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Short communication

# Synthesis of 3-fluoro-2-(diethoxyphosphoryl)imidazo[1,2-*a*]pyridine

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ABSTRACT

The first representative of 3-fluoro-2-(dialkoxyphosphoryl)imidazo[1,2-*a*]pyridines has been synthesized by the reaction of N-(pyridin-2-yl)-2,2,2-trifluoroacetimidoyl chloride with triethyl phosphite.



## 1. Introduction

Imidazoheterocyclic derivatives play an important role in the area of medicinal chemistry. These compounds have been found to exhibit cardiac stimulant [1], arrhythmic [1] or neurotropic [2,3] activities, exert cytoprotective and antitumor action [4]. Also they are promising candidates for treating Alzheimer's disease [5].

Previously, we have reported the new approach to the synthesis imidazoheterocycles. Derivatives of 3-fluoroimidazo[1,2-*a*]pyridines and 3-fluoroimidazo[1,2-*a*]pyrimidines were obtained by defluorocyclization of 2-pyridyl and 2-pyrimidinyl imines of hexafluoroacetone and methyl trifluoropyruvate with trimethyl phosphite [6–9] (Scheme 1). Later our method was extended to the synthesis of imidazo[2,1-*b*][1,3]thiazoles [10].It is known that N-arylimidoylchlorides interact with triethyl to form N-arylimidoyl phosphonates phosphite by the Arbuzov's reaction [11,12] (Scheme 2).

Herein, we present the combination of the Arbuzov's and defluorocyclization reactions for the synthesis of novel representatives of heterylphosphonic acids, namely, substituted 2-(dialkoxyphosphoryl)imidazo[1,2-*a*]pyridines. It should be noted that we know only one example of the synthesis of 2-(dialkoxyphosphoryl)imidazo[1,2-*a*]pyri(mi)dines using the cyclization of 2-bromo-1-oxophosphonates with 2-aminopyridine or 2-aminopyrimidine [13].

## 2. Results and discussion

Starting imidoyl chloride **2** was obtained by the addition of TFA and $SOCl_2$ to a solution of 2-aminopyridine in pyridine with further extraction and rectification. The pyridyl iminophosphonate intermediate **3** was not isolated in individual form because of it high reactivity towards triethyl phosphite. In $^{19}F$ NMR spectra of the reaction mixture there are signals as imine **3** as well as imidazopyridine **4** and difluoro(triethoxy)phosphorane (doublet at $\delta_F$ 15.2, $^1J_{FP}$ = 727 Hz). Desired imidazopyridine **4** was obtained using two equivalents of triethyl phosphite. The structure of imidazopyridine **4** was confirmed by treating with diisopropylamine. Thus, a fluorine atom in compound **4** was substituted by the diisopropylamine group affording imidazopyridine **5** (Scheme 3).

The spectral and analytical data of compound **4** are in the agreement with the proposed structure. The presence of C–F fragment in fluorinated heterocycle **4** is confirmed by the signal of C–F carbon (C-3) as doublet of doublet ($\delta$ 145.8) with coupling constants $^1J_{CF}$ = 282.5 Hz and $^2J_{CP}$ = 29.6 Hz in $^{13}C$ NMR spectra. In the spectra of compound **5** there are only one doublet ($\delta$ 140.1) with the similar value of the coupling constant ($^2J_{CP}$ = 37.5 Hz) that confirms the lacking of the fluorine atom.

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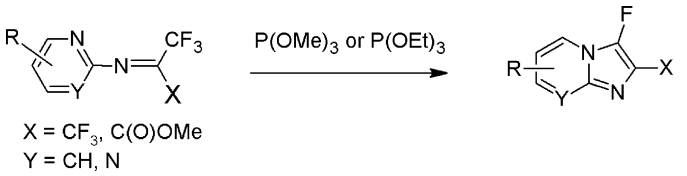
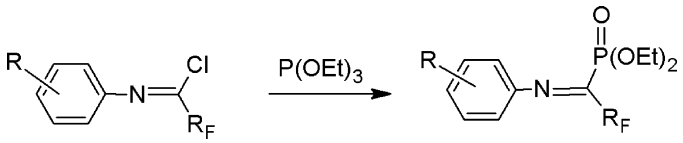
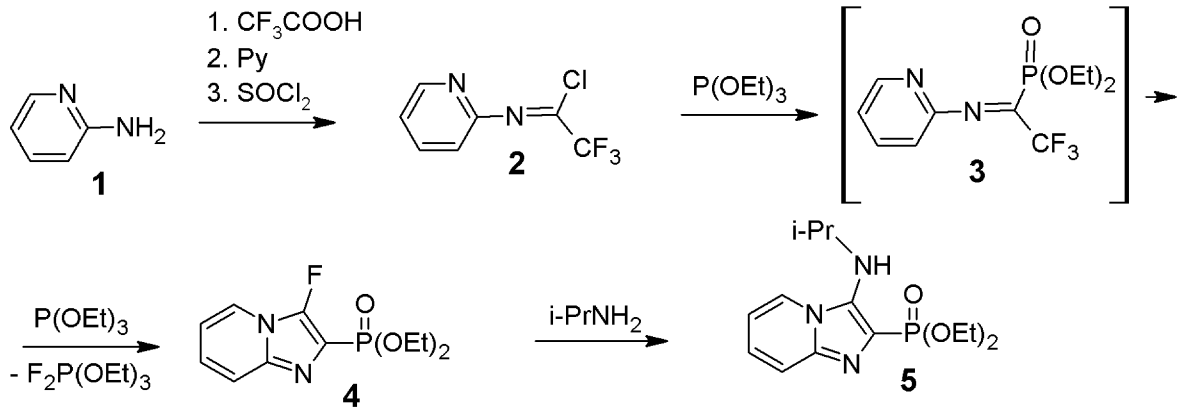



Scheme 1.




Scheme 2.




Scheme 3.

## 3. Conclusions

In summary, we developed an efficient method for the synthesis of imidazopyridines bearing fluorine atoms and phosphoryl functionality in an imidazole ring by the reaction of (pyrid-2-yl)imidoyl chloride with triethylphosphite. It was shown the fluorine atom in imidazopyridine 4 can be substituted by the amino group.

## 4. Experimental

### 4.1. General

$^{1}H$, $^{19}F$ and $^{31}P$ NMR spectra were recorded on a Bruker DPX 200 spectrometer relative to $Me_4Si$ (internal standard), $CF_3COOH$ and 85% $H_3PO_4$ (external standards), respectively.

### 4.2. 2,2,2-Trifluoro-N-(pyridin-2-yl)ethanimidoyl chloride 2

14.4 ml (0.2 mol) of $SOCl_2$ was added dropwise to a stirred mixture of 4.7 g (0.05 mol) of 2-aminopyridine and 5.7 g (0.05 mol) of $CF_3COOH$ in 16.1 ml (0.2 mol) pyridine at 5–10 °C and leave stand overnight. The resulting mixture was treated with 50 ml of $CH_2Cl_2$. The precipitate formed was filtered off and solvent was removed *in vacuo*. The residue was distilled to give 4.4 g of imidoyl chloride **2**.

Yield 40%; bp 75 °C/12 Torr. $^{1}H$ NMR (200 MHz, $CDCl_3$): $\delta$ 7.03 (1H, dt, $J_{HH}$ = 7.9, 0.9 Hz, H-3), 7.27 (1H, ddd, $J_{HH}$ = 7.9, 5.0, 0.9 Hz, H-5), 7.84 (1H, ddd, $J_{HH}$ = 7.9, 7.4, 1.9 Hz, H-4), 8.56 (1H, ddd, $J_{HH}$ = 5.0, 1.9, 0.9 Hz, H-6). $^{19}F$ NMR (188.29, $CDCl_3$): $\delta$ 5.69 s. $^{13}C$ NMR (50.32, $CDCl_3$): $\delta$ 116.0 (s, C-5), 117.2 (q, $^{1}J_{CF}$ = 277.4 Hz, $CF_3$), 122.6 (s, C-3), 136.2 (q, $^{2}J_{CF}$ = 43.5 Hz, $CF_3\underline{\mathbf{C}}$=N), 138.8 (s, C-4), 149.4 (s, C-6), 156.6 (s, C-2). Calc. for $C_7H_4ClF_3N_2$: C, 40.31, H, 1.93, N, 13.43%. Found: C, 40.04, H, 2.05, N, 13.52.

### 4.3. Diethyl (3-fluoroimidazo[1,2-a]pyridin-2-yl)phosphonate 4

To imidoyl chloride **2** (13 mmol) was added triethylphosphite (26 mmol) at 5–10 °C and leave stand overnight. The phosphonate **4** was obtained by silica-gel column chromatography into step: (a) eluent – $CHCl_3$:EtOH 10:1 and (b) eluent – $CHCl_3$:EtOH 20:1.

Yield 36%; colorless oil. $^{1}H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.39 (6H, t, $J_{HH}$ = 7.7, $CH_3$), 4.27 (4H, m, W½ = 19 Hz, $CH_2O$), 6.94 (1H, td, $J_{HH}$ = 7.0, 1.2 Hz, H-6), 7.24 (1H, ddd, $J_{HH}$ = 9.3, 7.0, 1.4 Hz, H-5), 7.57 (1H, ddt, $J_{HH}$ = 9.3, 1.2, $J_{HF}$ = 1.4 Hz, H-4), 7.96 (1H, dt, $J_{HH}$ = 7.0, 1.4 Hz, H-7). $^{19}F$ NMR (188.29, $CDCl_3$): $\delta$ −67.36 (dd, $J_{FP}$ = 13.0 Hz, $J_{HF}$ = 1.4 Hz). $^{31}P$ {H} NMR (81.01, $CDCl_3$): $\delta$ 8.71 (d, $J_{PF}$ = 13.0 Hz). $^{13}C$ NMR (50.32, $CDCl_3$): $\delta$ 16.7 (d, $^{3}J_{CP}$ = 6.5 Hz, $CH_3$), 63.3 (d, $^{2}J_{CP}$ = 5.8 Hz, $CH_2$), 112.7 (dd, $^{1}J_{CP}$ = 248.5 Hz, $^{2}J_{CF}$ = 3.0 Hz, C-2), 114.1 (s, C-5), 119.3 (s, C-7), 121.4 (s, C-4), 125.9 (s, C-6), 139.2 (dd, $^{3}J_{CP}$ = 23.2 Hz, $^{3}J_{CF}$ = 4.3 Hz, C-7a), 145.8 (dd, $^{1}J_{CF}$ = 282.5 Hz, $^{2}J_{CP}$ = 29.6 Hz, C-3). Calc. for $C_{11}H_{14}FN_2O_3P$: C, 48.54, H, 5.18, N, 10.29%. Found: C, 48.44, H, 5.06, N, 10.45.

### 4.4. Diethyl (3-diisopropylaminoimidazo[1,2-a]pyridin-2-yl)phosphonate 5

The solution of 4 (1 mmol) in 2 ml of diisopropylamine was heated in sealed ampoule at 70 °C for 6 h. Ampoule was opened, the excess of diisopropylamine was evaporated and residue purified by silica-gel column chromatography ($CHCl_3$:EtOH 20:1) give phosphonate **5**.

Yield 40%; colorless oil. $^{1}H$ NMR (200 MHz, $CDCl_3$): $\delta$ 1.24 (6H, d, $J_{HH}$ = 6.3, $\underline{CH_3}CH$), 1.35 (6H, t, $J_{HH}$ = 7.2, $\underline{CH_3}CH_2$), 3.45 (1H, septet, $J_{HH}$ = 6.3, $CH_3\underline{CH}$), 3.78 (1H, d, $J_{HP}$ = 11.2 Hz, NH), 4.19 (4H, m, W½ = 21 Hz, $CH_2O$), 6.80 (1H, td, $J_{HH}$ = 7.0 Hz, 1.2, H-6), 7.15 (1H, ddd, $J_{HH}$ = 9.3, 7.0, 1.2 Hz, H-5), 7.54 (1H, dt, $J_{HH}$ = 9.3, 1.2, H-4), 7.96 (1H, dt, $J_{HH}$ = 7.0, 1.4 Hz, H-7). $^{13}C$ NMR (50.32, $CDCl_3$): $\delta$ 16.7 (d, $^{3}J_{CP}$ = 6.5 Hz, $\underline{CH_3}CH_2$), 23.6 (s, Hz, $\underline{CH_3}CH$), 49.0 (d, $^{4}J_{CP}$ = 1.2 Hz, $CH_3\underline{CH}$), 62.8 (d, $^{2}J_{CP}$ = 5.8 Hz, $CH_2$), 112.7 (s, C-5), 119.2 (s, C-7), 120.0 (d, $^{1}J_{CP}$ = 238.8 Hz, C-2), 123.7 (s, C-4), 125.2 (s, C-6), 140.1 (d, $^{2}J_{CP}$ = 37.5 Hz, C-3), 143.1 (d, $^{3}J_{CP}$ = 23.2 Hz, C-7a). $^{31}P$ {H} NMR (81.01, $CDCl_3$): δ 13.85 (s). Calc. for $C_{14}H_{22}N_3O_3P$: C, 54.01, H, 7.12, N, 13.50%. Found: C, 54.26, H, 7.08, N, 13.38.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2012.02.005.

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