BuOH was refluxed for 8 h. The reaction mixture was evaporated under reduced pressure to dryness. The residue was recrystallized from a EtOH/H_2O mixture (1:1).

*5-(4-Chlorobenzoyl)-4-phenyl-7-trifluoromethyl-4,5-dihydrobenzo[e]imidazo[2,1-c][1,4,2]diazaphosphinine (**9**)*

(a) Isolation Method. To a stirred mixture of **4** (3 g, 8.2 mmol), Et_3N (2.4 ml, 17.2 mmol), and toluene (45 ml) was added $PhPBr_2$ (1.17 ml, 8.2 mmol) at −20°C. The reaction mixture was stirred for 1 h on a cooling bath, the temperature being allowed to rise to 0°C, and then kept overnight at room temperature. The workup procedure was as described above for **5**. Yield 75%. ^{31}P NMR (toluene): $\delta = 5.5$ ppm.

(b) Preparation of the Pyridine Solution of **9**. To a stirred solution of **4** (1.53 g, 4.2 mmol) in pyridine (20 ml) was added $PhPBr_2$(0.6 ml, 4.2 mmol) at −20°C. The reaction mixture was stirred for 1 h on a cooling bath, the temperature being allowed to rise to 0°C, and then kept overnight at room temperature. ^{31}P NMR: $\delta = 5.4$ ppm.

*5-(4-Chlorobenzoyl)-4-phenyl-4-thioxo-7-trifluoromethyl-4,5-dihydrobenzo[e]imidazo[2,1-c][1,4,2]diazaphosphinine (**10**)*

To the stirred solution of **9** in pyridine was added sulfur (140 mg, 4.4 mmol) and the reaction mixture was stirred at 110°C for 10 h, cooled to room temperature, and diluted with benzene (20 ml). The precipitate of the salts was filtered off and the filtrate was evaporated under reduced pressure. The residue was triturated with toluene (10 ml). The crystalline solid was filtered off and washed with toluene.

*4-Chloro-N-[2-{2-[di(4-morpholinyl)phosphothioyl]-1*H*-imidazol-1-yl}-5-(trifluoromethyl)phenyl] benzamide (**12a**) and 4-Chloro-N-[2-{2-[di(1-piperidinyl)phosphothioyl]-1*H*-imidazol-1-yl}-5-(trifluoromethyl)phenyl]benzamide (**12b**)*

To a pyridine solution of **5** were added the corresponding secondary amine (13.5 mmol) and sulfur (140 mg, 4.4 mmol). After having been stirred overnight, the reaction mixture was diluted with benzene (20 ml). The precipitate of the salts was filtered off and the filtrate was evaporated to dryness under reduced pressure. In the case of **12a**, the residue was treated with cold MeOH (∼5–10 ml). The formed crystalline solid was filtered off and washed with a small amount of cold MeOH. In the case of **12b**, the residue was repeatedly extracted with nonane.

*4-Chloro-*N*-[2-{2-[4-morpholinyl(1-piperidinyl)phosphothioyl]-1*H*-imidazol-1-yl}-5-(trifluoromethyl)phenyl]benzamide (**12c**)*

To a pyridine solution of **5**, preliminarily cooled below 0°C, were added Et_3N (0.6 ml, 4.3 mmol) and morpholine (4.1 mmol). After having been stirred for 40 min at room temperature, the mixture was treated with piperidine (4.5 mmol) and sulfur (140 mg, 4.4 mmol), stirred overnight, and diluted with benzene (20 ml). The precipitate of the salts was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was subjected to flash chromatography on silica gel using toluene as eluent. The product was purified by recrystallization from heptane.

*4-Chloro-*N*-[2-{2-[4-morpholinyl(phenyl)phosphothioyl]-1*H*-imidazol-1-yl}-5-(trifluoromethyl)phenyl]benzamide (**12d**) and 4-Chloro-*N*-[2-{2-[1-piperidinyl(phenyl)phosphothioyl]-1*H*-imidazol-1-yl}-5-(trifluoromethyl)phenyl]benzamide (**12e**)*

To a pyridine solution of **9** were added the corresponding amine (16.8 mmol) and sulfur (140 mg, 4.4 mmol). The reaction mixture was stirred overnight at room temperature, diluted with benzene (20 ml), and filtered. The filtrate was evaporated to dryness under reduced pressure. The products were extracted with heptane.

REFERENCES

[1] (a) Tolmachev, A. A.; Ivonin, S. P.; Charchenko, A. V.; Kozlov, E. S. Zh Obshch Khim 1990, 60, 2674–2679 (Russ.); Chem Abstr 1991, 115, 71717t; (b) Tolmachev, A. A.; Ivonin, S. P.; Charchenko, A. V.; Kozlov, E. S. Zh Obshch Khim 1989, 59, 1193–1194 (Russ.); Chem Abstr 1990, 112, 7750c.

[2] (a) Tolmachev, A. A.; Ivonin, S. P.; Chaikovskaya, A. A.; Terikovska, T. E.; Kudrya, T. N.; Pinchuk, A. M. Heteroat Chem 1999, 10, 223–230; (b) Ivonin, S. P.; Terikovska, T. E.; Chaikovskaya, A. A.; Marchenko, A. P.; Koydan, G. N.; Pinchuk, A. M.; Tolmachev, A. A. Heteroat Chem 1999, 10, 213–221; (c) Ivonin, S. P.; Anishenko, A. A.; Kurochkin, A. I.; Tolmachev, A. A. Heteroat Chem 1998, 9, 559–563; (d) Tolmachev, A. A.; Ivonin, S. P.; Anishenko, A. A.; Pinchuk, A. M. Heteroat Chem 1998, 9, 461–470; (e) Tolmachev, A. A.; Sviridon, A. I.; Kostyuk, A. N.; Pinchuk, A. M. Heteroat Chem 1995, 6, 449–459; (f) Tolmachev, A. A.; Ivonin, S. P.; Pinchuk, A. M. Heteroat Chem 1995, 6, 407–412.

[3] (a) Ivonin, S. P.; Pushechnikov, A. O.; Tolmachev, A. A. Heteroat Chem 2000, 11, 107–114; (b) Tolmachev, A. A.; Dovgopoly, S. I.; Kostyuk, A. N.; Kozlov, E. S.; Pushechnikov, A. O. Heteroat Chem 1997, 8, 495–499.

[4] (a) Tolmachev, A. A.; Dovgopoly, S. I.; Kostyuk, A. N.; Kozlov, E. S.; Pushechnikov, A. O.; Holzer, W. Heteroat Chem 1999, 10, 391–398; (b) Tolmachev, A. A.; Pushechnikov, A. O.; Krotko, D. G.; Ivonin, S. P.; Kostyuk, A. N. Chem Heterocycl Compd (N.Y.) 1999, 34(9), 1098–1099 (Eng. Transl).

[5] (a) Komarov, I. V.; Strizhak, A. V.; Kornilov, M. Yu.; Zarudnitskii, E. V.; Tolmachev, A. A. Synth Comm 2000, 30, 243–252; (b) Tolmachev, A. A.; Yurchenko, A. A.; Merkulov, A. S.; Semenova, M. G.; Zarudnitskii, E. V.; Ivanov, V. V.; Pinchuk, A. M. Heteroat Chem 1999, 10, 585–597; (c) Komarov, I. V.; Strizhak, A. V.; Kornilov, M. Yu.; Kostyuk, A. N.; Tolmachev, A. A. Synth Comm 1998, 28, 2355–2370.

[6] Watkin, D. J.; Prout, C. K.; Pearce, L. J. CAMERON; Chemical Crystallography Laboratory, University of Oxford: Oxford, 1996.

[7] Zefirov, N. S.; Palyulin, V. A. Dokl Acad Nauk SSSR 1980, 252, 111 (Russ.); Chem Abstr 1980, 93, 203935b.

[8] Naumov, V. A.; Vilkov, L. V. Molecular Structures of Organophosphorus Compounds; Nauka: Moscow, 1986 (Russ.); Chem Abstr 1987, 106, B 120063b.

[9] Allen, F. H.; Kennard, O.; Watson, D. G.; Brammer, L.; Orpen, A. G.; Taylor, R. J Chem Soc Perkin Trans II 1987, S.1.

[10] North, A. C. T.; Phillips, D. C.; Mathews, F. S. Acta Crystallogr 1968, A24, 351.

[11] Watkin, D. J.; Prout, C. K.; Carruthers, J. R.; Betteridge, P. W. CRYSTALS, Issue 10; Chemical Crystallography Laboratory, University of Oxford: Oxford, 1996.

[12] Carrythers, J. R.; Watkin, D. J. Acta Crystallogr 1979, A35, 698.