Reactions of isocyanatophosphoryl difluoride with π-abundant nitrogen heterocycles and carbonyl compounds

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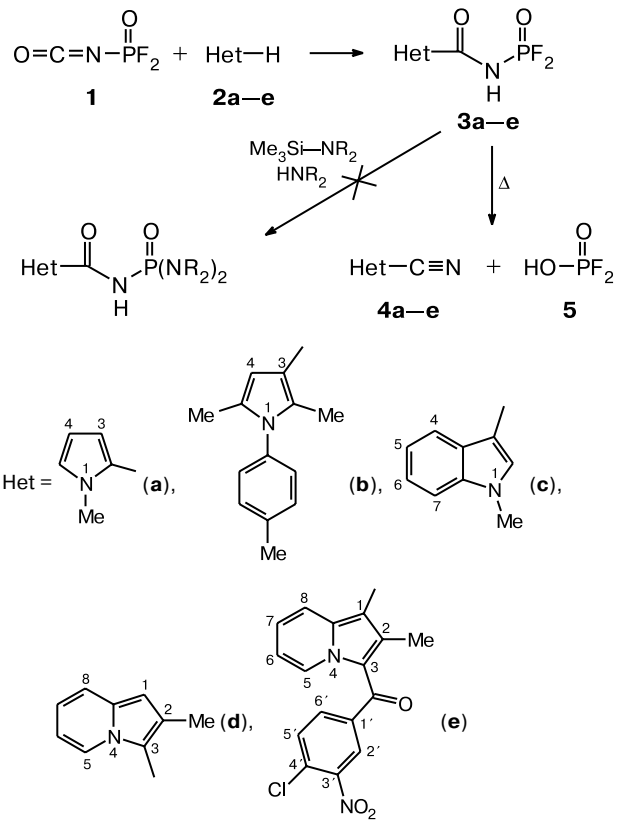
Reactions of electron-rich nitrogen heterocycles with isocyanatophosphoryl difluoride were studied. Novel heteroylaminophosphoryl difluorides were obtained in high yields. *N*-Phosphorylated imines were synthesized for the first time from carbonyl compounds and phosphorus isocyanates.

Key words: isocyanatophosphoryl difluoride, pyrroles, indoles, indolizines, heteroylaminophosphoryl difluorides.

Highly electrophilic isocyanates (such as aryl and halosulfonyl isocyanates) are widely used to functionalize C-nucleophilic substrates and carbonyl compounds.[1—5] The possibility of employing phosphorus isocyanates in such reactions has been investigated only since recently. We have found that isocyanatophosphoryl dichloride,[6] which is the most reactive and easily accessible representative of phosphorus isocyanates, is an efficient reagent for introduction of nitrile,[7] amide,[8] and *N*-phosphorylcarboxamide functions[9] into electron-rich heterocycles and enamines. The goal of the present work was to study the acylating properties of another representative of isocyanatophosphoryl dihalides, namely, isocyanatophosphoryl difluoride.[10]

We found that isocyanatophosphoryl difluoride **1**, like its dichloride analog,[9] actively carbamoylates pyrrole, indole, and indolizine derivatives **2a**—**e** at the C atom in heptane at room temperature to give heteroylaminophosphoryl difluorides **3a**—**e** (Scheme 1).

Scheme 1



The structures of difluorides **3a**—**e** were confirmed by ^{31}P and ^{1}H NMR and IR spectroscopy (Table 1). The IR spectra of compounds **3a**—**e** contain characteristic absorption bands of the C=O (1670—1680 cm^{-1}), P=O (1200—1210 cm^{-1}), and N—H bonds (3100—3300 cm^{-1}). It should be noted that the C-carbamoylation pathway did not change when passing from acid dichloride[9] to difluoride and is typical of this type of heterocycles.

Phosphoryl difluorides **3a**—**e** are colorless amorphous solids that decompose on melting; they are insoluble in saturated hydrocarbons, but are easily soluble in benzene, dichloromethane, dichloroethane, and acetonitrile. They are thermally less stable than analogous phosphoryl dichlorides.[7—9] For instance, compound **3a** is stable in the individual state at 20 °C only for a few hours. Its solutions in dichloromethane are also unstable: the stability diminishes with an increase in the concentration. Compounds **3a**—**e** decompose to the corresponding nitriles **4a**—**e** and orthophosphoric difluoride **5** (^{31}P NMR, δ: −15.7 (t, $J_{P,F}$ = 966 Hz)), which was determined from IR, NMR,

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 564—566, March, 2006.

Table 1. Physicochemical constants and yields of compounds **3a—e**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%)				Molecular formula	NMR (C_6D_6, δ, J/Hz)	
			C	H	N	P		^{31}P, t ($J_{P,F}$)	^{1}H
3a	93	49—50	34.60 34.63	3.45 3.39	13.41 13.46	14.90 14.88	$C_6H_7F_2N_2O_2P$	−20.2 (983)	3.79 (s, 3 H, NMe); 6.17 (dd, 1 H, H(4), $J_{H,H}$ = 3.5, $J_{H,H}$ = 2.4); 6.79 (m, 2 H, H(3)+H(5)); 13.32 (br.s, 1 H, NH)
3b	95	92—93	53.91 53.85	4.80 4.84	8.92 8.97	9.98 9.92	$C_{14}H_{15}F_2N_2O_2P$	−18.2 (973)	1.96, 2.14, 2.43 (all s, 3 H each, Me); 6.13 (s, H(4)); 7.05, 7.31 (both d, 2 H each, Ar, $J_{H,H}$ = 8.1)
3c	90	95—96	46.56 46.52	3.55 3.51	10.79 10.85	12.07 12.00	$C_{10}H_9F_2N_2O_2P$	−19.4 (980)	3.85 (s, 3 H, NMe); 7.03 (m, 3 H, Het); 7.56 (s, 1 H, Het); 7.60 (d, 1 H, Het, $J_{H,H}$ = 7.8)
3d	89	85—86	46.60 46.52	3.52 3.51	10.83 10.85	11.95 12.00	$C_{10}H_9F_2N_2O_2P$	−16.6 (969)	2.62 (s, 3 H, Me); 6.47 (s, 1 H, H(1)); 6.87 (t, 1 H, H(6), $J_{H,H}$ = 7.2); 7.20 (t, 1 H, H(7), $J_{H,H}$ = 7.2); 7.45 (d, 1 H, H(5), $J_{H,H}$ = 8.4); 9.24 (d, 1 H, H(8), $J_{H,H}$ = 7.5); 15.30 (br.s, 1 H, NH)
3e	94	225—226	46.18 46.23	2.56 2.51	9.55 9.51	7.04 7.01	$C_{17}H_{11}ClF_2N_3O_5P$	−19.4 (976)	2.17 (s, 3 H, Me); 7.12 (t, 1 H, H(6), $J_{H,H}$ = 7.0); 7.27 (s, 1 H, Ar); 7.51 (t, 1 H, H(7), $J_{H,H}$ = 7.1); 7.42 (m, 3 H Ar+Het); 8.16 (br.s, 1 H NH); 9.63 (d, 1 H, H(5), $J_{H,H}$ = 7.6)

and GC-MS data. Unlike the corresponding phosphoryl dichlorides,[9] difluorides **3a—e** did not react with aliphatic amines or their trimethylsilylated derivatives under mild conditions; under more drastic conditions, they decomposed to nitriles.

We monitored the reactions of isocyanatophosphoryl dichlorides and difluorides with 3-benzoylindolizine **2e** by ^{31}P NMR spectroscopy for equal concentrations of the starting reagents. According to the results obtained, difluoride **1** is less reactive than the dichloride (Table 2).

Reactions of chlorosulfonyl isocyanate and other sulfonylisocyanates with carbonyl compounds provide a convenient route to *N*-sulfonated azomethines.[2,3,11] Analogous reactions of isocyanatophosphoryl dihalides have not been studied earlier.

We found that isocyanate **1** in dichloromethane reacts with *N*,*N*-dimethylacetamide **6** and formylated indoline **8** to give phosphorylated imines **7** and **9** with evolution of an equivalent amount of CO_2[12] (Scheme 2). It should be noted that reactions of isocyanatophosphoryl dichloride[6] with carbonyl compounds yield complex mixtures of uni-

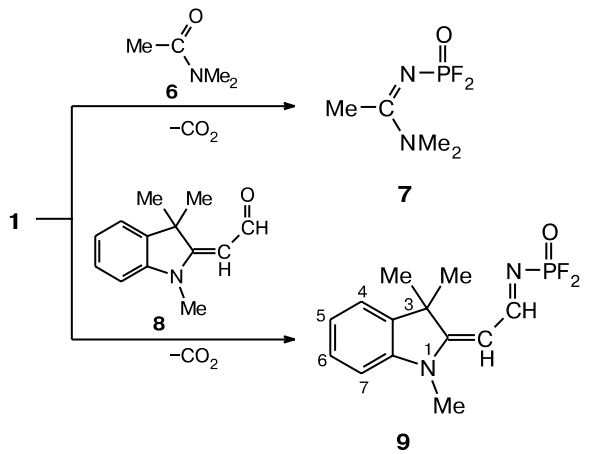
Table 2. Reactions of isocyanatophosphoryl difluoride and dichloride with indolizine **2e**[a] (monitoring by ^{31}P NMR spectroscopy)

t/min	Product (%)	
	$OCNP(O)F_2$	$OCNP(O)Cl_2$
15	—*	32.4
100	13.8	57.6
130	26.5	58.3

* The signal of the product is absent.

Note. Reagents and conditions: a 0.053 *M* solution of substrate **2e** and the corresponding acid dihalide in CH_2Cl_2 was kept in tubes at 20 °C for equal periods of time.

Scheme 2



dentified products, probably because of the involvement of the dichlorophosphoryl fragment in the reaction.

Difluorophosphoryl imines **7** and **9** were isolated in the individual state and characterized by ^{31}P, ^{1}H, and ^{19}F NMR spectroscopy. These compounds did not react with secondary amines even under drastic conditions (100 °C).

Thus, isocyanatophosphoryl difluoride proved to be a reactive C-carbamoylating reagent for pyrrole, indole, and indolizine derivatives. A number of novel heteroylaminophosphoryl difluorides were obtained in high yields. We discovered a route to phosphorylated imines *via* reactions of carbonyl compounds with derivatives of isocyanatophosphoric acid.

Experimental

^{1}H, ^{31}P, and ^{19}F NMR spectra were recorded on a Varian VXR-300 instrument (300, 121, and 282.2 MHz, respectively) with Me_4Si (^{1}H) and CCl_3F (^{19}F) as the internal standards and with 85% H_3PO_4 as the external standard (^{31}P). GC-MS spectra were recorded on an Agilent 1100 LS/MSD instrument. IR spectra were recorded on a UR-20 spectrophotometer (in KBr pellets for solids and in thin films on NaCl plates for oils).

Heteroylaminophosphoryl difluorides 3a—e (general procedure). A solution of isocyanatophosphoryl difluoride (1.27 g, 0.01 mol) in heptane (5 mL) was added dropwise at room temperature for ~10 min to a stirred solution or suspension of substrates **2a—e** (0.01 mol) in heptane (15 mL). According to ^{31}P NMR data (disappearance of the signal for isocyanate **1** at δ_P −30), the reaction was completed in 20 min (for substrate **2e**, in 5 h). The precipitate that formed was filtered off, washed twice with heptane, and dried *in vacuo* (0.05 Torr) at room temperature to a constant weight.

***N*-[1-(Dimethylamino)ethylidene]phosphorodifluoridamide (7).** Isocyanatophosphoryl difluoride **1** (1.27 g, 10 mmol) was added dropwise at room temperature to a solution of *N*,*N*-dimethylacetamide **6** (0.87 g, 10 mmol) in dichloromethane (10 mL). A moderate rate of CO_2 evolution was maintained by periodical cooling with liquid nitrogen. The reaction mixture was kept at room temperature for 20 min and then refluxed for 30 min. The solvent was removed *in vacuo* and the product was distilled. The yield was 0.95 g (56%), b.p. 88—92 °C (20 Torr). Found (%): C, 28.52; H, 5.45; F, 22.12. $C_4H_9F_2N_2OP$. Calculated (%): C, 28.23; H, 5.29; F, 22.35. ^{1}H NMR (C_6D_6), δ: 1.87 (s, 3 H, Me); 2.45 (s, 3 H, NMe); 2.59 (s, 3 H, NMe). ^{31}P NMR (CH_2Cl_2), δ: −17.20 (t, J = 960 Hz). ^{19}F NMR (CH_2Cl_2), δ: 82.08 (d, J = 960 Hz).

***N*-[2-(1,3,3-Trimethyl-1,3-dihydro-2*H*-indol-2-ylidene)ethylidene]phosphorodifluoridamide (9).** Difluoride **1** (1.27 g, 10 mmol) was added at room temperature to a solution of (1,3,3-trimethyl-1,3-dihydro-2*H*-indol-2-ylidene)acetaldehyde **8** (2.00 g, 10 mmol) in dichloromethane (25 mL). Mixing of the reagents was followed by vigorous evolution of CO_2 (the process was slightly exothermic). The reaction mixture was kept at room temperature until CO_2 ceased to evolve (~2 h). Drying *in vacuo* to a constant weight gave compound **9** as an amorphous orange powder. The yield was 2.72 g (96%). Found (%): C, 52.12; H, 5.36; F, 13.11. $C_{13}H_{15}F_2N_2OP$. Calculated (%): C, 54.93; H, 5.28; F, 13.38. ^{1}H NMR ($CDCl_3$), δ: 1.75 (s, 6 H, 2 Me); 3.64 (s, 3 H, NMe); 5.59 (d, 1 H, C—H, J = 6.0 Hz); 7.19 (t, 1 H, H(5), J = 6.0 Hz); 7.44 (m, 3 H, H_{Het}). ^{31}P NMR (CH_2Cl_2), δ: −14.90 (t, J = 955 Hz). ^{19}F NMR (CH_2Cl_2), δ: 84.00 (d, J = 955 Hz).

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Received September 1, 2005;
in revised form February 17, 2006