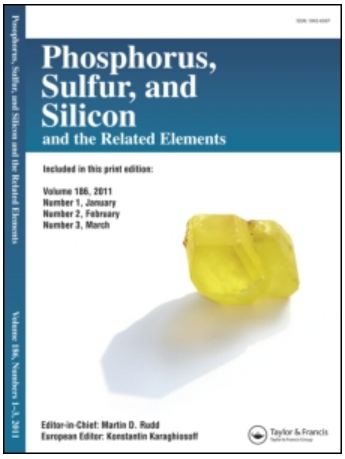

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Unprecedented C-Acylation of Imines with Tervalent Phosphorus Isocyanates

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Reaction of trifluoropyruvate N*-phosphorylimine with tervalent phosphorus isocyanates leads to unexpected acylation of the imine carbon atom to afford phosphorylaminocarbonylated trifluoroalanine derivatives.*

Keywords Acylation; *N*-phosphorylimines; phosphorus isocyanates; trifluoroalanine; umpolung

INTRODUCTION

Polyfluoroalkaneimines are promising building blocks for the synthesis of various acyclic and heterocyclic functionalized nitrogen-containing organofluorine compounds.[1—4] *N*-Phosphorylimines are considered as new reactive intermediates for stereoselective organic synthesis.[5] Recently we have developed a synthesis for α-trifluoromethyl-*N*-phosphoryliminocarboxylate **1**, the first representative of the highly electrophilic trifluropyruvate *N*-phosphorylimines.[6] It was shown that **1** reacts readily with C-, N-, O-, and S-centered nucleophiles and undergoes a Diels–Alder reaction with 1,3-dienes to afford functionalized derivatives of biorelevant trifluoromethyl substituted aminoacids.[6,7]

The highly polarized C=N bond makes possible the use of imine **1** as dipolarophile in reactions with 1,3-dipolar substrates, and this offers new perspectives for the synthesis of heterocyclic compounds bearing the trifluoroalanine fragment. In this article, we report on the

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Dedicated to Professor Marian Mikołajczyk from the CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.

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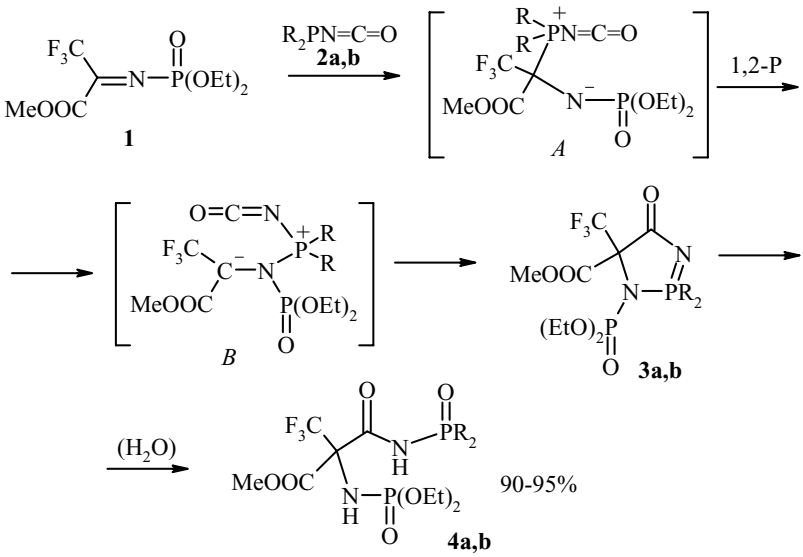
reaction of *N*-phosphoryliminocarboxylate **1** with tervalent phosphorus isocyanates, a reaction route that is novel for imines.

RESULTS AND DISCUSSIONS

We have found that imine **1** under mild conditions (ether, 0°C) easily reacts with tervalent phosphorus isocyanates **2a**,**b**. The final product of the reaction is rather unexpected: dipole R_2PNCO acylates the electrophilic imine carbon atom with its electrophilic center to afford *C*-acylated derivatives **3**, **4** (Scheme 1).



2a-4a R = EtO

2b-4b R = Ph

SCHEME 1

It is apparent that the transformation **1** → **3** is a complex process. The reaction most probably starts with the nucleophilic attack of the phosphite on the most electrophilic center of **1**, the imine carbon atom. The subsequent C—N migration of the phosphorus group in the dipolar intermediates *A* results in the formation of betaines *B* undergoing intramolecular cyclization to give heterocyclic iminophosphoranes **3**. Note that we have already reported examples of C—N transfer (similar

to $A \rightarrow B$) of other phosphorus groups upon nucleophilic phosphorylation of activated haloalkaneimines.[4,8–10]

Compounds **3** were identified only spectroscopically, as they are unstable and transform into the acylated trifluoroalanine derivatives **4** when kept at room temperature or during the work-up of the reaction mixture. Monitoring the progress of the reaction with ^{31}P, ^{19}F NMR spectroscopy reveals that conversion of **3a** into **4a** involves an intermediate [δ_P 49.7 (1P) and –4.5 (1P), δ_F –69]. At room temperature, the reaction is completed within 36 h.

Diagnostic for the structural identification of the 4*H*-diazaphosphol-4-ones **3** is the typical position of ^{31}P NMR signals of the endocyclic phosphazo group (δ_P 48.4–56.2) and of the exocyclic amidophosphate group (δ from –3.7 to –2.4 ppm) of equal intensities and rather strong spin–spin interaction ($^2J_{PP}$ = 40–58 Hz). A rather low value of the coupling constant of the endocyclic C-atom with the phosphorus nucleus in the ^{13}C NMR spectrum (δ_C 74.7, $^2J_{PC}$ = 7 Hz,$^2J_{CF}$ = 28 Hz) indicates the absence of a P—C bond in compounds **3**. The observed doublet for N—C=O (δ_C 161.9, $^2J_{PC}$ = 5 Hz) and singlet for C(O)O group (δ_C 163.8) suggests that heterocycle **3** is formed with the participation of the NCO moiety rather than the COOMe group. The spectroscopic and analytical data of the acylated compounds **4** are in complete agreement with their structure.

The new direction found for the reaction of imine **1** with P^{III}-isocyanates (Scheme 1) has no analogies in the literature. In particular, chloral aldimines, when treated with phosphorus isocyanates, give [3 + 2]-cycloaddition products in which a P-C bond with the imine carbon atom is formed.[11–13] The reaction of *N*-benzoyltrifluoroacetimidoyl chloride, $CF_3C(Cl)=NCOPh$, with **2a** proceeds as the cheletropic 1,4-cycloaddition of the P-atom of the phosphite to the heterodiene C=NC=O fragment, whereas the isocyanate group remains unaltered.[14] These differences result most probably from the simultaneous influence of electronic and steric effects of the substiutents in imine **1** on the reaction route. The three strongly electron-withdrawing groups at the N- and C-atoms favor stabilization of the anionic center in dipolar ion *A*. Moreover, C-N migration of the phosphorus group ($A \rightarrow B$) is promoted by the release of steric strains at the quaternary carbon atom in intermediate *A* and is accompanied by umpolung of C- and N-reaction centers.

It is worthwhile to note that despite the complexity and multistep character of the process in Scheme 1, the final compounds are formed in high yields, and this fact is indicative of high chemoselectivity. Taking into account the ease of the transformation, the new reaction can find

application in the synthesis of biorelevant C-acylated trifluoroalanine derivatives.

EXPERIMENTAL

IR spectra were obtained with an UR-20 spectrophotometer. ^{1}H, ^{19}F, ^{31}P, and ^{13}C NMR spectra were recorded with a Varian VXR-300 spectrometer at 299.95, 282.20, 121.42, and 75.43 MHz, respectively. Chemical shifts are reported relative to TMS (^{1}H, ^{13}C), and $CFCl_3$ (^{19}F) as internal standards or relative to external 85% H_3PO_4 (^{31}P). Solvents were dried before use according to standard methods. All reactions were carried out under atmosphere of argon in oven-dried glassware.

Reaction of Imine 1 with Isocyanate 2a

A solution of imine **1** (0.41 g, 1.4 mmol) in benzene (5 mL) was cooled to 5°C, and isocyanate **2a** (0.23 g, 1.4 mmol) was added. After 15 min at room temperature, the ^{19}F and ^{31}P NMR spectra show the formation of 1-diethoxyphosphoryl-2,2-diethoxy-5-methoxycarbonyl-4-oxo-5-trifluoromethyl-1,3,2-diaza-2-phospholine (**3a**). ^{19}F NMR (C_6H_6): $\delta = -65$. ^{31}P NMR (C_6H_6): $\delta = -3.7$ (d, $^{2}J_{PP} = 58$ Hz, 1P), 56.2 (d, $^{2}J_{PP} = 58$ Hz, 1P). After 48 h, the solvent was evaporated in vacuo, and the residue was washed with petroleum ether to give methyl 2-[(diethoxyphosphoryl)amino]-2-[[(diethoxyphosphoryl)amino]carbonyl]-3,3,3-trifluoropropanoat (**4a**) as colorless oil; 0.54 g (90%). IR (film, ν, cm^{1}): 1050 (POC), 1280 (P=O), 1720 (C=O), 1775 (C=O), 3150 (NH). ^{1}H NMR ($CDCl_3$): $\delta = 1.30–1.38$ (m, 12H, CH_3CH$_2$), 3.91 (s, 3H, CH_3O), 4.09–4.28 (m, 8H, CH_2O), 4.89 (d, $^{3}J_{PH} = 7.2$ Hz, 1H, NH), 9.08 (d, $^{3}J_{PH} = 7.5$ Hz, 1H, NH). ^{19}F NMR ($CDCl_3$): $\delta = -72.8$. ^{31}P NMR ($CDCl_3$): δ –4.0 (1P), 2.7 (1P). Anal. Calcd. for $C_{13}H_{25}F_3N_2O_9P_2$(472.30): C, 33.06; H, 5.34; P, 13.12. Found: C, 32.94; H, 5.39; P, 13.28%.

Reaction of Imine 1 with Isocyanate 2b

A solution of imine **1** (0.07 g, 0.23 mmol) in benzene-d_6 (1 mL) was cooled to 5°C, and isocyanate **2b** (0.05 g, 0.23 mmol) was added. After 1 h at room temperature, the ^{1}H, ^{13}C,^{19}F, and^{31}P NMR spectra show the formation of 1-diethoxyphosphoryl-2,2-diphenyl-5-methoxycarbonyl-4-oxo-5-trifluoromethyl-1,3,2-diaza-2-phospholine (**3b**).^{1}H NMR (C_6D_6): $\delta = 1.32–1.34$ (m, 6H, CH_3C), 3.21 (s, 3H, CH_3O), 4.41–4.60 (m, 4H,

CH_2O), 7.19–7.35 (m, 6H, Ph), 8.00–8.15 (m, 4H, Ph).^{13}C NMR (C_6D_6): δ = 16.1 (d, $^3J_{PC}$ = 6 Hz, *Me*C), 52.6 (s, MeO), 64.1 (d,$^2J_{PC}$ = 5 Hz, OCH_2), 64.8 (d,$^2J_{PC}$ = 5 Hz, OCH_2), 74.7 (dq,$^2J_{CF}$ = 28 Hz, $^2J_{PC}$ = 7 Hz, CF_3C), 125.2 (q, $^1J_{CF}$ = 283 Hz, CF_3), 123.0–134.0 (Ph), 161.9 (d, $^2J_{PC}$ = 5 Hz, NCO), 163.8 (s, *C*OOMe). ^{19}F NMR (C_6D_6): δ = –62.8. ^{31}P NMR ($CDCl_3$): δ = –2.4 (d, $^3J_{PP}$ = 40.5 Hz, 1P), 48.4 (d, $^3J_{PP}$ = 40.5 Hz, 1P).

After 48 h, the solvent was evaporated in vacuo, and the residue was washed with diethyl ether to give methyl 2-[(diethoxyphosphoryl)amino]-2-[[(diphenylphosphinoyl)amino]-carbonyl]-3,3,3-trifluoropropanoat (**4b**) as white powder, 0.11 g (95%), mp 139–140°C. IR (KBr, ν, cm^1): 1050 (POC), 1230 (P=O), 1280 (P=O), 1730 (C=O), 1770 (C=O), 3150 (NH). ^{1}H NMR ($CDCl_3$): δ = 1.30–1.38 (m, 6H, CH_3C), 3.69 (s, 3H, CH_3O), 4.27–4.31 (m, 4H, CH_2O), 4.76 (d, $^2J_{PH}$ = 9.6 Hz, 1H, NH), 7.48–7.55 (m, 6H, Ph), 7.81–7.89 (m, 4H, Ph), 9.37 (d, $^2J_{PH}$ = 9 Hz, 1H, NH). ^{13}C NMR ($CDCl_3$): δ = 15.8 (d, $^3J_{PC}$ = 6 Hz, *Me*C), 53.0 (s, MeO), 58.2 (q,$^2J_{CF}$ = 34 Hz, CF_3C), 65.3 (d,$^2J_{PC}$ = 5 Hz, OCH_2), 122.1 (q, $^1J_{CF}$ = 283 Hz, CF_3), 152.2 (d, $^2J_{PC}$ = 8 Hz, CONH), 163.3 (s, *C*OOMe). ^{19}F NMR ($CDCl_3$): δ = 66.4. ^{31}P NMR ($CDCl_3$): δ = 2.4 (1P), 17.0 (1P). Anal. Calcd. for $C_{21}H_{25}F_3N_2O_7P_2$(536.39): C, 47.02; H, 4.70; N, 5.22; P, 11.55. Found: C, 47.05; H, 4.71; N, 5.25; P, 11.73%.

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