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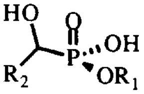
Combinatorial Method for the Synthesis of α-Hydroxy Phosphonates on Wang Resin

Xiaodong Cao and Adnan M. M. Mjalli*

Ontogen Corporation, 2325 Camino Vida Roble, Carlsbad, California 92009, U.S.A

Abstract: *An efficient synthesis of α-hydroxy phosphonates has been achieved via the reaction of polymer supported H-phosphonate ester•DBU salts with aldehydes.*

Phosphonate containing molecules show a wide range of biological activity. Examples include inhibitors of EPSP synthase,[1] HIV protease,[2] renin[3] and more recently PTPases.[4] As part of our combinatorial chemistry program, the development of an efficient method for the synthesis of α-hydroxy phosphonates of general formula **1** was initiated. The need for rapid synthesis and isolation of pure compounds prompted us to adopt a solid support methodology.



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Traditional solution phase syntheses of α-hydroxy phosphonates **1** include the reaction of a trialkylphosphite with an aldehyde in the presence of a Lewis acid[5] or, alternatively, the deprotonation of a dialkyl H-phosphonate with strong base[6] (NaH, LDA, *n*-BuLi, *etc.*) and an aldehyde. Hence, the attachment of an H-phosphonate onto Wang resin as in **4** was expected to provide a facile entry into a combinatorial library of formula **1**. This combinatorial method would have two different inputs R_1 and R_2.

Herein we report a solid phase method for the synthesis of compounds of general formula **1**. The reaction of Wang resin with 2-chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one[7] in CH_2Cl_2-pyridine provided **3** which was hydrolyzed with aqueous $NaHCO_3$-TEA[8] to give salt **4**. Polymer **4** was synthesized in multi-gram quantities and then used as a building block for the library synthesis. Reaction of polymer **4** with pivaloyl chloride provided the activated ester **5** on solid support.[9] Nucleophilic displacement of the "mixed anhydride" was achieved with a wide range of nucleophiles (e.g. R_1OH)[10] as the "first input" of the library. Reaction of the deprotonated form of **6** with a wide range of electrophiles such as aldehydes[11] provided the "second input" needed for the combinatorial approach.

Thus, the reaction of polymer **5** with a series of alcohols R_1OH provided ethers **6** which upon treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and a series of aldehydes R_2CHO, afforded the desired polymer-bound α-hydroxy phosphonates. The use of strong anionic bases and low reaction temperatures in the case of polymer supported H-phosphonates **5** was found to be unnecessary. In fact, the use of DBU provided excellent yields of the desired product **7** after 30 minutes at room temperature. Finally, treatment of polymer **7** with 10%TFA in CH_2Cl_2 provided the desired compounds **1a-i** **(Table 1).**

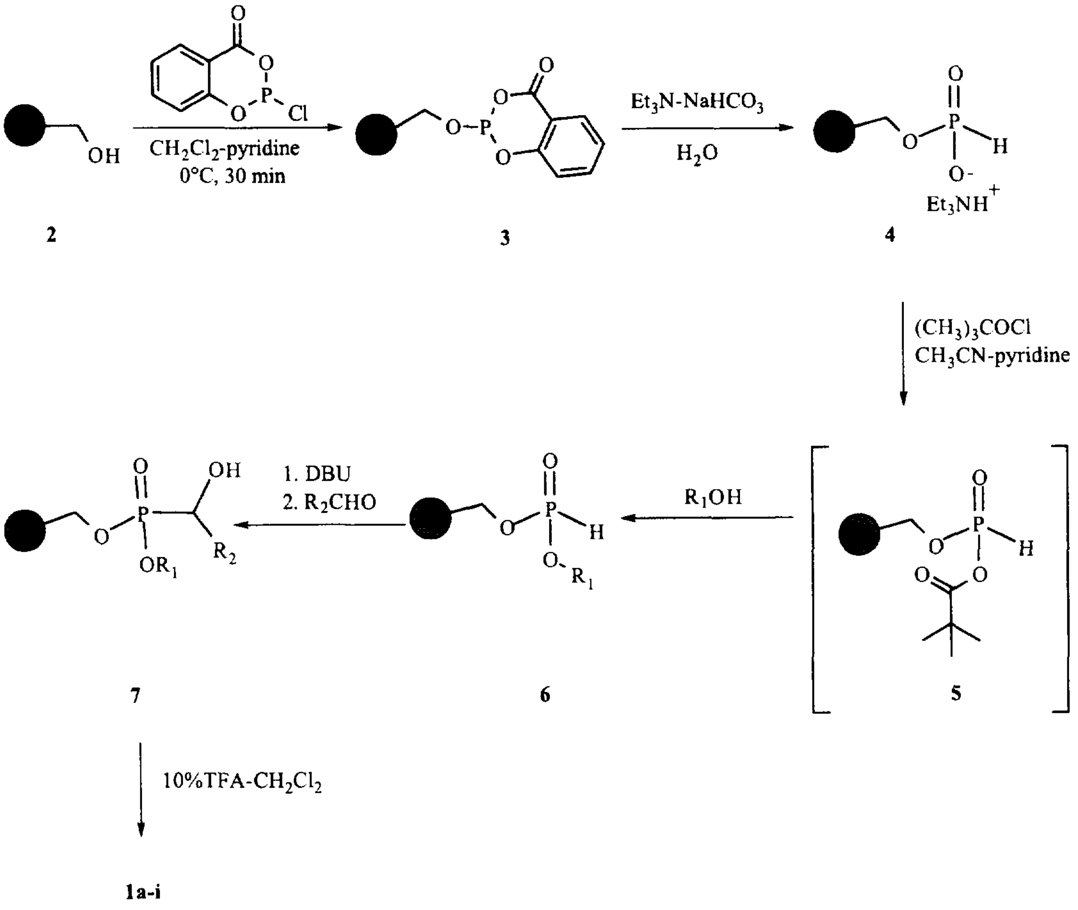

Figure 1. Solid phase synthesis of α-hydroxy phosphonates **1a-i**.

Synthesis of **4**: A 1.0M solution of 2-chloro-4*H*-1,3,2-benzo-dioxaphosphorin-4-one (267 mmol, 267 μL, 3.0 equiv.) in dry CH_2Cl_2 was added to a suspension of Wang Resin **2** (89 mmol, 100 mg, 1.0 equiv.) in dry CH_2Cl_2 (1.0 mL) and dry pyridine (0.5 mL) at 0°C. The reaction mixture was warmed to 23°C and gently stirred for an additional 30 minutes to provide **3**. Subsequently, **3** was treated with a cold solution of 1:1 Et_3N-$NaHCO_3$ in H_2O to provide the triethylammonium phosphonate polymer **4** which was filtered, washed sequentially with H_2O, CH_3CN, CH_2Cl_2 and dried *in vacuo* over P_2O_5.

Synthesis of α-hydroxy phosphonates **1**: In a typical procedure, the dry polymer **4** was treated with 1.0M solution of the alcohol (5 equiv.) in CH_3CN followed by the addition of a 1.0M solution of pivaloyl chloride (5 equiv.) in 1:1 CH_3CN-pyridine.[9] After stirring at 23°C for 15 minutes, the resulting polymer **6** was filtered, washed with dry CH_3CN and treated with a 1.0M solution of DBU in CH_3CN. The mixture was stirred at 23°C for 10 minutes, and then a 1.0M solution of the aldehyde (5 equiv.) in CH_3CN was added. After 30 minutes at 23°C, the polymer was filtered, washed with CH_3CN and CH_2Cl_2 to provide **7**. Upon treatment with 10% TFA in CH_2Cl_2 (2x1 mL, 23°C, 20 minutes) the desired α-hydroxy phosphonate **1** was obtained in good yield and in reasonable purity (> 90%) as indicated by proton NMR. The product was submitted for bioassay directly without the need for a further purification step.[12] Some of these compounds **1a-i** are purified on silica gel and shown in **Table** 1. Our study indicates that close to 30,000 possible compounds can be synthesized by this method based on commercially available aldehydes (200) and alcohols (150).

Table 1. α-Hydroxy Phosphonates **1** Synthesized on Solid Support

Entry	R_1	R_2	%Yield[a]
1a	H[b]	*p*-F-Ph	86
1b	CH_3CH_2	*p*-F-Ph	90
1c	$PhCH_2$	*n*-Pr	87
1d	$PhCH_2$	Ph	92
1e	$PhCH_2$	*p*-MeO-Ph	77
1f	$PhCH_2$	*p*-F-Ph	88
1g	$PhCH_2$	2-naphthyl	72
1h	$PhCH_2$	3-thienyl	72
1i	2-CF_3-$PhCH(CH_3)$	Ph	79

a) Yields represent the mass balance of isolated material after TFA cleavage and silica gel purification based upon the loading of the resin **4** (0.56mmol/g).

b) R_1OH is *t*-BuOH which upon treatment with TFA/CH_2Cl_2, the *t*-butyl group was cleaved.

In summary, the method described above allows for the preparation of multigram quantities of the triethylammonium salt **4** which can be used as a bifunctional phosphonate building block in order to generate a diverse library of α-hydroxy phosphonates. This methodology has been found to be useful with other nucleophiles such as thiols, amines and other electrophiles such as ketones, imines and Michael acceptors. These results will be published in due course.

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8. The stock solution was prepared by adding 1.0 mol of Et_3N and 1.0 mol of $NaHCO_3$ to 1 L of H_2O. During addition to the resin, the pH of the mixture was kept below 8.5.
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10. Acid labile alcohols such as *t*-butyl and electron rich benzyls such as 2,4-dimethoxy benzyl are cleaved during TFA treatment to provide the corresponding phosphate derivatives.
11. A wide range of aldehydes such as straight/branched aliphatics and electron rich/poor aromatics can be used in this reaction.
12. The proton NMR and the mass spectral data for compounds **1e** and **1f** are as follows: compound **1e** : ^{1}H-NMR (400MHz, *d*-acetone/10% *d*-methanol) δ 3.63 (s, 3H); 4.62 (d, 2H); 5.08 (br. 1H); 6.92-7.40 (m, 9H). MS(negion): required 308.2, found 307.1 and compound **1f**: ^{1}H-NMR (400 MHz, *d*-acetone/10% *d*-methanol) δ 4.62 (s, 2H); 5.13 (d, 1H, J = 13.2 Hz); 6.64-7.38 (m, 9H). required 295.9, found 294.7.

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