Hetero-Diels-Alder reactions of N-phosphoryltrihaloacetimidoyl chlorides with 1,3-butadienes

Mykola V. Kolotylo, Oleksii A. Synytsya, and Petro P. Onys’ko*

Institute of Organic Chemistry, National Academy of Sciences,
5 Murmans’ka St, 02660, Kyiv, Ukraine
E-mail: onysko@rambler.ru

Dedicated to Prof. Pawel Kafarski to honor the achievements within his career

DOI: http://dx.doi.org/10.3998/ark.5550190.0013.410

Abstract
Hetero-Diels-Alder reactions of N-phosphoryltrihaloacetimidoyl chlorides with 1,3-butadienes led to new 2-chloro-2-trihalomethyl substituted tetrahydropyridine adducts. Cycloadducts with CF\(_3\) group undergo thermal or acid catalyzed dehydrochlorination affording respective dihydropyridines and subsequent aromatization to form 2-trifluoromethylypyridines. Trichloromethyl analogs under similar conditions undergo aromatization accompanied by unusual reduction of CCl\(_3\) group to form respective 2-dichloromethyl substituted pyridines.

Keywords: Aza-Diels-Alder reaction, imidoyl chlorides, tetrahydropyridines, dihydropyridines, pyridines

Introduction
Imidoyl chlorides combine the properties of acid chlorides and azomethynes. They are reactive and versatile chemical agents and have found wide application in organic synthesis and in the study of chemical reactivity.\(^1\) Trihaloacetimidoyl chlorides are regarded as new promising building blocks for regioselective introduction of (poly)haloalkyl groups into acyclic or heterocyclic compounds.\(^2\) Cycloaddition across C=N bond of trihaloacetimidoyl chlorides would offer additional opportunities connected with the possibility to introduce regioselectively trihalomethyl group into a molecule and further transformations of primary products via chlorine atom participation. Replacement of hydrocarbon groups in molecules with their fluorinated analogs imparts a variety of useful properties to certain medicines, including enhanced binding interactions and metabolic stability.\(^3\) As a result, fluorine containing compounds are becoming increasingly important in both agrochemistry and medicine.\(^4\) On the other hand polychloroalkyl
derivatives reveals as a rule greater herbicidal and fungicidal activity than their fluorinated counterparts.\(^5\) In the pyridine and dihydropyridine series a number of compounds bearing polyfluoro- and/or polychlorohaloalkyl substituents was found to possess useful pharmacological properties.\(^6\) At the same time the use of imidoyl chlorides for construction of heterocyclic ring by means of hetero-Diels-Alder reactions with 1,3-dienes remains almost unexplored.\(^7\)

Now we report on a novel approach for hydrogenated \(\alpha\)-polyhalomethyl containing pyridines and respective pyridines based on cycloaddition reactions of \(N\)-phosphoryltribromoacetimidoyl chlorides with 1,3-butadienes.

**Results and Discussion**

We have found that \(N\)-dichlorophosphoryltribromoacetimidoyl chlorides 1a,b readily react with 1,3-dienes 2a,b under mild conditions to afford functionalized tetrahydropyridines 3a-d (Scheme 1). Remarkably, the reaction with non-symmetrical diene 2b proceeds regioselectively with the formation of 4-methyl substituted isomers 3b,d.

\[
\begin{align*}
\text{X}_3\text{C}&\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\ quad
its reactivity toward 2. The reaction of respective imidoyl chloride, CF<sub>3</sub>C(=N)P(=O)(OEt)<sub>2</sub>, with diene 2a proceeds only at prolonged heating in benzene; cycloaddition under these conditions is accompanied by other processes leading to a complex mixture. As a result, cycloaddition product 6 was not isolated and detected only spectrally (δ<sub>F</sub> -63.7 ppm, δ<sub>P</sub> 8.3 ppm).

![Chemical structures](image)

Tetrahydropyridines 3c,d bearing trichloromethyl group are relatively stable crystalline compounds and can be kept at room temperature for several months. At the same time their trifluoro analogs 3a,b upon distillation in vacuum eliminate hydrogen chloride to afford dihydropyridines 7a,b (Scheme 2).

![Scheme 2](image)

**Scheme 2.** Reagents and conditions: i) Δ or CF<sub>3</sub>COOD; ii) aq HCl-dioxane or Δ.

Slow transformation 3a→7a occurs even at room temperature. Nitrogen bases (DBU, DABCO, Et<sub>3</sub>N) or carboxylic acid additives favor the reaction. Thus, in solutions of CF<sub>3</sub>COOD the elimination of HCl from 3a,b is completed within 24 hrs at room temperature. The same is true for CF<sub>3</sub>COOH or AcOH solutions but in these cases the formation of 7 is complicated by their partial transformation into respective pyridines 8. Dihydropyridines 7 are oily rather unstable compounds, easily soluble in organic solvents. Even at room temperatures they are gradually (~4 weeks) converted into resinous-like hardly soluble substances. Upon thermal distillation or heating in aq HCl-dioxane compounds 7 undergo aromatization to afford 2-trifluoromethyl substituted pyridines 8 in 63-81% yields.
The behavior of 2-trichloromethyl tetrahydropyridines 3c,d is quite different from that of their trifluoromethyl analogs. Upon distillation in vacuum, heating in aq HCl-dioxane solution, or on treatment with CF₃COOH, they give 2-dichloromethyl pyridines 9 (Scheme 3) rather than expected pyridines with trichloromethyl group.

![Scheme 3](image)

**Scheme 3**

Reduction of trichloromethyl group during conversion of tetrahydropyridines 3c,d to respective pyridines 9a,b is quite unexpected. The following peculiarities are characteristic of this unusual transformation: 1) the reaction is promoted by acids; 2) the intermediate dihydropyridines analogous to 7 (Scheme 2) were not detected in the course reaction; 3) the performance of the reaction in CF₃COOD does not lead to incorporation of the of deuterium into dichloromethyl group of 9. Hydrophosphoryl compounds were reported to convert activated trichloromethyl group into dichloromethyl one.¹ In view of these data we first regarded the possibility of reduction of CCl₃ group with the participation of Cl₂POH, that could be in principle generated from 3c,d. However, our attempts to execute reduction of trichloromethyl group of model 4,5-dimethyl-2-(trichloromethyl)pyridine¹⁰ by reacting it with diethylphosphonate, (EtO)₂P(O)H, under different conditions, failed.

Taking into account the above observations the following pathway of reaction should be outlined (Scheme 4).

Generation of positive charge at phosphorus atom in intermediate A promotes the rupture of P-N bond and facilitates the elimination of POCl₃. Release of sterical strains caused by voluminous 1,2-substituents in A also favours transformation A→B. The greater sterical volume of trichloromethyl group as compared with trifluoromethyl one is likely one of the reasons accounting for distinctions in behavior of tetrahydropyridines 3a,b and 3c,d. Electron-attracting CCl₃ group and positive charge on nitrogen atom obviously promotes 1,3-proton shift (B→C) in C-N=C triad;² moreover, in azaallylic triad proton tends to migrate to the carbon atom bearing more electron-attracting substituent.¹¹,¹² Finally, elimination of hydrogen chloride in C, favored by the presence of onium center, and subsequent aromatization of intermediate D by means of prototropic shift affords dichloromethylpyridines 9. It is worthwhile to note that according to proposed scheme hydrogen of CHCl₂ groups comes from hydrogenated...
pyridine ring rather than from outer source, accounting for the absence of H-D exchange in the cause of CCl₃→CHCl₂ conversion.

\[
\begin{align*}
3c,d & \xrightarrow{H^+} \begin{array}{c}
\text{R} \\
\text{N} \\
\text{Cl} \\
\text{Cl} \\
\text{H} \\
\text{C} \\
\text{C} \\
\text{Cl} \\
\text{Cl} \\
\text{H} \\
\end{array} \quad \text{CCl}_3 \\
\text{HO-} \quad \text{P}^+ \quad \text{Cl} \\
A & \quad \text{R} \\
\text{N} \\
\text{H} \\
\text{C} \\
\text{C} \\
\text{Cl} \\
\text{Cl} \\
\text{H} \\
\end{array} \\
\begin{array}{c}
\text{Cl} \\
\text{P}^+ \\
\text{OH} \\
\text{Cl} \\
\text{H} \\
\end{array} \quad \xrightarrow{-\text{POCl}_3} \begin{array}{c}
\text{R} \\
\text{N} \\
\text{Cl} \\
\text{Cl} \\
\text{H} \\
\text{C} \\
\text{C} \\
\text{Cl} \\
\text{Cl} \\
\text{H} \\
\end{array} \\
B & \quad 1,3-\text{H} \\
\begin{array}{c}
\text{R} \\
\text{N} \\
\text{H} \\
\text{C} \\
\text{C} \\
\text{Cl} \\
\text{Cl} \\
\text{H} \\
\end{array} \quad \xrightarrow{-\text{HCl}} \begin{array}{c}
\text{R} \\
\text{N} \\
\text{H} \\
\text{C} \\
\text{C} \\
\text{Cl} \\
\text{Cl} \\
\end{array} \\
C & \quad 9a,b \\
\begin{array}{c}
\text{R} \\
\text{N} \\
\text{H} \\
\text{C} \\
\text{C} \\
\text{Cl} \\
\text{Cl} \\
\end{array} \quad \xrightarrow{1,3-\text{H}} \begin{array}{c}
\text{R} \\
\text{N} \\
\text{H} \\
\text{C} \\
\text{C} \\
\text{Cl} \\
\text{Cl} \\
\end{array} \\
D & \quad 9a,b
\end{align*}
\]

Scheme 4

The spectral and analytical data of compounds obtained are in complete agreement with their structure. The hydrogenated trifluoromethylpyridines 3a,b, 7a,b, and pyridines 8a,b give clearly distinguishable \(^{19}\text{F}\) NMR characteristics (\(\delta_F \approx -75.8 \div -77.4\) ppm, \(-63.2 \div -63.3\) ppm, and \(-67.4 \div -68.8\) ppm, respectively) that allow easy monitoring of the process and identification of the products in the reaction mixture. The regiochemistry of cycloaddition with non-symmetrical diene 2b was unambiguously confirmed by \(^1\text{H}\) NMR spectra of pyridines 8b, 9b in which characteristic splitting of the 6-H signals was observed: \(\delta 8.4\)–8.6 ppm, \(^3J_{H_6,H_5}5\) Hz.

Conclusions

In summary, based on hetero Diels-Alder reactions of \(N\)-phosphoryltrihaloacetimidoyl chlorides with 1,3-butadienes, we have developed a simple and efficient synthesis of functionalized 2-trihalomethyl tetrahydropyridines, 2-trifluoromethyl dihydropyridines, and pyridines bearing CHCl₂ or CF₃ group in \(\alpha\)-position.
Experimental Section

**General.** IR spectra were obtained with an UR-20 instrument. $^1$H, $^{13}$C NMR spectra were recorded on Bruker Avance DRX 500 instrument operating at 500.07 and 125.76 MHz, respectively. $^{19}$F NMR and $^{31}$P NMR spectra – on Gemini 200 Varian instrument operating at 188.14 and 80.95 MHz respectively. Chemical shifts are reported relative to TMS ($^1$H, $^{13}$C), and CFCl$_3$ ($^{19}$F) as the internal standards or relative to external 85% H$_2$PO$_4$ ($^{31}$P). APCI MS spectra were recorded using Agilent 1100 instrument. Melting points are uncorrected. Solvents were dried before use according to standard methods. All reactions were carried out under argon atmosphere.

**2-Chloro-1-dichlorophosphoryl-4,5-dimethyl-2-(trifluoromethyl)-1,2,3,6-tetrahydro-pyridine (3a).** A solution of the 2,3-dimethylbutadiene 2a (1.2 g, 15 mmol) in 5 mL of diethyl ether was added to a stirred solution of imidoyl chloride 1a$^{13}$ (2.48 g, 10 mmol) in 10 mL of diethyl ether. After stirring at room temperature for 5 hrs the reaction mixture was evaporated in vacuum at 40-50 °C to afford compound 3a. Yield: 2.67 g (81%), white solid; mp 81-83°C (hexane). $^1$H NMR (CDCl$_3$): $\delta$ = 1.88 (s, 6H, 4,5-Me$_2$), 2.82 (m, 2H, CCH$_2$), 3.68 (dd, $^2$J$_{HH}$ = 13 Hz, $^3$J$_{HP}$ = 14 Hz, 1H, NCH$_A$), 3.92 (dd, $^2$J$_{HH}$ = 13 Hz, $^3$J$_{HP}$ = 15 Hz, 1H, NCH$_B$). $^{13}$C NMR (CDCl$_3$): $\delta$ = 17.05, 18.60 (4-Me, 5-Me), 42.29 (d, $^3$J$_{CP}$ = 6 Hz, 3-C), 50.77 (d, $^2$J$_{CP}$ = 4 Hz, 6-C), 81.78 (q, $^2$J$_{CP}$ = 33 Hz, 2-C), 122.50 (q, $^1$J$_{CP}$ = 285 Hz, CF$_3$) 126.62 (d, $^2$J$_{CP}$ = 13 Hz, 5-H). $^{19}$F NMR (CDCl$_3$): $\delta$ = 9.32 (m, 1H, NCH$_B$), 4.06 (m,1H, NCH$_A$), 45.59 (d, $^3$J$_{CP}$ = 5 Hz, 3-C), 53.43 (d, $^2$J$_{CP}$ = 5 Hz, 6-C), 93.82, 105.86 (2-C, CCl$_3$) 128.36, 134.66.

**2-Chloro-1-dichlorophosphoryl-4-methyl-2-(trifluoromethyl)-1,2,3,6-tetrahydropyridine (3b)** was synthesized analogously to 3a by stirring ethereal solution of imidoyl chloride 1a (2.48 g, 10 mmol) and 2-methylbutadiene 2b (1.02 g, 15 mmol) for 25 hrs at room temperature. Compound 3b was purified by column chromatography (silica gel, hexane/ethyl acetate 10:1). Yield: 2.2 g (70%), yellow oil. $^1$H NMR (CDCl$_3$): $\delta$ = 1.91 (s, 3H, Me), 2.85 (m, 2H, CCH$_2$), 3.78 (m,1H, NCH$_A$), 4.06 (m,1H, NCH$_B$), 5.89 (br, 1H, 5-H). $^{13}$C NMR (CDCl$_3$): $\delta$ = 22.32 (Me), 41.49 (d, $^2$J$_{CP}$ = 4 Hz, 3-C), 46.18 (d, $^2$J$_{CP}$ = 5 Hz, 6-C), 81.48 (q, $^2$J$_{CP}$ = 35 Hz, 2-C), 118.73 (d, $^3$J$_{CP}$ = 5 Hz, 5-C), 122.50 (q, $^1$J$_{CP}$ = 284 Hz, CF$_3$), 134.66 (4-C). $^{19}$F NMR (CDCl$_3$): $\delta$ = −77.42.

**2-Chloro-1-dichlorophosphoryl-4,5-dimethyl-2-(trichloromethyl)-1,2,3,6-tetrahydropyridine (3c)** was synthesized analogously to 3a by refluxing ethereal solution of imidoyl chloride 1b$^{14}$ (2.98 g, 10 mmol) and dimethylbutadiene 2a (1.2 g, 15 mmol) for 5 hrs. Yield: 2.95 g (78%), white solid, mp 158-160 °C (hexane-benzene, 3:1). $^1$H NMR (CDCl$_3$): $\delta$ = 1.92 (s, 3H, Me), 1.94 (s, 3H, Me), 3.21 (m, 2H, CCH$_2$), 3.83 (dd, $^2$J$_{HH}$ ~ 14 Hz, $^3$J$_{HP}$ ~ 15 Hz, 1H, NCH$_A$), 4.03 (dd, $^2$J$_{HH}$ = 14 Hz, $^3$J$_{HP}$ ~ 15 Hz, 1H, NCH$_B$). $^{13}$C NMR (CDCl$_3$): $\delta$ = 17.22, 18.24 (4-Me, 5-Me), 45.59 (d, $^3$J$_{CP}$ = 5 Hz, 3-C), 53.43 (d, $^2$J$_{CP}$ = 5 Hz, 6-C), 93.82, 105.86 (2-C, CCl$_3$) 128.36.
128.44 (4-C, 5-C). $^{31}$P NMR (CDCl$_3$): $\delta = 13.26$ (t, $^3J_{PH} \sim 15$ Hz). Anal. Calcd for C$_8$H$_{16}$Cl$_6$NOP: C 25.30; H 2.65; Cl 56.00; N 3.69; P 8.15. Found: C 24.98; H 2.91; Cl 55.87; N 3.57; P 7.87.

Compounds 3d, 4 and 5 were synthesized analogously to 3a by refluxing benzene solution of imidoyl chloride 1b (2.98 g, 10 mmol) and methylbutadiene 2b (1.02 g, 15 mmol) for 3 hrs. Column chromatography (silica gel, hexane/ethyl acetate 10:1) afforded tetrahydropyridines 3d, 5 and dihydropyridine 4.

2-Chloro-1-dichlorophosphoryl-4-methyl-2-(trichloromethyl)tetrahydropyridine (3d). Yield 1.83 g (50%), yellow oil. $^1$H NMR (CDCl$_3$): $\delta = 2.00$ (s, 3H, Me), 3.26 (m, 2H, CCH$_2$), 3.74 (m, 1H, NCH$_A$), 4.25 (m, 1H, NCH$_B$), 6.11 (m, 1H, 5-H). $^{13}$C NMR (CDCl$_3$): $\delta = 22.57$ (Me), 44.56 (d, $^2J_{CP} = 5$ Hz, 3-C), 48.51 (d, $^2J_{CP} = 6$ Hz, 6-C), 92.57, 105.90 (2-C, CCl$_3$), 121.00 (5-C), 137.68 (4-C). $^{31}$P NMR (CDCl$_3$): $\delta = 13.4$ (t, $^3J_{PH} = 16$ Hz). Anal. Calcd for C$_7$H$_6$Cl$_6$NOP: C 22.98; H, 2.20; Cl 58.15; N, 3.83; P, 8.47. Found: C 22.73; H 2.14; Cl 57.76; N 3.51; P 8.36.

5-Chloro-6-(dichloromethyl)-1-dichlorophosphoryl-4-methyl-1,2-dihydropyridine (4). Yield 0.35 g (12%), white solid, mp 129-131°C. $^1$H NMR (CDCl$_3$): $\delta = 1.92$ (s, 3H, Me), 3.85 (m, 1H, NCH$_A$), 4.18 (m, 1H, NCH$_B$), 5.18 (br, 1H, 5-H), 6.66 (s, 1H, CHCl$_2$). $^{13}$C NMR (CDCl$_3$): $\delta = 20.48$ (Me), 46.33 (d, $^2J_{CP} = 7$ Hz, 2-C), 54.20 (CHCl$_2$), 120.59 (d, $^3J_{CP} = 7$ Hz, 3-C), 126.06 (d, $^3J_{CP} = 9$ Hz, 5-C), 130.92 (4-C), 133.63 (d, $^2J_{CP} = 1$ Hz, 6-C). $^{31}$P NMR (CDCl$_3$): $\delta = 9.2$ (t, $^3J_{PH} = 12$ Hz). Anal. Calcd for C$_7$H$_6$Cl$_6$NOP: C, 25.53; H, 2.14; Cl 53.82; N 4.25; P 9.40. Found: C 25.37; H 2.09; Cl 53.27; N 4.21; P 9.26.

2-Chloro-4-methyl-2-(trichloromethyl)-1,2,3,6-tetrahydropyridine (5). Yield 0.06 g (3%), oil. $^1$H NMR (CDCl$_3$): $\delta = 2.03$ (s, 3H, Me), 3.34 (s, 2H, CCH$_2$), 4.04 (d, 1H, $^2J_{HH} = 16$ Hz, NCH$_A$), 4.72 (dd, 1H, $^2J_{HHH}=16$ Hz, $^3J_{HH}=6$ Hz, NCH$_B$), 6.11 (m, 1H, 5-H). $^{13}$C NMR (CDCl$_3$): $\delta = 22.53$ (Me), 44.76, 51.17 (6-C, 3-C), 90.49, 92.51 (2-C, CCl$_3$), 121.04 (5-C), 136.45 (4-C). Anal. Calcd for C$_7$H$_6$Cl$_6$N: C 33.77; H 3.64; Cl 56.96; N 5.63. Found: C 33.41; H 3.58; Cl 56.61; N 5.51.

1-Dichlorophosphoryl-3,4-dimethyl-6-(trifluoromethyl)-1,2-dihydropyridine (7a). A solution of the tetrahydropyridine 3a (3.3 g, 10 mmol) in 3 mL of trifluoroacetic acid-d$_1$ was stirred for 25 hrs, the solvent was evaporated in vacuum at 30-35°C to afford oily compound 7a, which was purified by column chromatography (silica gel, hexane/ethyl acetate 10:1). Yield: 1.85 g (64%). $^1$H NMR (CDCl$_3$): $\delta =$1.83 (s, 3H, Me), 1.86 (s, 3H, Me), 4.09 (d, 2H, $^3J_{HP} = 6$ Hz, NCH$_2$), 6.55 (s, 1H, 5-H). $^{19}$F NMR (CDCl$_3$): $\delta =$-63.2. $^{31}$P NMR (CDCl$_3$): $\delta =$14.9 (t, $^3J_{PH} = 26$ Hz). Anal. Calcd for C$_7$H$_6$Cl$_2$F$_3$NOP: C, 32.68; H, 3.09; Cl, 24.11; N, 4.76; P, 10.53. Found: C, 32.81; H, 3.19; Cl, 23.68; N, 4.61; P, 9.97.

1-Dichlorophosphoryl-4-methyl-6-(trifluoromethyl)-1,2-dihydropyridine (7b) was obtained by thermal distillation of the tetrahydropyridine 3b (3.16 g, 10 mmol) in vacuum (0.05 mmHg). Yield: 1.9 g (67%); bp 118-121°C/0.05 mmHg.). $^1$H NMR (CDCl$_3$): $\delta =$1.80 (s, 3H, Me), 4.19 (dd, $^3J_{HP} = 26$ Hz, $^3J_{HH} = 2.5$ Hz, NCH$_2$), 5.7 (br, 1H, 3-H), 6.47 (s, 1H, 5-H). $^{19}$F NMR (CDCl$_3$): $\delta =$-63.3. $^{31}$P NMR (CDCl$_3$): $\delta =$14.1 (t, $^3J_{PH} = 26$ Hz). Anal. Calcd for C$_7$H$_5$Cl$_2$F$_2$NOP: C30.03; H 2.52; Cl 25.32; N 5.00; P 11.06. Found: C 29.83; H 2.49; Cl 25.91; N 4.87; P 10.84.
General procedures for the synthesis of pyridines (8) and (9).
The mixture of respective tetrahydropyridine 3 or dihydropyridine 7 (10 mmol), dioxane (15 mL) and 35% aq HCl (15 mL) was refluxed for 3 hrs. After cooling to r.t. the mixture was neutralized with 10% NaOH, extracted with dichloromethane (2x25 mL), dried (MgSO₄), and the solvent was removed in vacuum at 50-60 °C.

4,5-Dimethyl-2-(trifluoromethyl)pyridine (8a). Yield 63% (from 3a) or 66% (from 7b); bp 75-80 °C (14 mm) (lit.¹⁵ bp 85 °C (17 mm) ¹H NMR (CDCl₃): δ = 2.29 (s, 3H, Me), 2.33 (s, 3H, Me), 7.41 (s, 1H, 3-H), 8.40 (s, 1H, 6-H). ¹⁹F NMR (CDCl₃): δ = -67.40.

4-Methyl-2-(trifluoromethyl)pyridine (8b). Yield: 81% (from 3b); nD²⁰ 1.4292 (lit.¹⁶ nD²⁰ 1.429). ¹H NMR (CDCl₃): δ = 2.44 (s, 3H, Me), 7.27 (d, 1H, ³JHH = 5 Hz, 5-H), 7.49 (s, 1H, 3-H), 8.56 (d, 1H, ³JHH = 5 Hz, 6-H). ¹⁹F NMR (CDCl₃): δ = -68.77. m/z (APCI) 162.2 (M+1, 100%). Calculated for C₇H₉F₃N, M = 161.13.

Compound 8b was prepared also by the following procedure: 3.17 g (10 mol) of tetrahydropyridine 3b was distilled, fraction with bp 170-180 °C was collected, dissolved in dichloromethane (50 mL), washed with 10% NaOH and dried (MgSO₄). The solvent was removed in vacuum at 50-60 °C to afford 1.1 g (68%) of pyridine 8b.

2-(Dichloromethyl)-4,5-dimethylpyridine (9a). Yield: 1.2 g (63%); bp 115-120 °C (14 mm); mp 70-72 °C (hexane-benzene 3:1). ¹H NMR (CDCl₃): δ = 2.19 (s, 3H, Me), 2.25 (s, 3H, Me), 6.63 (s, 1H, CHCl₂), 7.45 (s, 1H, 3-H), 8.19 (s, 1H, 6-H). ¹³C NMR (CDCl₃): δ = 16.28 (Me), 19.43 (Me), 71.48 (CHCl₂), 121.77 (3-C), 133.61 (5-C), 147.71 (4-C), 148.74 (6-C), 155.50 (2-C). Anal. Calcd for C₇H₆Cl₂N: C 50.55; H 4.77; Cl 37.30; N 7.37. Found: C 49.97; H 4.68; Cl 37.26; N 7.41.

2-(Dichloromethyl)-4-methylpyridine (9b). Yield: 1.1 g (68%); bp 160-170 °C (lit.¹⁷ bp 74-75 °C (14 mm); ¹H NMR (CDCl₃): δ = 2.43 (s, 3H, Me), 6.71 (s, 1H, CHCl₂), 7.14 (d, 1H, ³JHH = 5 Hz, 5-H), 7.58 (s, 1H, 3-H), 8.43 (d, 1H, ³JHH = 5 Hz, 6-H). ¹³C NMR (CDCl₃): δ = 21.12 (Me), 71.59 (CHCl₂), 121.73, 125.38 (3-C, 5-C), 148.50, 149.13 (4-C, 6-C), 157.68 (2-C).

References


