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One-pot synthesis of new highly substituted allylic phosphorodiamidates

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ABSTRACT

A one-pot synthesis of new substituted allylic phosphorodiamidates was performed through phosphorylation of the corresponding alcohols followed by aminolysis. The intermediate allylic phosphorodichoridates could only be isolated when the starting allylic alcohol contains a trifluoromethyl group at the γ-position. These phosphorodiamidates were obtained as mixtures of two (*Z* and *E*) isomers in 41–72% yield. They were characterized by multinuclear (^{1}H, ^{13}C, ^{31}P and ^{19}F) NMR, IR spectroscopy and HRMS.

1. Introduction

Phosphoramidates are attracting increasing interest as important structural motifs that are found in a variety of naturally occurring compounds [1–6]. A number of molecules containing these motifs were also shown to have potent antifungal, antitumor and anti-HIV activities [7]. In addition, phosphoramidates are used as ligands [8] in asymmetric synthesis and catalysis [9], as flame retardants [10] and as labeling groups in spectrometric applications [11]. In particular, they are useful precursors to aziridines [12], azetidines [13], amines [14], imines [15] and heterocycles [16]. This has led to an increasing interest in developing different approaches toward the synthesis of phosphoramidates [17–20]. The most common method involves phosphorylation of alcohols with phosphorus halides in the presence of a proton scavenger such as triethylamine followed by aminolysis [21,22]. This has been widely used for the synthesis and design of nucleotide prodrugs [23].

In continuation of our exploration in the reactivity of variously substituted β-chloro-α,β-unsaturated aldehydes [24,25], we have very recently reported on the use of corresponding allylic alcohols as substrates to produce allylic phosphates [26]. Herein, we describe the synthesis of a series of new phosphoramidates starting from the same allylic alcohols. The products were obtained in good yields and fully characterized by multinuclear (^{1}H, ^{13}C, ^{31}P and ^{19}F) NMR, IR and HRMS.

2. Results and discussion

The synthesis of the new phosphorodiamidates **5–13** was carried out using allylic alcohols **2(a–c)** as substrates. These alcohols were cleanly prepared starting from the corresponding unsaturated aldehydes (**1(a–c)**), obtained by Vilsmeier-Haack reaction [27–29]. The latter were reduced with $NaBH_4$ in THF as previously described [30] to give the allylic alcohols **2(a–c)** (Scheme 1).

We have initially attempted to prepare the intermediate phophorochloridates **3(a-c)** as shown in Scheme 2, which can then undergo aminolysis to give the targeted phosphoramidates.

For instance and despite that the reaction carried out at 0 °C for fluorinated alcohols **2a** and **2b** led to both the desired phosphorochloridates **3a** and **3b** and the chlorination products **4a** and **4b**, no

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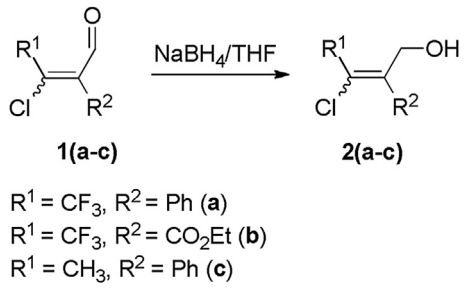


Scheme 1. Preparation of the starting alcohols **2(a–c)**.

phosphorochloridates could be generated at 0 °C from the non fluorinated alcohol **2c**, leading exclusively to the chlorinated product **4c.** However, when the latter reaction was carried out at −78 °C both the phosphorochloridate **3c** and the chlorination product **4c** were obtained. For example, the reaction of alcohol **2a** at 0 °C led to phosphorochloridate **3a** and chloride **4a** in a 2.5:1 ratio. Furthermore, reaction of **2c** yielded only the chloride **4c** at 0 °C and gave both the phosphorochloridate **3c** and chloride **4c** at 3–78 °C.

It is worthnoting that the phosphorochloridates **3a** and **3b** are stable at 0 °C and are converted to chlorides **4a** and **4b** after 24 h, whereas phosphorochloridate **3c** could be generated only at −78 °C and is spontaneously converted at rt even at 0 °C to the thermodynamically more stable allylic chloride **4c** (Scheme 2). This clearly shows the difference in the reactivity between the trifluoromethylated alcohols **2a** and **2b** and the non fluorinated analog **2c**, suggesting that phosphorylation of the allylic alcohol substrates **2(a–c)** and their subsequent chlorination are competitive under these conditions, particularly for the non fluorinated derivative **2c**.

The kinetic conversion of phosphorochloridates **3(a–c)**, isolated from the reaction after 1 h, into chlorides **4(a–c)** was studied using ^{1}H NMR which shows complete conversion after 48 h (Fig. 1). The structure of the phosphorochloridates **3(a–c)** were confirmed by proton coupled ^{31}P NMR spectra which display two triplets for the two isomers due to coupling with the two methylene protons (Fig. 2), whereas chlorides **4(a–c)** were identified by their proton NMR spectra with a characteristic signal at about 4.45 ppm assigned to the methylene protons (Fig. 1).

Due to the instability of the intermediate phosphorochloridates **3(a–c)** as described above, we have therefore decided to prepare the corresponding phosphorodiamidates (**5–13)** in a one-pot process by the sequential treatment of allylic alcohols **2(a–c)** with $P(O)Cl_3$ followed by reaction with different secondary amines (Table 1). The reaction was monitored by ^{31}P NMR to ensure complete conversion of the intermediate phosphorochloridates **3 (a–c)** (δp at ∼8 *vs.* ∼20 ppm for the phosphoradiamidates **5–13**). The phosphoramidates were thus obtained together with the chlorides **4(a–c)** generated *in situ* from the first step (Scheme 3) which were then separated by silica gel chromatography as

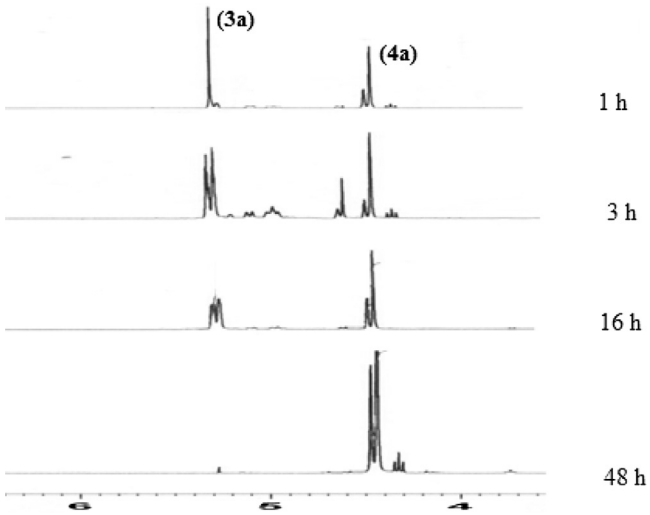


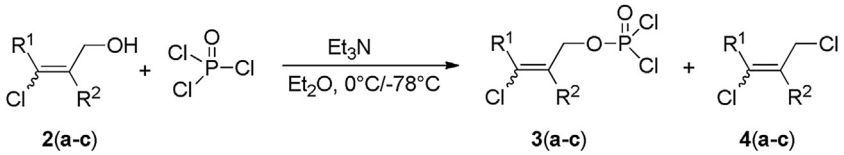
Fig. 1. The methylene ^{1}H NMR region of the phosphorylation step, showing the conversion of the phosphorochloridate (**3a**) to the corresponding chloride (**4a**) at rt with time.

mixtures of two (*E* and *Z*) isomers in 41–72% yield (Table 1). In addition, it was found that the percentage of the chloride obtained from step 1 did not change in step 2 since it formed from rearrangement of the intermediate phosphorochloridates which were aminolysed *in situ* at 0 °C, preventing its formation in the second step.

The proportion of the chlorides **4(a–c)** formed from the first step was thus more easily estimated from the crude product of the second step (Scheme 3). As expected, the percentage of chloride **4c** obtained from phosphorylation of non-fluorinated alcohol **2c** is more important than that of **4a** formed from the fluorinated analog **2a**. In order to further confirm this, we used an alcohol containing an ester group in β-position of the allylic moiety (**2b**) which also showed the same trend as that of alcohol **2a**. This clearly indicates the effect of the trifluoromethyl group at the γ-position on the reactivity of such alcohols towards $P(O)Cl_3$, giving the desired phosphorodiamidates in better yields compared to non fluorinated counterpart (Table 1).

Alternatively, the phosphoramidates (**5–13)** could be prepared by treatment of $P(O)Cl_3$ sequentially with the secondary amine and allylic alcohol in the presence of Et_3N and DMAP to yield the desired phosphoramidates (Scheme 4). Although this procedure gives comparable yields, it is less convenient because of the need to use strong bases and longer reaction times.

All the phosphorodiamidates **5–13** shown in Table 1 were fully characterized by ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectroscopy. For example, the ^{31}P NMR spectrum of each of the phosphoramidates **5–13** shows, as expected, two unequal intensity signals indicating the presence of the two *Z* and *E* isomers in different proportions (Fig. 3). The integration of these signals gave approximately the



Scheme 2. Preparation of the intermediate phosphorochloridates **3(a–c)**.