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An Efficient Strategy for the Synthesis of 1-Chloroethyl Phosphates and Phosphoramidates

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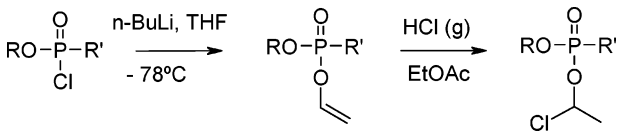
Received June 30, 2005



A versatile, efficient, and simple method for the preparation of various 1-chloroethyl phosphates and phosphoramidates is described. The protected chlorophosphates or phosphoramidates are synthesized to the vinyl derivative under mild conditions, followed by conversion to the chloroethylidene phosphate or phosphoramidate by dry HCl gas, resulting in good to excellent yields. 1-Chloroethyl phosphates and phosphoramidates are excellent building blocks for the synthesis of novel ethylidene-linked phosphate prodrugs.

Phosphates and phosphoramidates are widely used as prodrug moieties to enhance water solubility[1] or therapeutic potential of a parent drug.[2−4] The phosphoramidates are also used to synthesize phosphate esters with different protecting groups by the replacement of amide with an ester group.[5,6] In addition, they can be used to synthesize a monoester phosphate prodrug by hydrolyzing the phosphoramide bond[7] to yield limited enhancement of the water solubility of the parent compound. Phosphate promoieties are often attached to the parent drug via an oxymethyl spacer group,[8−10] which is a problem due to highly toxic formaldehyde[11] released systemically during metabolism of the oxymethyl group in the body.[12,13] To overcome this drawback, we were interested in developing ethylidene-linked prodrugs, which are metabolized to the less toxic acetaldehyde. Previously, an ethylidene spacer group was used in (acyloxy)alkyl prodrugs,[14,15] but no descriptions of ethylidene-linked phosphate prodrugs as ways to increase the water solubility of a drug molecule have been published. The compounds described in the present study are excellent starting materials for the preparation of ethylidene-linked phosphate prodrugs.

The ethylidene phosphate prodrugs could be prepared via addition of 1-chloroethyl phosphates or phosphoramidates to an appropriate functional group (e.g., hydroxyl or amine group) of the drug molecule. However, there is no efficient and practical method to synthesize 1-chloroethyl phosphates or phosphoramidates. The 1-chloroethyl derivatives of carboxylic acids are traditionally prepared from the acetaldehyde and the corresponding acid chloride using $ZnCl_2$ as the catalyst.[16] However, this method was not successful for the synthesis of 1-chloroethyl phosphates. The only reported approach to synthesize 1-chloroethyl phosphates is a method in which diethyl 1-chloroethyl phosphate is synthesized from ethyl phosphorodichloridate using hazardous chemicals and methods (chlorine gas, mercury vapor lamp).[17] In the present study, we report an efficient and practical synthetic approach for the preparation of 1-chloroethyl phosphates and phosphoramidates, in which the protected chlorophosphates or phosphoramidates are synthesized to the vinyl derivative under mild conditions, followed by the conversion to the 1-chloroethyl phosphate or phosphoramidate by dry HCl gas.

The desired vinyl intermediates were prepared from the corresponding chlorophosphates **1**, which are commercially available (**1b**,**c**,**e**,**g**) or prepared by the known method from phosphorus trichloride[18,19] (**1a**,**d**,**f**,**h**) or from diethyl phosphorodichloridate[20] (**1i**). Nine different vinyl phosphates or phosphoramidates were prepared by treat-

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10.1021/jo0513562 CCC: $30.25
Published on Web 09/27/2005

SCHEME 1. Synthesis of Vinyl (2a−i) and 1-Chloroethyl Phosphates and Phosphoramidates (3a−i)

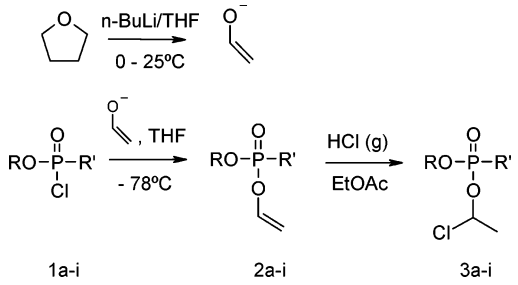
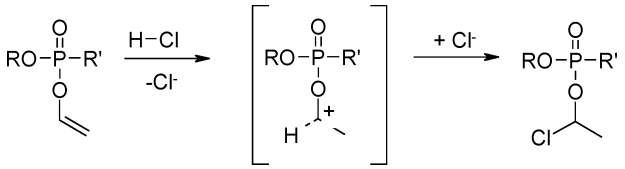


TABLE 1. Synthesis of Vinyl and Chloroethylidene Phosphates and Phosphoramidates

entry	R	R′	**2**: yield (%)	**3**: yield (%)[a]	time[b] (h)
1a	Me	OMe	**2a**: 52	**3a**: 86	29 (12)[c]
1b	Et	OEt	**2b**: 64	**3b**: 91	24 (7)[c]
1c	Cl_3Et	OCl_3Et	**2c**: 68	**3c**: 66	912 (195)[c]
1d	Me	OPh	**2d**: 54	**3d**: 87	500 (50)[c]
1e	(2,6-Me_2)Ph	O-(2,6-Me_2)Ph	**2e**: 35	**3e**: 92	480 (90)[c]
1f	-$CH_2CH_2CH_2O$-		**2f**: 76	**3f**: 98	30 (12)[c]
1g	Ph	OPh	**2g**: 70	**3g**: −	−[d]
1h	Bz	OBz	**2h**: 30	**3h**: 68	48[e]
1i	Me	NEt_2	**2i**: 88	**3i**: 91	21[e]

[a] Yield without purification. [b] The reaction times are the total reaction times of step 2, with the times of HCl bubbling in parentheses. [c] Reaction conditions: HCl bubbling, room temperature. [d] Did not react under any kind of conditions. [e] Reaction conditions: EtOAc saturated with HCl, 4 °C.

SCHEME 2. Electrophilic Addition Reaction of HCl to Vinyl Phosphate



ing **1** with the enolate of acetaldehyde[21] with reasonable good yields (Scheme 1, Table 1). The vinylation occurred under mild conditions, which makes it a suitable method for different kinds of molecules.

The electrophilic addition reaction of HCl to the vinyl double bond was obtained by bubbling dry HCl gas through a solution of **2** in dry ethyl acetate. The reaction occurs via the attack of H^+ to yield an intermediate carbocation, which quickly undergoes a reaction with a negative halide ion to yield an alkyl halide (Scheme 2). The results listed in Table 1 show that there are remarkable differences in the reaction times and conditions depending on the chemical nature of the phosphate substituents. The compounds **3h** and **3i** were readily obtained under mild conditions, but on the other hand, the diphenyl derivative **2g** did not react at all, even though several common catalysts and overpressure (5 atm) were tested.

All 1-chloroethyl products, except **3h**,[22] could be purified and isolated with silica gel column chromatography, but some of the products partially decomposed during the purification procedure. Since the crude products from the synthesis of **3** did not contain any major impurities according to ^1H, ^{13}C, and ^{31}P NMR, these building blocks should be used without further purification. Thus the yields of **3a−i** presented in Table 1 are reported without purification and are estimated from the actual chemical yields according to purity of ^1H and ^{31}P NMR spectra, but the NMR data, GC−MS analyses, and elemental analyses (CHNS) were obtained from the purified products.

In conclusion, the first method for the synthesis of 1-chloroethyl phosphates and phosphoramidates was developed. The synthetic route was started with vinylation of chlorophosphate or phosphoramidate as the starting material, followed by addition of hydrogen chloride to the vinyl double bond to yield 1-chloroethyl phosphate or phosphoramidate. This method was found to be versatile and a simple way to synthesize phosphates and phosphoramidates with various protecting groups and is thus applicable for a wide range of molecules. 1-Chloroethyl phosphates and phosphoramidates are excellent building blocks for the synthesis of ethylidene-linked prodrugs.

Experimental Section

A General Method for the Preparation of Vinyl Phosphates 2. To a 100-mL round-bottom flask was added dry THF (50 mL) under argon and cooled to 0 °C, followed by adding 1.6 M *n*-butyllithium (15 mL, 24 mmol) in hexane at 0 °C. The reaction mixture was stirred for 0.5 h at 0 °C and then overnight at 25 °C. After 18 h without cooling, this enolate of acetaldehyde was added dropwise to the chlorophosphate or phosphoramidate **1** (25.2 mmol, 1.05 equiv) in THF (5 mL) during 15 min at −78 °C. After the addition was complete, the reaction mixture was allowed to reach room temperature over 45 min and the solvents were evaporated. The residue was dissolved in CH_2Cl_2 (50 mL), washed with 10% sodium phosphate buffer (pH 7.0, 5 × 15 mL), dried with Na_2SO_4, and evaporated to dryness. The residue was purified by column chromatography to yield vinyl derivative **2**. The chromatography purification conditions are described in detail along with each molecule description.

Phosphoric Acid Dimethyl Ester Vinyl Ester 2a: 52%, colorless oil. Chromatography eluent EtOAc/petrol ether, 2:3. ^1H NMR ($CDCl_3$) δ 6.579 (1H, ddd, J = 13.52 Hz, 5.86 Hz, $^3J_{HP}$ = 6.52 Hz), 4.933 (1H, ddd, J = 13.52 Hz, 2.17 Hz, $^4J_{HP}$ = 1.19 Hz), 4.601 (1H, ddd, J = 5.86 Hz, 2.17 Hz, $^4J_{HP}$ = 2.67 Hz), 3.825 (6H, d, $^3J_{HP}$ = 11.24 Hz Hz); ^{13}C NMR ($CDCl_3$) δ 142.14 (d, $^2J_{CP}$ = 5.7 Hz), 100.11 (d, $^3J_{CP}$ = 10.2 Hz), 54.69 (d, $^2J_{CP}$ = 6.0 Hz); ^{31}P NMR ($CDCl_3$) δ −2.10. GC−MS *m/z* 151 (M − 1).

A General Method for the Synthesis of Chloroethylidene Phosphates 3. To a 10-mL round-bottom flask was added vinyl phosphate **2** (5.6 mmol) and EtOAc (2 mL) under argon. Dry gaseous HCl was bubbled through the solution (**2a−f**). In the case of **3h**,**i**, the solution on **2** in EtOAc was cooled to 4 °C followed by addition of EtOAc saturated with HCl (2 mL). The progress of the HCl addition was monitored by measuring ^1H and ^{31}P NMR spectra from the reaction mixture. After the appropriate reaction time, the solvents were evaporated and the residue was purified by column chromatography. The reaction time and conditions varied between the reactions and are illustrated in detail in Table 1.

Phosphoric Acid 1-Chloroethyl Ester Dimethyl Ester 3a: 86% (without purification), colorless viscose oil. Chromatography eluent hexane/EtOAc, 1:1. ^1H NMR ($CDCl_3$) δ 6.242

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(22) **3h** was found to be extremely labile, since it decomposed during warming, column chromatography, and GC−MS/HPLC−MS analysis.

(1H, dq, J = 5.62 Hz, $^3J_{HP}$ = 7.62 Hz), 3.837[23] (3H, d, $^3J_{HP}$ = 11.44 Hz), 3.802[23] (3H, d, $^3J_{HP}$ = 11.31), 1.856 (3H, dd, J = 5.62 Hz, $^4J_{HP}$ = 1.09 Hz); ^{13}C NMR ($CDCl_3$) δ 85.78 (d, $^2J_{CP}$ = 6.4 Hz), 54.82[23] (d, $^2J_{CP}$ = 6.1 Hz), 54.55[23] (d, $^2J_{CP}$ = 6.0 Hz), 27.54 (d, $^3J_{CP}$ = 8.4 Hz); ^{31}P NMR ($CDCl_3$) δ −0.76. GC−MS *m/z* 189 (M + 1), 153 (M − Cl). Anal. Calcd for $C_4H_{10}ClO_4P$·0.7 HCl: C, 22.44; H, 5.04. Found: C, 22.53; H, 4.76.

Acknowledgment. We thank Mrs. Miia Reponen and Mrs. Maritta Salminkoski for their skillful technical assistance. This study was financially supported by the Graduate School of Bioorganic and Medicinal Chemistry, the National Technology Agency of Finland, the Academy of Finland, Research Foundation of Orion Corporation, and Association of Finnish Chemical Societies.

(23) Due to their chiral center, OMe signals have different chemical shifts.

Supporting Information Available: General methods, NMR, and GC−MS data for compounds **2b**−**i** (except **2g**, only NMR data) and NMR, GC−MS, and CHNS data for **3b**−**i** (except **3h**, only NMR data). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0513562