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A Facile Synthesis of New 1,2-Dihydro-2λ^5-[1,3]oxazolo[5,4-*d*][1,3,2]diazaphosphinine Derivatives Starting from 2-Benzoylamino-3, 3-dichloroacrylonitrile

Oleg V. Shablykin,[1] Andrei A. Gakh,[2] Vladimir S. Brovarets,[1] Eduard B. Rusanov,[3] and Boris S. Drach[1]

[1]*Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, Kyiv, Ukraine*

[2]*Oak Ridge National Laboratory, Oak Ridge, TN 37831-6242*

[3]*Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Kyiv, Ukraine*

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ABSTRACT: *Easily accessible 2-benzoylamino-3,3-dichloroacrylonitrile, when treated successively with primary amines, phosphorus pentachloride, sulfur dioxide, and various N- or S-nucleophiles, furnishes the corresponding derivatives of 1,2-dihydro-2λ^5-[1,3]oxazolo[5,4-d][1,3,2]diazaphosphinine, a novel fused heterocycle. The structure of the compounds obtained is unequivocally confirmed by spectroscopic methods and X-ray diffraction analysis.* Heteroatom Chem 19:506–511, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20470

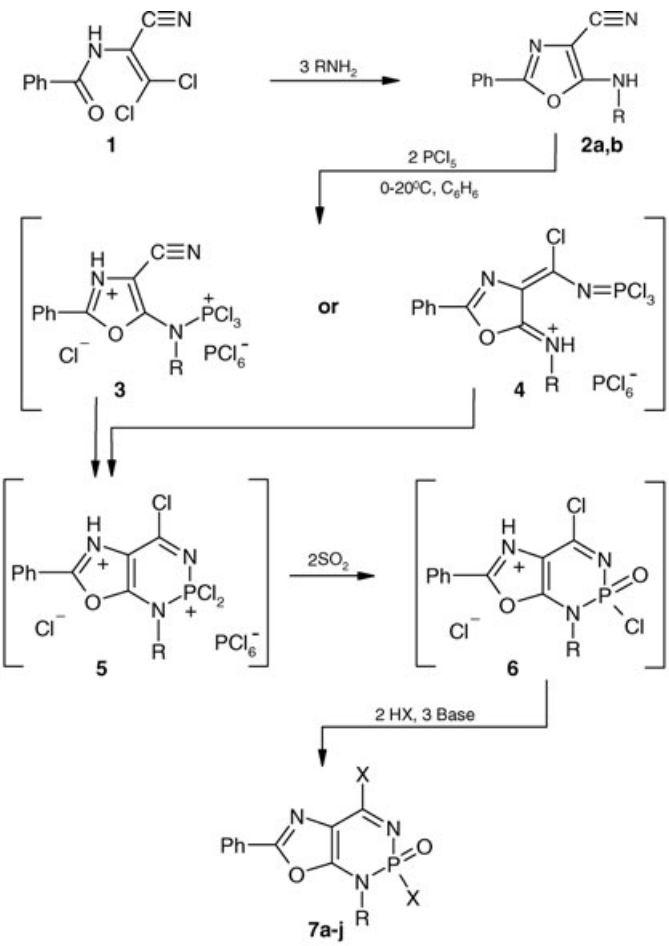
INTRODUCTION

Starting from 2-acylamino-3,3-dichloroacrylonitriles used as polycentric electrophiles, synthetic routes were previously developed to access various derivatives of 1,3-oxazole [1–8], 1,3-thiazole [7], imidazole [9], pyrazole [10,11], 1,3,4-oxadiazole [12], 1,3,4-thiadiazole [13], pyrazolo[1,5-*a*]pyrimidine [11], and 1,3-oxazolo[4,5-*d*]pyrimidine [14]. In the present study, we suggest a facile method of converting the above-mentioned electrophilic reagents into the derivatives of 1,2-dihydro-2λ^5-[1,3]oxazolo[5,4-*d*][1,3,2]diazaphosphinine, a novel fused heterocyclic system (Scheme 1 and Table 1).

Correspondence to: Boris S. Drach; e-mail: drach@bpci.kiev.ua.

RESULTS AND DISCUSSION

As found formerly [2], 2-benzoylamino-3,3-dichloroacrylonitrile **1** treated with strongly basic amines readily cyclizes to give 5-alkylamino-2-phenyl-1,3-oxazole-4-carbonitriles **2a, b** (Scheme 1). Here we study, for the first time, the reaction of compounds **2a, b** with phosphorus pentachloride. It appears that the condensation is most conveniently performed at 5–20°C in benzene with excess phosphorus pentachloride. The initially formed phosphorylation products could not be isolated in the pure state, and they were reacted further with sulfur dioxide and then with excess methylamine, benzylamine, pyrrolidine, or morpholine to yield compounds **7a–g**. Similar products **7h–j** result from the reaction of intermediate phosphorylation



2,7	a	b	c	d	e	f	g	h	i	j
R	Me	$PhCH_2$	$PhCH_2$	Me	$PhCH_2$	Me	$PhCH_2$	Me	$PhCH_2$	$PhCH_2$
X	$PhCH_2NH$	MeNH	$PhCH_2NH$					$PhCH_2S$	$PhCH_2S$	4-MeC_6H_4S

Base=$MeNH_2$, $PhCH_2NH_2$,  ,  , Et_3N.

SCHEME 1

products with mercaptans or thiophenols in the presence of triethylamine (Table 2).

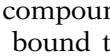
The final products of the conversion presented in Scheme 1 have been structurally determined by IR as well as ^1H and ^{31}P NMR spectra, which corroborate the presence of the characteristic group  in compounds **7a–j**. Since the phosphoryl group is bound to only one residue of a N- or S-nucleophile, one can assume that the phosphorus atom is incorporated into a heterocyclic system. X-ray diffraction analysis of compound **7b** has enabled unequivocal structural identification of the heterocycle. The perspective view of molecule **7b** and selected geometrical parameters are given in Fig. 1 and Table 3, respectively. The central bicyclic N(1–3)O(3)C(1–4) bond system is planar (deviations from the least-squares plane do not exceed 0.031 Å), and the P(1) atom is 0.174 Å above this plane. The benzene ring C(13–18) is almost planar, whereas the C(7–12) benzene ring is perpendicular to this plane, the corresponding dihedral angles being 17.0° and 81.8°. The P(1)N(2)N(3)C(2–4) six-membered cycle has an *envelope* conformation; the dihedral angle between the P(1)N(2)N(3) and N(2)N(3)C(2–4) planes

TABLE 1 Physical and Analytical Data of Compounds **7**

Compound	mp (°C)	Yield (%)[a]	Molecular Formula (Mol. Wt.)	Analysis (%) Found (Calcd.) C	H	N	P	S
7a	205–206[b]	30	$C_{25}H_{24}N_5O_2P$ (457.5)	65.46 (65.64)	5.31 (5.29)	15.09 (15.31)	6.59 (6.77)	–
7b	265–266[c]	44	$C_{19}H_{20}N_5O_2P$ (381.4)	59.55 (59.84)	5.37 (5.29)	18.58 (18.36)	8.33 (8.12)	–
7c	231–232[c]	66	$C_{31}H_{28}N_5O_2P$ (533.6)	69.51 (69.78)	5.50 (5.29)	13.41 (13.13)	5.59 (5.80)	–
7d	241–242[b]	39	$C_{19}H_{24}N_5O_2P$ (385.4)	59.42 (59.21)	5.97 (6.28)	18.44 (18.17)	8.31 (8.04)	–
7e	239–240[c]	56	$C_{25}H_{28}N_5O_2P$ (461.5)	65.35 (65.06)	6.29 (6.12)	15.05 (15.17)	6.52 (6.71)	–
7f	234–235[b]	46	$C_{19}H_{24}N_5O_4P$ (417.4)	54.39 (54.67)	6.63 (5.80)	16.55 (16.78)	7.44 (7.42)	–
7g	271–272[c]	62	$C_{25}H_{28}N_5O_4P$ (493.5)	61.06 (60.85)	5.91 (5.72)	13.90 (14.19)	6.13 (6.28)	–
7h	170–171[b]	29	$C_{25}H_{22}N_3O_2PS_2$ (491.6)	60.88 (61.09)	4.66 (4.51)	8.70 (8.55)	6.14 (6.30)	13.11 (13.05)
7i	229–230[c]	53	$C_{31}H_{26}N_3O_2PS_2$ (567.7)	65.71 (65.59)	4.45 (4.62)	7.33 (7.40)	5.34 (5.46)	11.24 (11.30)
7j	197–198[c]	45	$C_{31}H_{26}N_3O_2PS_2$ (567.7)	65.27 (65.59)	4.43 (4.62)	7.31 (7.40)	5.28 (5.46)	11.22 (11.30)

[a]For twice-crystallized compounds.
[b]Recrystallization from benzene.
[c]Recrystallization from EtOH.

TABLE 2 Spectroscopic Data of Compounds **7**

Compound	^1H NMR δ (ppm)	^{13}C NMR δ (ppm)	^{31}P NMR δ (ppm)
7a	2.98 (d, J = 7.3 Hz, 3H, CH_3), 3.44–3.82 (m, 2H, CH_2), 4.43–4.67 (m, 2H, CH_2), 5.50 (m, 1H, NH), 7.04–7.95 (m, 15H, $3C_6H_5$), 8.57 (m, 1H, NH)	29.21, 43.51, 45.27, 106.75, 125.83 (×2), 127.14 (×2), 127.40, 127.91, 128.20 (×2), 127.47 (×2), 128.83 (×2), 129.75, 129.81 (×2), 130.65, 140.20, 141.34, 151.17, 154.93, 157.93	8.0
7b	2.14 (m, 3H, CH_3), 2.88 (d, J = 3.5 Hz, 3H, CH_3), 4,73–4,91 (m, 2H, CH_2), 4.81 (m, 1H, NH), 7.22–7.82 (m, 10H, $2C_6H_5$), 8.00 (m, 1H, NH)	26.77 (×2), 46.32, 106.43, 124.75 (×2), 126.10, 127.09, 127.96 (×2), 128.06 (×2), 128.85 (×2), 129.70, 137.26, 150.39, 154.53, 156.57	9.7
7c	3.50–3.81 (m, 2H, CH_2), 4.28–4.76 (m, 4H, $2CH_2$), 5.62 (m, 1H, NH), 7.09–7.79 (m, 20H, $4C_6H_5$), 8.64 (m, 1H, NH)	–	8.4
7d	1.76 (m, 4H, $2CH_2$), 1.84 (m, 2H, CH_2), 1.99 (m, 2H, CH_2), 2.96 (m, 4H, $2CH_2$), 3.21 (d, J = 7.5 Hz, 3H, CH_3), 3.51 (m, 2H, CH_2), 4.03 (m, 2H, CH_2), 7.52–7.97 (m, 5H, C_6H_5)	–	2.2
7e	1.63 (m, 4H, $2CH_2$), 1.89 (m, 2H, CH_2), 2.00 (m, 2H, CH_2), 2.89 (m, 4H, $2CH_2$), 3.57 (m, 2H, CH_2), 4.06 (m, 2H, CH_2), 4.64–4.92 (m, 2H, CH_2), 7.21–7.85 (m, 10H, $2C_6H_5$)	–	3.5
7f	2.92 (m, 4H, $2CH_2$), 3.27 (d, J = 7.2 Hz, 3H, CH_3), 3.35 (m, 2H, CH_2), 3.51 (m, 4H, $2CH_2$), 3.70 (m, 4H, $2CH_2$), 4.22–4.76 (m, 2H, CH_2), 7.45–7.98 (m, 5H, C_6H_5)	–	4.1
7g	2.86 (m, 4H, $2CH_2$), 3.24–3.57 (m, 4H, $2CH_2$), 3.64–3.98 (m, 6H, $3CH_2$), 4.22–4.62 (m, 2H, CH_2), 4.66–4.95 (m, 2H, CH_2), 7.22–7.85 (m, 10H, $2C_6H_5$)	–	3.9
7h	3.08 (d, J = 7.4 Hz, 3H, CH_3), 3.32 (m, 1H, CH_2), 3.75 (m, 1H, CH_2), 4.41 (m, 2H, CH_2), 6.95–7.97 (m, 15H, $3C_6H_5$)	–	23.0
7i	3.45 (m, 1H, CH_2), 3.78 (m, 1H, CH_2), 4.43 (m, 2H, CH_2), 4.48 (m, 1H, CH_2), 4.84 (m, 1H, CH_2), 7.01–7.77 (m, 20H, $4C_6H_5$)	–	23.9
7j	2.07 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 5.09 (m, 2H, CH_2), 7.05–7.87 (m, 18H, $2C_6H_5$, $2C_6H_4$)	20.53, 20.95, 47.77, 114.72, 121.50, 121.60, 124.96, 125.73 (×2), 128.07, 128.49 (×2), 128.76 (×2), 129.19 (×2), 129.68 (×2), 130.10 (×2), 131.09, 135.20 (×2), 135.38, 135.46 (×2), 139.89, 140.21, 151.94, 157.15, 170.43	24.0

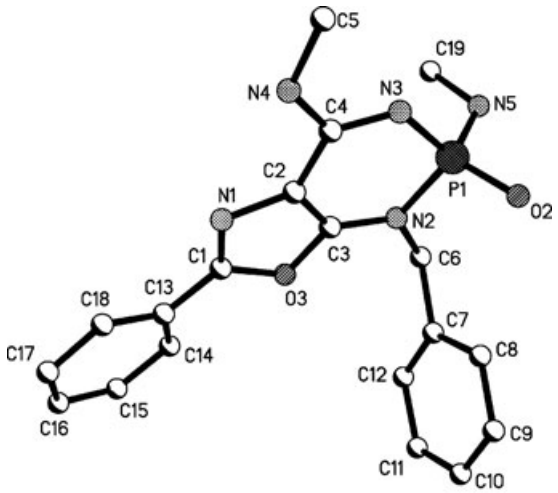
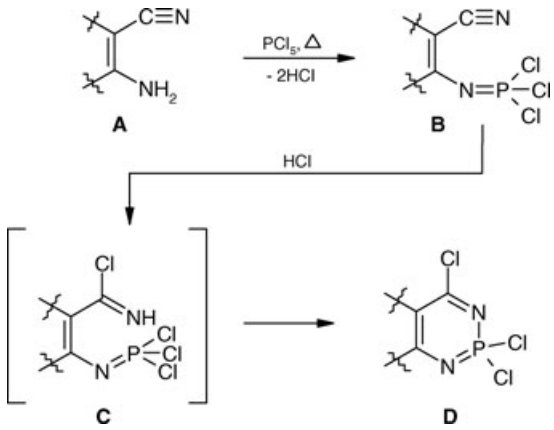


FIGURE 1 Perspective view and labeling scheme for molecule **7b**.



SCHEME 2

is 11.3°. The N(2), N(4), and N(5) atoms have a trigonal–planar bond configuration (the sum of the bond angles is equal to 359.9°, 360.0°, and 358.4°, respectively). The P(1) atom adopts a significantly distorted tetrahedral coordination geometry. Because of the n_N-π conjugation, the N(4)–C(4) bond is notably shortened (1.315(3) Å) and is thus outside the standard range for the N(sp^2)–C(sp^2) single bonds (1.43–1.45 Å) [15,16].

Thus, the molecular structure has been firmly established for the whole family of compounds **7**. Nevertheless, a detailed mechanism of the cascade conversion **2** $\Rightarrow$ **7** has yet to be elucidated. At first glance, it would seem that the reactions concerned represent a particular case of phosphorylation of various β-enaminonitriles [17–20] and 2-aminobenzonitriles [21] with phosphorus pentachloride or related reagents. This process normally involves the successive conversions A → B → C → D shown in Scheme 2.

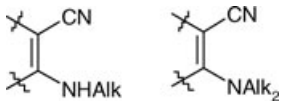
However, compounds **2a, b** lack a primary amino group and hence the initial stage of their phosphorylation should proceed differently from the A → B conversion. The latter gives rise to the N=P bond formation, and it may be conjectured, by analogy, that phosphorylation of a secondary amino group results in structure **3** bearing the N—P bond. At the same time, one cannot rule out initial phosphorylation at the cyano group leading to structure **4**, provided the reaction is performed under very mild conditions. This phosphorylation pathway was established, e.g., for malononitrile and its derivatives [22]. This is, of course, only indirect evidence that phosphorylation can initially yield two alternative

TABLE 3 Selected Bond Lengths (Å) and Bond Angles (°) of **7b**

Bond Length (Å)			*Bond Angle (°)*
C(1)–N(1)	1.291(3)	N(1)–C(1)–O(3)	113.5(2)
C(1)–O(3)	1.405(3)	C(3)–O(3)–C(1)	103.6(2)
C(2)–C(3)	1.363(3)	O(3)–C(3)–C(2)	108.8(2)
C(2)–N(1)	1.392(3)	C(3)–C(2)–N(1)	109.0(2)
C(3)–O(3)	1.356(2)	C(3)–C(2)–C(4)	120.7(2)
C(2)–C(4)	1.432(3)	N(1)–C(2)–C(4)	130.2(2)
C(3)–N(2)	1.343(3)	N(2)–C(3)–O(3)	122.6(2)
C(4)–N(3)	1.315(3)	N(2)–C(3)–C(2)	128.5(2)
N(2)–P(1)	1.723(2)	N(3)–C(4)–C(2)	120.5(2)
N(3)–P(1)	1.617(2)	N(3)–P(1)–N(2)	105.4(1)
N(5)–P(1)	1.611(2)	O(2)–P(1)–N(2)	110.1(1)
O(2)–P(1)	1.474(2)	O(2)–P(1)–N(5)	110.6(1)
		O(2)–P(1)–N(3)	115.6(1)
		N(5)–P(1)–N(3)	109.6(1)
		N(5)–P(1)–N(2)	105.0(1)

intermediates, **3** and **4**, which are likely to cyclize readily to the same intermediate **5**. The further conversions **5** → **6** → **7** appear quite trivial, since processes of this kind are widespread.

To conclude, although formation of intermediates **3–6** or possibly of some other species has a conjectural status, this in no way minimizes the preparative importance of the cascade conversion **2** ⇒ **7**, which affords the derivatives of a novel fused heterocycle, 1,2-dihydro-2λ^5-[1,3]oxazolo[5,4-*d*][1,3,2]diazaphosphinine. Moreover, a remarkable ease of phosphorylation observed for compounds **2a, b** suggests the great potentialities of the reaction between various enaminonitriles containing the characteristic moieties



and phosphorus pentachloride.

EXPERIMENTAL

The NMR spectra were recorded on a Varian Gemini 300 spectrometer at 300 (^{1}H), 100.60 (^{13}C), and 80.95 MHz (^{31}P) in DMSO-d_6. ^{1}H NMR and ^{13}C NMR chemical shifts are given in δ (ppm) relative to Me_4Si as an internal standard. ^{31}P NMR spectra were recorded relative to 85% H_3PO_4 as an external standard. IR spectra were measured on a corresponding UR-20 spectrometer for KBr disks.

General Procedure for the Synthesis of 1-Alkyl-2,4-bis[benzylamino(methyl amino, morpholino,pyrrolidino)]-6-phenyl-1,2-dihydro[1,3]oxazolo[5,4-d][1,3,2]diazaphosphinin-2-ones **7a–g**

To a vigorously stirred solution of PCl_5 (1.2 mmol) in C_6H_6 (15 mL), **2a, b** (0.5 mmol) obtained by the known procedure [2,5] were added at 5°C. The reaction mixture was stirred at ambient temperature for 20 h, saturated with SO_2, evaporated under vacuum (1 Torr) at 40°C. The residue was treated with diethyl ether (5 mL), filtered off, and suspended in THF (10 mL), followed by adding the corresponding amine (2.5 mmol in THF (5 mL) at 20°C. The reaction mixture was stirred for 6 h at 30°C. Then it was treated with water (50 mL), filtered, washed with EtOH and ether, and purified by recrystallization from an appropriate solvent to give **7a–g** (Table 1).

General Procedure for the Synthesis of 1-Alkyl-2,4-bis[benzylthio(4-methylphenylthio)]-6-phenyl-1,2-dihydro[1,3]oxazolo[5,4-d][1,3,2]diazaphosphinin-2-ones **7h–j**

They were obtained similarly to compounds **7a–g** using benzylmercaptan (1 mmol) or 4-methylbenzenethiol (1 mmol) as a nucleophilic reagent and triethylamine (1.5 mmol) as a base.

X-Ray Structure Determination for **7b**

Crystal Data. $C_{19}H_{20}N_5O_2P$, M = 381.37, monoclinic, space group $C2/c$ (N 15), a = 19.312(3), b = 6.4046(9), c = 31.583(4) Å, β = 102.902(2)°, V = 3807.9(9) Å^3, Z = 8, d_c = 1.330 g cm^{-3}, μ = 0.169 mm^{-1}, $F(000)$ = 1600, crystal size ca. 0.50 × 0.22 × 0.05 mm^3.

Data Collection. All crystallographic measurements were performed at room temperature on a Bruker Smart Apex II diffractometer. The cell parameters were obtained from the least-squares treatment of 1934 reflections in the θ range of 2.16–24.13°. The intensity data were collected within the range of $2.16° \le \theta \le 26.24°$ using Mo K_α radiation (λ = 0.71078 Å). The intensities of 7662 reflections were collected (3763 unique reflections, R_{int} = 0.030). Data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement. The structure was solved by direct methods and refined by the full-matrix least-squares technique in the anisotropic approximation for non-hydrogen atoms using the SHELXS97 and SHELXL97 programs [23,24]. Hydrogen atoms were located in the difference Fourier maps and refined isotropically. The SADABS absorption correction was applied (the ratio of the minimum-to-maximum apparent transmission is 0.533). In the refinement, 3763 reflections (2507 reflections with $I \ge 2\sigma(I)$) were used. Convergence was obtained at R_1 = 0.0462 and wR_2 = 0.0973, GOF = 1.028 (324 parameters; obs./var. ratio = 7.74; the largest and minimal peaks in the final difference map are 0.21 and −0.30 e/Å^3, the weighting scheme is as follows: $\omega = 1/[\sigma^2(F_o^2) + (0.0436P)^2 + 1.5472P]$, where $P = (F_o^2 + 2F_c^2)/3$). Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for these materials should quote the full literature citation and reference number CCDC 670139.

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