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One-pot synthesis of hydrogen phosphonate derivatives of d4T and AZT

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A simple and one-pot route for the synthesis of d4T or AZT hydrogen phosphonate derivatives *via* reaction of d4T or AZT with phosphorus trichloride, then alcoholysis and dealkylation in the presence of the corresponding alcohol is described.

Nucleoside analogs have attracted much attention as anti-HIV agents since they are inhibitors of HIV reverse transcriptase (RT). Among them, 2′,3′-didehydro-2′,3′-dideoxythymidine (d4T) and 3′-azido-2′,3′-dideoxythymidine (AZT) are antiviral drugs for the treatment of AIDS.[1] However, it is found that d4T, AZT and other nucleoside analogs do not exert antiviral activity directly after penetrating cells through a passive process, but are successively phosphorylated to the corresponding mono-, di- and triphosphates by cellular kinases to terminate the viral DNA elongation through strong inhibition of HIV-RT. Therefore d4T and AZT are considered as cell-activation-dependent nucleoside analogs.[2] In addition, many adverse effects, such as neutropenia and anemia associated with AZT, peripheral neuropathy associated with d4T and drug resistance of AZT or d4T are frequently observed clinically.[3]

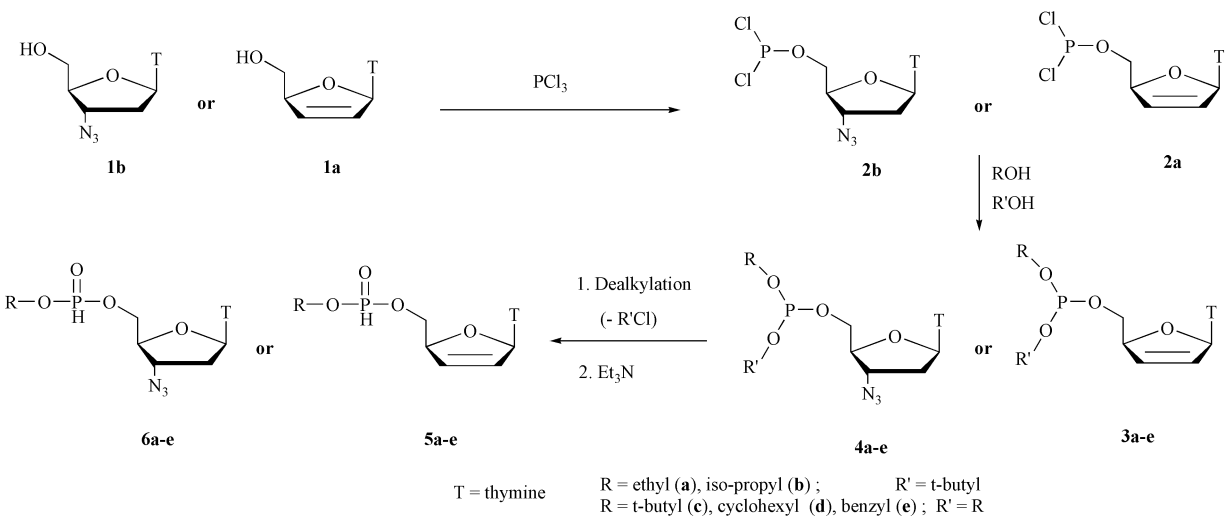
Thus, great efforts have been continuously made to develop and optimize the structures of d4T and AZT.[4] One class of such analogs are the O-alkyl-5′-H-phosphonates of d4T or AZT, which have proved to cause less nucleoside-resistant mutants of HIV, lower cytotoxicity, and higher anti-HIV activity due to easier membrane permeability of these derivatives resulting from the presence of the lipophilic group. Among them, the O-cyclohexyl-5′-H-phosphonate of AZT and the O-isopropyl-5′-H-phosphonate of d4T are the most active for anti-HIV in clinical trials.[5]

Generally, hydrogen phosphonate diesters of nucleosides are synthesized by condensation of the H-phosphonate monoester with a hydroxylic component in the presence of a condensing agent, or the transesterification of diphenyl phosphite.[6] Cardona has prepared the O-benzyl-H-phosphonate of d4T or AZT using the H-phosphonate monoester/oxalyl chloride system.[7] The other active O-alkyl analogs are also synthesized by the same method.[5] However, the use of condensing agent and pyridine in this multi-step reaction prevents its application as a large scale preparative method. There is therefore a need for a convenient and economical synthetic route.

In this paper we describe an efficient and economical one-pot synthesis of asymmetrical O-alkyl-H-phosphonate of d4T or AZT giving reasonable yields using a phosphorus trichloride/alcohol system (Scheme 1). This novel method can be applied on a large scale for the preparation of anti-HIV prodrugs.

For example, treatment of d4T (**1a**) or AZT (**1b**) with phosphorus trichloride (10 eq.) in dichloromethane at −30 °C for 1 h and rt for 6 h gave **2a** or **2b**, as confirmed by ^{31}P NMR and MS analysis. After evaporating the excess of phosphorus trichloride, **2a** or **2b** was alcoholysed by the corresponding alcohol to form **3a**–**e** or **4a**–**e** respectively. Subsequently dealkylation occurred and finished during 30 minutes' stirring at 0 °C, as determined by ^{31}P NMR. Concentration *in vacuo* followed by silica gel chromatography then gave the pure O-alkyl-5′-H-phosphonate of d4T or AZT (**5a**–**e** or **6a**–**e**),† as shown‡ in Table 1.

It is worth noting that through Arbuzov reaction the dealkylation of **3a**–**e** or **4a**–**e** proceeds with the assistance of hydrogen chloride generated during the alcoholysis of **2a** or **2b** by eliminating one eq. of alkyl chloride to yield the O-alkyl-H-phosphonate of d4T or AZT. Moreover, it is found that by using a mixture of ethanol and *tert*-butanol (1 : 1) as alcoholysis agent, to prevent dealkylation occurring at the nucleoside moiety, the yield of O-ethyl-5′-H-phosphonate of d4T or AZT (**5a** or **6a**) is higher than when ethanol alone is used. The situation for the O-isopropyl-5′-H-phosphonates of d4T and AZT (**5b** or **6b**) is similar to that for **5a** and **6a**. This can be explained by the fact that the tertiary carbonium ion is more stable than the secondary, which in turn is more stable than the primary. Thus the tertiary is eliminated more easily than the primary. In



Scheme 1

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Table 1 Reaction of d4T (**1a**) or AZT (**1b**) with PCl_3/alcohol system

Entry	**1**	Alcohol used	R	Product[a]	Yield (%)[b]
1	d4T	Ethanol : *tert*-butanol (1 : 1)	Ethyl	**5a**	61
	d4T	Ethanol	Ethyl	**5a**	22
2	d4T	Isopropyl alcohol : *tert*-butanol (1 : 1)	Isopropyl	**5b**	66
3	d4T	*tert*-Butanol	*tert*-Butyl	**5c**	60
4	d4T	Cyclohexanol	Cyclohexyl	**5d**	73
5	d4T	Benzyl alcohol	Benzyl	**5e**	53
6	AZT	Ethanol : *tert*-butanol (1 : 1)	Ethyl	**6a**	67
	AZT	Ethanol	Ethyl	**6a**	18
7	AZT	Isopropyl alcohol : *tert*-butanol (1 : 1)	Isopropyl	**6b**	76
8	AZT	*tert*-Butanol	*tert*-Butyl	**6c**	88
9	AZT	Cyclohexanol	Cyclohexyl	**6d**	58
10	AZT	Benzyl alcohol	Benzyl	**6e**	72

[a] All compounds were characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and ESI-MS analysis, among which **5e** and **6e** were compared with authentic samples[7]. [b] The silica gel column chromatography isolated yields based on **1a** or **1b**.

addition, the O-*tert*-butyl, cyclohexyl or benzyl H-phosphonates of d4T or AZT were formed when *tert*-butanol, cyclohexanol or benzyl alcohol, respectively, were used as alcoholysis agents. Therefore, a range of O-alkyl-H-phosphonates of d4T or AZT can be prepared by this method.

In conclusion, we have developed a facile and one-pot approach for the preparation of O-alkyl-H-phosphonates of d4T and AZT under mild conditions and with reasonable yields. Thus, the prodrug H-phosphonates of d4T or AZT diesters can be synthesized on a large scale conveniently and economically.

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Notes and references

† Typical reaction procedure: To a flask containing 1.38 g (10 mmol) PCl_3 in 10 mL dichloromethane, d4T **1a** or AZT **1b** (1 mmol) is added in portions within 10 minutes at −30 °C. The reaction mixture is stirred at that temperature for 1 h and rt for 6 h. After evaporation of the solvent and excess of PCl_3, the residue is dissolved in 10 mL dichloromethane. Subsequently, 2.5 mmol alcohol in 5 mL dichloromethane is dropped into it on an ice bath and stirred at 0 °C for 30 minutes and then 0.202 g (2 mmol) triethylamine is added. 10 min later the solvent is removed *in vacuo* and **5a**–**e** or **6a**–**e** are purified over silica gel chromatography using CH_2Cl_2/MeOH (20 : 1) as eluent.

‡ Spectral data for the representative products: **5b**) ^{31}P NMR ($CDCl_3$) δ 7.17, 6.72 ppm; ^{1}HNMR ($CDCl_3$) δ 10.10 (s, 1H), 7.75, 6.00 (d, 1H, $J_{P\text{-}H}$ = 700 Hz), 7.32 (d, 1H, J = 19.2Hz), 7.06 (m, 1H), 6.36 (d, 1H, J = 6 Hz), 5.94 (d, 1H, J = 6 Hz), 5.03 (m, 1H), 4.80 (m, 1H), 4.30 (m, 2H), 1.92 (s, 3H), 1.36 (d, 6H, J = 6 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 164.05, 150.96, 135.64, 132.77, 127.52, 111.00, 89.33, 84.32, 71.68, 65.08, 23.68, 12.21 ppm; ESI-MS: 331(M + H)$^+$, 353(M + Na)$^+$, 369(M + K)$^+$. **6c**) ^{31}P NMR ($CDCl_3$) δ 3.54, 3.09 ppm; ^{1}H NMR ($CDCl_3$) δ 9.43 (s, 1H), 7.84, 6.09 (d, 1H, $J_{P\text{-}H}$ = 700 Hz), 7.40 (d, 1H, J = 12.68 Hz), 6.23 (t, 1H), 4.35 (m, 2H), 4.26 (m, 1H), 4.04 (m, 1H), 2.39 (m, 2H), 1.94 (s, 3H), 1.55 (s, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 163.82, 150.34, 135.33, 111.58, 85.10, 84.93, 82.30, 63.96, 60.13, 37.44, 30.42, 12.54 ppm; ESI-MS: 388(M + H)$^+$, 410(M + Na)$^+$, 426(M + K)$^+$.

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