Isocyanatophosphoryl Dichloride as Reagent for Introduction of Carbamoyl Group into Molecules of π-Excessive Heterocycles and Enamines

Radomir V. Smaliy,*[a] Aleksandra A. Chaikovskaya,[a] Aleksandr M. Pinchuk,[a] Andrei A. Tolmachev[b]

[a] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, Murmanskaya 5, Kyiv-94, 02094, Ukraine

[b] Research and Development Center for Chemistry and Biology, National Taras Shevchenko University, 62 Volodymyrska st., Kyiv-33, 01033, Ukraine

Fax +38(44)5732643; E-mail: iochkiev@ukrpack.net

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Abstract: A study on the stepwise hydrolysis of hetarene- and cycloalkenecarboxamidophosphoryl dichlorides afforded the synthesis of hitherto unknown hetarene- and cycloalkenecarboxamidophosphoric acids as well as allowing the introduction of unsubstituted carbamoyl group in the molecules of pyrroles, indoles, indolizines, and some enamines.

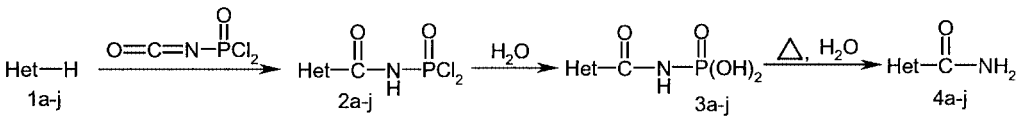
Key words: carboxamides, isocyanatophosphoryl dichloride, carbonylamidophosphoric acids, indoles, pyrroles, indolizines, enamines

Primary amides of heteroaromatic carboxylic acids are important compounds in organic synthesis.[1–3] Introduction of a carbamoyl group into the molecules of π-excessive heteroaromatics often involves multistage synthetic pathways and a variety of reagents, which are often highly toxic substances like phosgene or triphosgene. Among known carbamoylation techniques, treatment of heterocycles with chlorosulfonyl isocyanate (the Graf isocyanate) followed by hydrolysis[4,5] is remarkable for its ease. It appears reasonable to extend this strategy to another reactive and readily available isocyanate, i.e. isocyanatophosphoryl dichloride, which was efficiently employed by us earlier to introduce a diaminophosphorylcarbamoyl as well as a cyano group into the molecules of π-excessive heterocycles and enamines.[6,7]

In the present paper we report the application of isocyanatophosphoryl dichloride for converting a number of π-excessive heterocycles and enamines into primary amides of hetarene- and cycloalkenecarboxylic acids. The method developed involves hydrolytic cleavage of the initially forming products **2** from isocyanate addition (see Scheme 1). The data relevant to the synthesis are listed in Table 1. The hydrolysis of carboxamidophosphoryl dichlorides **2** is carried out in two steps. First carboxamidophosphoric acids **3** are obtained under mild conditions (at room temperature) and then they are boiled in water or in aqueous alcohol to produce the corresponding carboxamides **4**. Hetarene- and cycloalkenecarboxamidophosphoric acids **3** appear as colorless or pale-colored crystalline substances and some of them decompose on melting (see Table 2). These compounds are similar in properties to the previously described arenecarboxamidophosphoric acids[8] though the former are less stable in storage.

An attempted synthesis of compounds **4** without isolating products **2** and **3** in the pure states results in drastically lowered yields, which is attributable to the formation of the corresponding hetarenenitriles, among other possible factors. We have also found the hetarenenitriles to be formed in small amounts (2–4%) together with desired compounds **4** during the hydrolysis of carboxamidophosphoric acids **3**. This is evidently due to the tendency of acids **3** and their derivatives to thermally decompose to nitriles.[6,9] A minor impurity consisting of readily soluble nitriles in target carboxamides **4** is easily removed by recrystallization.

On the whole, the synthesis of carboxamides **4** is rather straightforward, requires no sophisticated equipment, and affords high yields with respect to the starting substrate, as the conversions **1** → **2** and **2** → **3** proceed nearly quantitatively. When substrates **1i**,**j** are utilised in the reaction, the enamine moiety hydrolyzes to give β-carbonyl-substituted carboxamidophosphoric acids **3i**,**j** which in turn hydrolyze further to carboxamides **4i**,**j** containing a β-carbonyl group.



Scheme 1

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In conclusion, it has been shown that the hydrolysis of hetarenecarboxamidophosphoryl dichlorides **2** and their alicyclic analogues furnish a number of hitherto unknown hetarene- or cycloalkenecarboxamidophosphoric acids. Moreover, a convenient carbamoylation method for pyrroles, indoles, indolizines, and enamines has been suggested.

Table 1 Structures and Yields

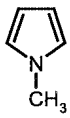
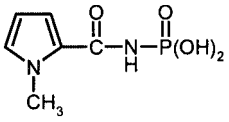
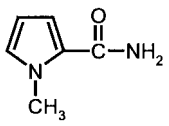
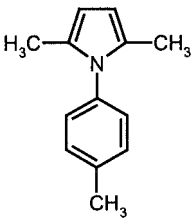
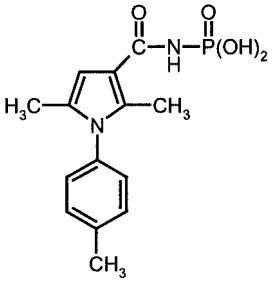
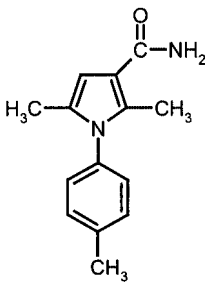
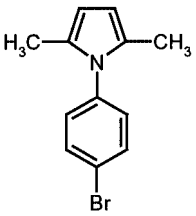
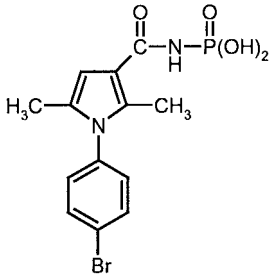
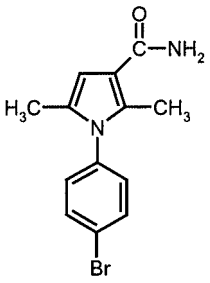
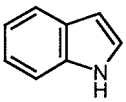
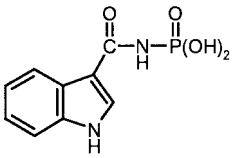
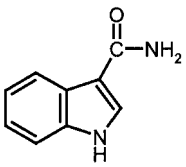
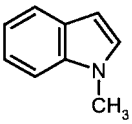
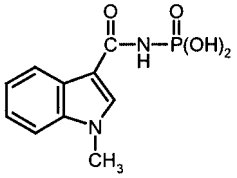
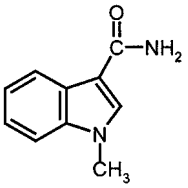
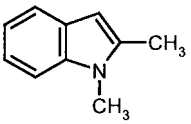
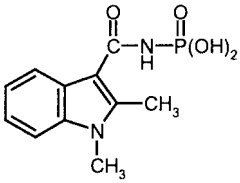
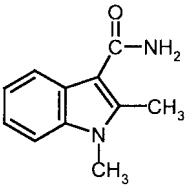
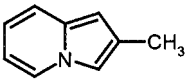
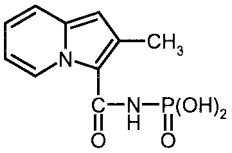
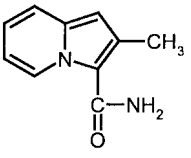
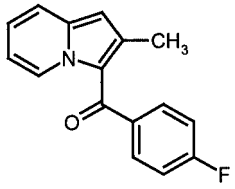
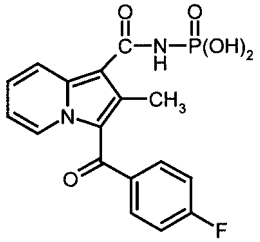
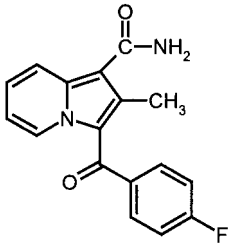
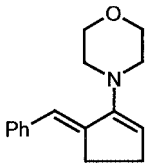
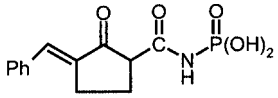
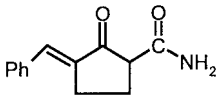
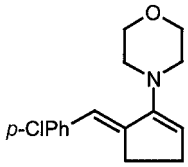
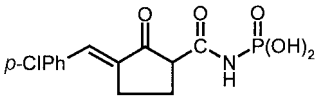
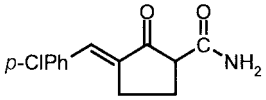
Compound	Substrate **1**	Acid **3**	Amide **4**[a]	Yield (%)[b,c]	Yield (%)[b,d]
a				98	88
b				93	94
c				96	83
d				91	70
e				99	86
f				99	96
g				89	90

Table 1 Structures and Yields (continued)

Compound	Substrate **1**	Acid **3**	Amide **4**[a]	Yield (%)[b,c]	Yield (%)[b,d]
h				93	91
i				73	60
j				69	68

[a] Compounds **4a**,**d**,**e**,**g** were previously described in the literature.[3,4]
[b] Isolated yields.
[c] Conversion of **1** → **3**.
[d] Conversion of **3** → **4**.

Table 2 Physicochemical, Spectroscopic and Analytical Data[a] of Compounds **2h–j**, **3a–j**,[b] and **4a–j**[c]

Compound	^{1}H and ^{31}P NMR Data (DMSO-d_6) δ, *J* (Hz)	Mp (°C)
2h	^{31}P: 6.20	153–155 (dec.)
2i	^{31}P: 3.09	153–155 (dec.)
2j	^{31}P: 3.36	153–155 (dec.)
3a	^{1}H: 3.85 (s, 3 H, N-CH_3), 6.03 (t, *J* = 3.35, 1 H, H_4-Het), 6.16 (br s, OH), 6.99 (s, 1 H, H_5-Het), 7.18 (d, *J* = 3.9, 1 H, H_3-Het), 8.98 (d, *J* = 9.4, 1 H, NH). ^{31}P: –2.98	103–105
3b	^{1}H: 1.93 (s, 3 H, 5-CH_3), 2.22 (s, 3 H, 5-CH_3), 2.41 (s, 3 H, Ar-CH_3), 5.67 (br s, OH), 6.31 (s, 0.4 H, H_4-Het), 6.60 (s, 0.6 H, H_4-Het), 7.12 (d, *J* = 7.8, 2 H, Ar), 7.32 (d, *J* = 7.8, 2 H, Ar), 8.58 (d, *J* = 9.9, 1 H, NH) ^{31}P: –2.5	122–123
3c	^{1}H: 1.95 (s, 3 H, 5-CH_3), 2.22 (s, 3 H, 5-CH_3), 6.26 (br s, OH), 6.62 (s, 1 H, H_4-Het), 7.25 (m, 2 H, Ar), 7.71 (m, 2 H, Ar), 7.98 (d, *J* = 9.3, 0.5 H, NH), 8.62 (d, *J* = 9.3, 0.5 Hz, NH) ^{31}P: –2.5	142–143 (dec.)
3d	^{1}H: 7.12 (m, 2 H, $H_{5,6}$-Het), 7.42 (d, *J* = 7.8, 1 H, H_7-Het), 8.16 (d, *J* = 7.3, 1 H, H_4-Het), 8.43 (d, *J* = 2.9, 1 H, H_2-Het) 9.20 (d, *J* = 9.1, 1 H, NH), 11.03 (br s, OH), 11.82 (s, 1 H, NH-Het) ^{31}P: –1.97	145–146 (dec.)
3e	^{1}H: (s, 3 H, N-CH_3), 7.18 (m, 2 H, $H_{5,6}$-Het), 7.42 (d, *J* = 8.1, 1 H, H_7-Het), 8.18 (d, *J* = 7.5, 1 H, H_4-Het) 8.58 (d, *J* = 9.0, 1 H, NH), 11.03 (br s, OH) ^{31}P: –1.96	132–133 (dec.)
3f	^{1}H: 2.61 (s, 3 H, 2-CH_3), 3.7 (s, 3 H, N-CH_3), 6.20 (br s, OH), 7.12 (m, 2 H, $H_{5,6}$-Het), 7.37 (d, *J* = 7.9, 1 H, H_7-Het), 7.78 (d, *J* = 7.0 1 H, H_4-Het) ^{31}P: –3.14	150–151 (dec.)

Table 2 Physicochemical, Spectroscopic and Analytical Data[a] of Compounds **2h–j**, **3a–j**,[b] and **4a–j**[c] (continued)

Compound	^{1}H and ^{31}P NMR Data (DMSO-d_6) δ, *J* (Hz)	Mp (°C)
3g	^{1}H: 2.53 (s, 3 H, 2-CH_3), 6.30 (s, 1 H, H_1-Het), 6.70 (t, *J* = 6.8, 1 H, H_6-Het), 6.95 (t, *J* = 6.7, 1 H, H_7-Het), 7.42 (d, *J* = 8.4, 1 H, H_8-Het), 7.96 (d, *J* = 8.4, 1 H, NH), 9.19 (d, *J* = 6.9, 1 H, H_5-Het) ^{31}P: –3.45	133–135
3h	^{1}H: 2.10 (s, 3 H, 2-CH_3), 7.43 (t, *J* = 7.3, 1 H, H_6-Het), 7.33 (m, 3 H, H_7-Het, 2 H-Ar + H_7-Het), 7.71 (m, 2 H, 2H-Ar), 8.02 (m, 2 H, H_8-Het, NH), 9.38 (d, *J* = 6.9, 1 H, H_5-Het) ^{31}P: –3.8	269–270
3i	^{1}H: 2.23 (br t, 2 H, CH_2), 2.80 (br t, 2 H, CH_2), 6.72 (s, 1 H, CH=), 7.40 (m, 5 H, Ar), 7.57 (d, *J* = 8.2, 1 H, NH) ^{31}P: –5.0	148–150
3j	^{1}H: 2.55 (br t, 2 H, CH_2), 2.82 (br t, 2 H, CH_2), 6.72 (s, 1 H, CH=), 7.47 (m, 5 H, Ar + NH) ^{31}P: –4.5	166–167
4a	^{1}H: 3.84 (s, 3 H, N-CH_3), 5.95 (t, *J* = 3.35, 1 H, H4-Het), 6.74 (br s, 1 H, NH_2), 6.75 (d, *J* = 3.9, 1 H, H_5-Het), 6.78 (s, 1 H, H_3-Het), 7.34 (br s, 1 H, NH_2)	52–53 (Et_2O)
4b	^{1}H: 1.93 (s, 3 H, 5-CH_3), 2.19 (s, 3 H, 5-CH_3), 2.41 (s, 3 H, Ar-CH_3), 6.26 (s, 1 H, H_4-Het), 6.43 (br s, 1 H, NH_2), 6.96 (br s, 1 H, NH_2), 7.10 (d, *J* = 8.1 2 H, Ar), 7.30 (d, *J* = 8.1, 2 H, Ar)	150–151 (50% aq EtOH)
4c	^{1}H: 1.97 (s, 3 H, 5-CH_3), 2.23 (s, 3 H, 5-CH_3), 6.31 (s, 1 H, H_4-Het), 6.51 (br s, 1 H, NH_2), 7.05 (br s, 1 H, NH_2), 7.23 (d, *J* = 8.1, 2 H, Ar), 7.69 (d, *J* = 8.1, 2 H, Ar)	153–154 (dec.) (Et_2O)
4d	^{1}H: 6.85 (br s, 2 H, NH_2), 7.09 (m, 2 H, $H_{5,6}$-Het), 7.39 (d, *J* = 7.2, 1 H, H_7-Het), 7.99 (d, *J* = 2.9, 1 H, H_2-Het), 8.15 (d, *J* = 7.2, 1 H, H_4-Het), 11.37 (br s, 1 H, NH-Het)	200–201 (30% aq MeOH)
4e	^{1}H: 3.81 (s, 3 H, N-CH_3), 6.73 (br s, 1 H, NH_2), 7.12 (m, 3 H, $H_{5,6}$-Het + NH), 7.38 (d, *J* = 7.5, 1 H, H_7-Het), 7.95 (s, 1 H, H_2-Het), 8.15 (d, *J* = 8.1, 1 H, H_4-Het)	183–184 (50% aq EtOH)
4f	^{1}H: 2.65 (s, 3 H, 2-CH_3), 3.70 (s, 3 H, N-CH_3), 6.86 (br s, 2 H, NH_2), 7.12 (m, 2 H, $H_{5,6}$-Het), 7.39 (d, *J* = 7.5, 1 H, H_7-Het), 7.77 (d, *J* = 7.5, 1 H, H_4-Het)	222–223 (sub-lim.) (Me_2C=O)
4g	^{1}H: 2.50 (s, 3 H, 2-CH_3), 6.25 (s, 1 H, H_1-Het), 6.74 (m, 4 H, $H_{6,7}$-Het, NH_2), 7.35 (d, *J* = 8.2, 1 H, H_8-Het), 9.31 (d, *J* = 6.2, 1 H, H_5-Het)	178–180 (Me_2C=O)
4h	^{1}H: 2.08 (s, 3 H, 2-CH_3), 6.99 (t, *J* = 7.3, 1 H, H_6-Het), 7.11 (s, 2 H, NH_2), 7.28 (m, 3 H, H_7-Het, 2 H-Ar, H_7-Het), 7.69 (m, 2 H, 2H-Ar), 8.02 (d, *J* = 8.7, 1 Hz, H_8-Het), 9.38 (d, *J* = 6.9, 1 H, H_5-Het)	264–265 (*i*-PrOH)
4i	^{1}H: 2.56 (br t, 2 H, CH_2), 2.83 (br t, 2 H, CH_2), 6.68 (s, 1 H, =CH), 7.35 (m, 7 H, NH_2, 5 H-Ar), 12.37 (br s, 1 H, OH)	173–175 (50% aq EtOH)
4j	^{1}H: 2.53 (br t, 2 H, CH_2), 2.81 (br t, 2 H, CH_2), 6.66 (s, 1 H, =CH), 7.36 (m, 6 H, NH_2, 4 H-Ar), 12.73 (br s, 1 H, OH)	186–187 (50% aq EtOH)

[a] All compounds showed satisfactory elemental analyses C±0.08, H±0.08, N±0.04, P±0.1.
[b] IR (KBr): 1200–1210 (P=O), 1650–1660 (C=O) cm^{-1}.
[c] IR (KBr): 1640–1650 (C=O), 3180 (N–H) cm^{-1}.

^{1}H NMR spectra were recorded on Varian Gemini – 300 spectrometer at 300 MHz using TMS as an internal standard. Solvents were dried and purified prior to use. Compounds **2h–j** were obtained in a similar way to previously described **2a–g**[7] (for their characterization data see Table 2).

Carboxamidophosphoric Acids 3a–j and Carboxamides 4 a–j; General Procedure

To a stirred solution of substrate **1** (10 mmol) in heptane (30 mL) was added isocyanatophosphoryl dichloride (1.6 g, 10 mmol). The mixture was further stirred at r.t. for 40 min (until the ^{31}P NMR signal at –14.0 ppm disappeared).[7] The precipitate of compound **2** was filtered off and washed with heptane (20 mL). Then ice water (30 mL) and acetone (1 mL) were poured onto it. After 5 h the mixture was triturated and within 24 h the precipitate of compound **3** was filtered off, washed with water (60 mL), and dried in the open air. For subsequent preparation of amide **4**, however, drying is not needed.

Compound **3** was placed into a 50 mL flask and 10% aq EtOH (30 mL) was poured onto it. The mixture was then boiled under a reflux condenser for 5 h. On cooling to r.t., the mixture was neutralized with $NaHCO_3$ to pH 6. The solid precipitate was filtered off and washed on the filter with water (60 mL). When dried, the precipitate obtained contained 85–97% pure compound **4** and was finally purified by recrystallization from an appropriate solvent (see Table 2). Product **4a** was extracted from the reaction mixture with CH_2Cl_2 (30 mL) and the solvent was removed under vacuum.

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