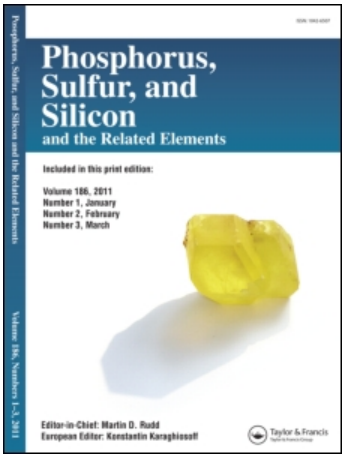

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Chengye Yuan; Weisheng Huang

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AN EFFICIENT AND REGIOSELECTIVE SYNTHESIS OF 1-ARYL(ALKYL)-4-DIETHOXYPHOSPHORYL-5-TRIFLUOROMETHYLIMIDAZOLES

CHENGYE YUAN, WEISHENG HUANG
Shanghai Institute of Organic Chemistry, Chinese Academy of Science,
354 Fenglin Lu, Shanghai 200032, China.

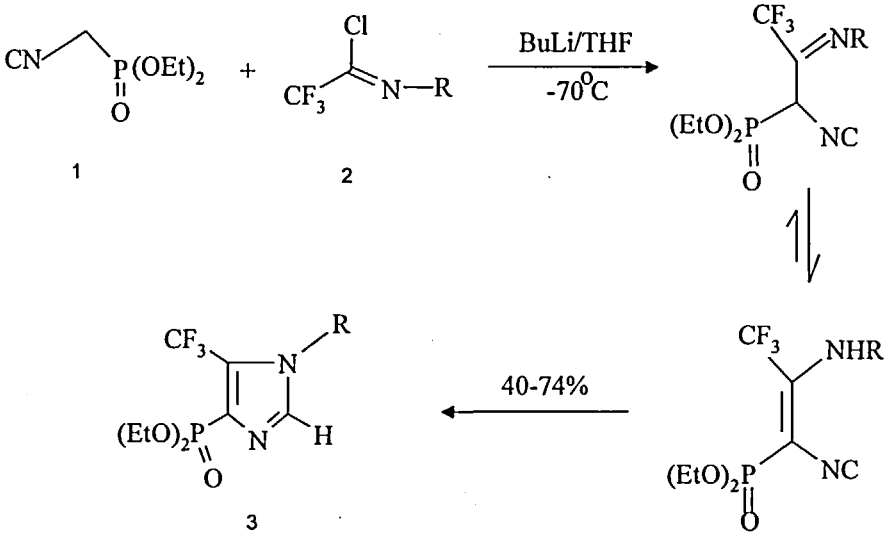
Abstract 1-Substituted-4-diethoxyphosphoryl-5-trifluoromethylimidazoles are prepared regioselectively from diethyl isocyanomethylphosphonate and N-substituted trifluoroacetimidoyl chlorides. The reaction mechanism was discussed.

Key words: trifluoromethylimidazole, phosphorylimidazole, regioselective synthesis.

Organophosphorus compounds received a renewed interest in the past decades with the discovery of more and more naturally occurring C-P compounds, which exibit significant biological activity. On the other hand, heterocyclic compounds have been attracting attention of chemists because of their pharmaceutical importance and extensive application in organic synthesis. Heterocycles in which the phosphoryl group is directly linked to the nucleus are difficult to prepare by the conventional reactions for C-P bond formation. However, the building block strategy can be exploited to undo this knot. Schollkopf and his co-workers synthesised phosphoryl oxazole and thiazole by the reaction of isocyanomethylphosphonate with acyl chlorides or carbon disulfide.[1] We also demonstrated that diethyl isocyanomethylphosphonate was useful synthetic block for 2-phosphorylpyrrole in its reaction with conjugated nitroolefins.[2] Herein we wish to report a base-induced cycloaddition of diethyl isocyanomethylphosphonate **1** to N-substituted trifluoroacetimidoyl chloride **2** , providing 1-substituted-4-diethoxyphosphoryl-5-trifluoromethylimidazole **3** . To the

best of our knowledge, neither synthesis of phosphoryl imidazole nor reaction of isocyanomethylphosphonate with C=N bond has been reported.

As shown in Scheme 1, the carbanion derived from **1** with BuLi at -70°C displaced smoothly the chlorine of **2** to form an imine intermediate, which upon rearrangement followed by cyclization, gave **3** in moderate to good yields. Signals at 7.60-7.79ppm(N=CHN) in ^{1}H NMR spectra definitely revealed the formation of imidazole. The yields of compound **3a** and **3b** were somewhat lower than that of 1-aryl derivatives, presumably due to the base-induced isomerization of corresponding imidoyl chlorides.[3] Usually, the addition of amine to isocyano-carbon requires the participation of the catalyst.[4] The driving force of such cyclization seems to be the tendency towards aromatization. Attempt to isolate the imine or the enamine intermediate was not successful.



R = n-C_8H_{17}(a), $PhCH_2CH_2$(b), C_6H_5(c), p-MeC_6H_4(d), m,p-$Me_2C_6H_3$(e), p-MeC_6H_4(f), p-ClC_6H_4(g), p-$NO_2C_6H_4$(h).

SCHEME 1

TABLE 1 Data of compounds **3**

Entry	Yield (%)	mp (°C)	IR(film) (cm^{-1}) P=O	C-F	^{19}F NMR	^{31}P NMR	MS (M+1)
3a	48	oil	1240	1180	21.7(s)	8.18(s)	385
3b	40	oil	1240	1180	21.2(s)	8.15(s)	377
3c	64	46-48	1250	1170	23.6(s)	7.99(s)	349
3d	62	56-58	1255	1160	23.3(s)	8.12(s)	363
3e	74	44-46	1250	1160	23.6(s)	8.14(s)	377
3f	60	40	1250	1180	23.2(s)	8.13(s)	379
3g	72	58-60	1240	1170	23.6(s)	7.64(s)	383
3h	70	116	1255	1185	24.0(s)	7.11(s)	393(M)

Replacement of BuLi by NaH in this reaction failed to give imidazole compounds. Quenching of the reaction mixture produced a complex which was difficult to separate by column chromatography.

The regiochemistry of this reaction deserved more attention. The single chemical shift in ^{31}P NMR and ^{19}F NMR spectra demonstrated the only structure of the products. The regioisomers of 1-substituted 2-phosphoryl-5-trifluoromethylimidazole, which may be resulted from 1,3-dipolar cycloaddition, were not detected. The ^{13}C NMR spectra confirmed the regiochemistry. The doublets of C-2 and C-4 and the dq signals of C-5 indicated that the phosphoryl group was linked to C-4.

Meanwhile, another pathway where the cyclization precedes the elimination of chlorine is possible.[5] This addition-cyclization-prototropic-elimination process, however, was precluded since the reaction of diethyl 1-isocyanoethylphosphonate with N-phenyltrifluoroacetimidoyl chloride gave 1-isocyano-2-imino phosphonate rather than imidazoline derivative. This result means that the elimination of chlorine from the N-anion is more rapid than the cyclization.

Consequently, the suggested effective and regioselective synthesis of 1-aryl(alkyl)-4-diethoxyphosphoryl-5-trifluoromethylimidazole from **1** and **2** undergoes an addition-elimination-isomerization-cyclization mechanism.

As shown by us, the logarithm values of ^{31}P NMR chemical shifts for resulted **3** correlated linearly with the σ parameters of the nuclear substituents in benzene ring, located on N-1 position.

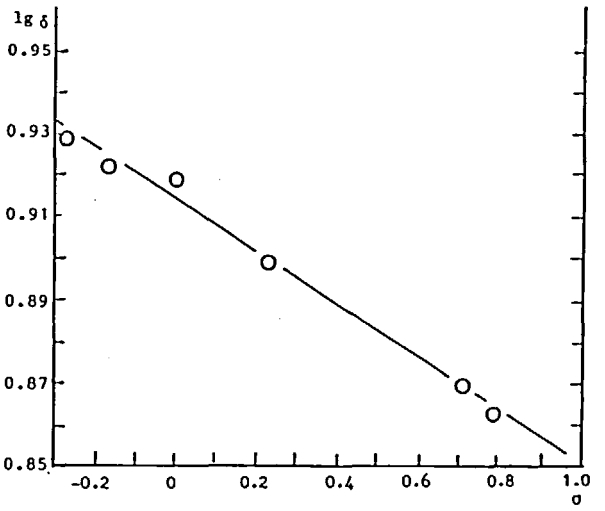


FIGURE 1 ^{31}P NMR chemical shift as the function of Hammett constant of phosphoryl imidazoles

$\log \delta = -0.0584\,\sigma + 0.898$ (n=6, r=99.33%)

The present method is convenient since both trifluoroacetimidoyl chlorides[6] and diethyl isocyanomethylphosphonate [7] are easily obtainable.

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