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An improved route to the synthetic of diphenyl α-(diethoxythiophosphorylamino) methylphosphonates

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Abstract

An improved method for the synthesis of Diphenyl α-(diethoxythiophosphorylamino)methylphosphonates under mild conditions is described. It consists of the reaction of diethyl thiophosphoramidate (**1**) with triphenyl phosphite (**3**) and a substituted benzylaldehyde or ketone (**2**) by a one-pot procedure with the aid of acetyl chloride.

Keywords: Mannich type reaction; Thiophosphate-phosphonate derivatives; Acetyl chloride; X-ray crystal structure

1. Introduction

Organophosphorus compounds have found a wide range of applications in the areas of industrial, agricultural, and medicinal chemistry owing to their biological and physical properties as well as their utility as synthetic intermediates [1–4]. α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds. α-Aminophosphonates are important compounds due to their applications as enzyme inhibitors, antibiotics, pharmacological agents and many other applications are well

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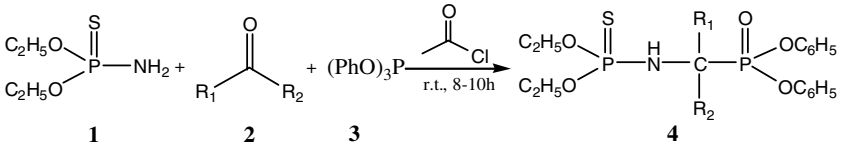
documented [5,6]. α-Aminophosphoryl compounds have recently been proved to be biologically active and have been shown to inhibit the enzymes renin, EPSP synthase and HIV protease [7,8]. Also a large number of thiophosphate-phosphonate derivatives, bearing a P–N–C–P bond structure were synthesized and their significant herbicidal, antiviral, and fungicidal activities were reported [9–12].

Among numerous synthetic methods for the preparation of α-aminophosphonic acids derivatives, the three-component condensation involving substituted amide, aldehyde (or ketone) and phosphorus ester is of significant interest [13–16]. We report here a facile synthetic method for the preparation of α-amino-substituted thiophosphate-phosphonates derivatives with the aids of a versatile reagent acetyl chloride.

2. Results and discussion

The Mannich type reaction of trivalent phosphines has proved facile for the preparation of new phosphorus α-aminoalkanephosphonate compounds. As shown in Scheme 1, diethyl thiophosphoramidate (**1**) was allowed to react with triphenyl phosphite (**3**) and various substituted ketones or benzaldehyde (**2**) in acetyl chloride to give the target Diphenyl α-(diethoxythiophosphorylamino)methylphosphonates **4a–g** in moderate to good yields ranging from 56 to 90%. It was found that the use of aromatic adehydes led to much better yields than that of ketones. The reactions were carried out using one-pot procedure. All the products were isolated from reaction mixture by column chromatography, and their structures were characterized by ^{1}H NMR, ^{31}P NMR, ^{13}C NMR, and mass spectrum.

The ^{31}P NMR spectra of compound **4** showed two doublets due to the P–P splitting as shown by identical coupling constants. Similar results were reported by C.Y. Yuan [13–15]. The ^{31}P NMR spectra showed at around $\delta = 20$ and at $\delta = 69$ ppm, the first one being attributable to the P-atom of the diphenoxyphosphinyl group, and the second one to the P-atom of the *N*-thiophosphoryl group. In the ^{1}H NMR spectra of **4**, the CHP proton appears as a doublet–triplet ($\delta = 5.03$–5.15) due to the pair of phosphorus atoms coupling with coupling constant $^{2}J_{P,CH}$ of 23.2 Hz and $^{3}J_{P,CH}$ of 11 Hz and NH coupling with a coupling constant $^{3}J_{NH,CH}$ of 11 Hz. The IR spectra of **4** show normal



1 **2** **3** **4**

4	R_1	R_2	Yield (%)	4	R_1	R_2	Yield (%)
4a	H	Ph	89	**4e**	$(CH_2)_4$		76
4b	H	4-MeC_6H_4	90	**4f**	$(CH_2)_5$		67
4c	H	4-MeOC_6H_4	77	**4g**	$(CH_2)_6$		63
4d	Ph	CH_3	56				

Scheme 1. Preparation of diphenyl α-(diethoxythiophosphorylamino) methylphosphonates.