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A Combinatorial Method for the Solid Phase Synthesis of α-Amino Phosphonates and Phosphonic Acids*

Chengzhi Zhang and Adnan M. M. Mjalli*

Ontogen Corporation, 2325 Camino Vida Roble, Carlsbad CA 92009

Abstract: *Lewis acids or ultrasound catalyze the condensation of imines with Wang resin bound H-phosphonates to give high yields of the corresponding α–amino phosphonates or phosphonic acids.* Copyright © 1996 Elsevier Science Ltd

Recent synthetic and technological advances in the field of combinatorial chemistry have inspired the design of a variety of small molecule libraries on solid support.[1] High speed synthesis[2,3] of chemical libraries[1,4] promises to dramatically shorten the time required for lead discovery and optimization. In general, α-Amino phosphonates and phosphonic acids exhibit a wide range of biological activities. For example, many of these compounds are potent antibiotics[5a] and enzyme inhibitors.[5b-d] As part of our continuing effort to generate diverse chemical libraries, we now describe an efficient method for the synthesis of α-amino phosphonate and phosphonic acid derivatives on solid support via condensation of imine **4** with polymer bound H-phosphonates **3** (Figure 1).

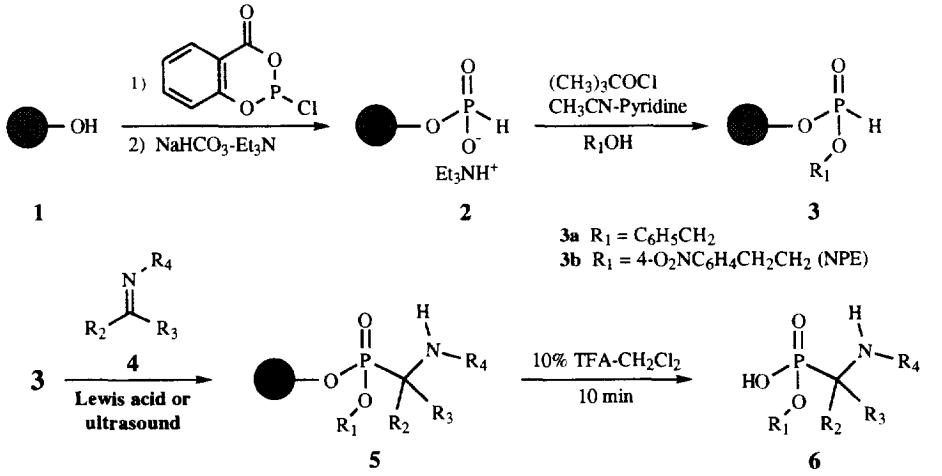


Figure 1

Treatment of Wang resin[6] (**1**) with 2-chloro-4*H*-1,3,2-benzodioxaphosphorin-4-one followed by $NaHCO_3$-TEA hydrolysis provided Wang resin bound H-phosphonate salt **2** (Figure 1).[7] Esterification of **2** with benzyl alcohol or *p*-nitrophenylethanol (NPE) (1.0 M in CH_3CN, 5.0 equiv) and pivaloyl chloride (1.0 M in 1:1 CH_3CN-pyridine, 5.0 equiv),[7] gave H-phosphonate esters **3a** and **3b** in 60% overall yield.[8] DBU or *t*-BuOK promoted condensation of H-phosphonate esters with electrophiles are well precedented.[9] However, these

conditions proved to be either inefficient or incompatible with these polymers. Since Wang resin is relatively stable to mild acidic conditions,[4a,b] we surveyed a series of Lewis acid catalysts for the condensation of resin **3** with imine **4**.[10] For example, the reaction of **3a** with imine **4a** (R_2 = 4-MeO-Ph, R_3 = H, R_4 = *n*-Bu)[11] failed to give any desired product in the presence of LiCl, $LiBF_4$, $(i\text{-PrO})_4Ti$, TMSCl and *bis*-trimethylsilylacetamide. However, $ZnCl_2$ (0.05M in THF) did catalyze the condensation of **3a** and **4a** (0.5 M in THF) to provide polymer bound α-amino phosphonate **5a**. Treatment of **5a** with 10% TFA-CH_2Cl_2 followed by preparative TLC purification provided the corresponding α-amino phosphonate **6a** in 38% yield. Further studies showed $La(OTf)_3$ and $Yb(OTf)_3$[12] to be superior to $ZnCl_2$. Under identical conditions, $La(OTf)_3$ and $Yb(OTf)_3$ provided **6a** in 58 and 86% yield respectively.

We also found that sonication[13] of resin **3a** in the presence of imine **4a** (0.5M in toluene)[11] for 3 h at 50-55°C gave a 46% yield of **6a** (Table 1, entry 1). Longer reaction times (up to 7.5 h) did not increase the product yield. Further studies revealed that after sonicating for 2.5 h and *in the absence of imine 4a*, more than 50% of the H-phosphonate ester linker was cleaved off resin **3a**. The fact that prolonged sonication time (2.5 h *vs.* 7.5 h) did not decrease the yield of the resin bound α-amino phosphonate suggested that the low yield of **6a** in the above experiments was due to decomposition of resin **3a** and not resin **5a**. Increasing the concentration of the imine from 0.5 M to 2.0 M improved the yield of **6a** to 56% (Table 1, entries 1 and 2). In both instances, the ^1H NMR spectra of crude material indicated partial loss of the benzyl group as a result of phosphonate ester cleavage during sonication. In fact, re-esterification after the sonication step improved the yields significantly (Table 1, entries 3 and 4). The choice of solvent had very little effect on the outcome of the reaction. Except for CH_3CN, sonication in 1,2-dichloroethane (1,2-DCE), toluene, THF, and DMF followed by re-esterification gave **6a** in high yield (87-90%, Table 1, entries 4 to 8).

Table 1.

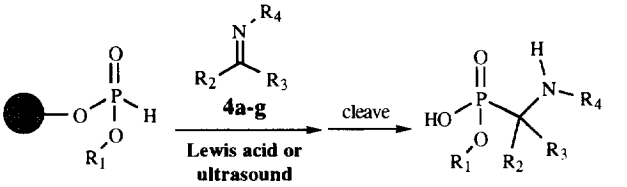
Entry	[4a]	Solvents	Method[a]	6a[b]	Entry	[4a]	Solvents	Method[a]	6a[b]
1	0.5 M	toluene	A	46%	5	2.0 M	1,2-DCE	B	87%
2	2.0 M	toluene	A	56%	6	2.0 M	CH_3CN	B	66%
3	0.5 M	toluene	B	70%	7	2.0 M	THF	B	87%
4	2.0 M	toluene	B	90%	8	2.0 M	DMF	B	90%

(a) **Method A**: resin sonicated at 50-55°C for 3 h. **Method B**: resin sonicated at 50-55°C for 3 h, filtered, washed with CH_2Cl_2, and treated with R_1OH (1.0 M in CH_3CN) and $(CH_3)_3COCl$ (1.0 M in 1:1 CH_3CN-pyridine) for 15 min. (b)Yields of preparative TLC purified material based on the loading of **3a**.

In order to determine the scope of the reaction, a series of imines (**4a-g**)[11] were screened at two different concentrations (0.5 and 2.0 M) using sonication or $Yb(OTf)_3$. The results are summarized in Table 2.[14] Both methods worked equally well at 2.0 M with yields of purified products ranging from 70 to 99%. Sonication was superior to $Yb(OTf)_3$ if imines of aniline were employed (Table 2, entries 4 to 6). On the other hand, when the amine and the aldehyde were not preincubated overnight, $Yb(OTf)_3$ gave 94% yield of the product versus a sonication yield of 37% (Table 2, entry 3). In this case, a small amount (~5%) of the corresponding α-hydroxy phosphonate was also isolated from the sonication reaction. As shown in Table 2, this method is suitable for a variety of aldehydes and amines. Preliminary results indicate that ketimines should also be good substrates under these reaction conditions (Table 2, entry 11).

Our initial attempts at synthesizing α-amino phosphonic acids directly from resin **2** were not successful. However, treatment of resin bound α-amino phosphonate **5h** (R_1 = NPE) with DBU[15] followed by TFA cleavage gave the corresponding α-amino phosphonic acid **6i** in good yield (Table 2, entry 13).

Table 2.



3a or 3b **6a-i**

Entry	6	R_1	R_2	R_3	R_4	[4] (M)	Sonication[a,b]	$Yb(OTf)_3$[a,c]
1	**6a**	Bn	4-MeO-Ph	H	n-C_4H_9	0.5	70%	86%
2	**6a**	Bn	4-MeO-Ph	H	n-C_4H_9	2.0	90%	99%
3	**6a**	Bn	4-MeO-Ph	H	n-C_4H_9	2.0[d]	37%[e]	94%
4	**6b**	Bn	4-F-Ph	H	Ph	2.0	70%	25%
5	**6c**	Bn	4-MeO-Ph	H	Ph	0.5	51%	0
6	**6c**	Bn	4-MeO-Ph	H	Ph	2.0	83%	31%
7	**6d**	Bn	Ph	H	2-F-Bn	0.5	70%	31%
8	**6d**	Bn	Ph	H	2-F-Bn	2.0	95%	88%
9	**6e**	Bn	Ph	H	Bn	2.0	92%	94%
10	**6f**	Bn	n-C_3H_7	H	4-MeO-Bn	2.0	81%	quant
11	**6g**	Bn	Ph	CH_3	n-C_4H_9	2.0	96%	quant
12	**6h**	NPE	4-MeO-Ph	H	Ph	2.0	87%	--[g]
13	**6i**	H	4-MeO-Ph	H	Ph	2.0	89%[f]	--[g]

(a) Yields of preparative TLC purified material based on the loading of **3a**. (b) Reactions run in toluene using method B in Table 1. (c) Reactions run in THF: Resin **3a** was stirred with $Yb(OTf)_3$ (0.05M) and imine at 23°C for 5 h, filtered, washed and cleaved with 10% TFA-CH_2Cl_2 (23°C, 10 min.). (d) Aldehyde and amine were not preincubated. (e) 5% of α-hydroxy phosphonate was also isolated. (f) Resin **5** was treated with DBU (1.0 M in CH_3CN, 1 h) before cleavage. (g) Reaction not done.

In summary, we have developed a versatile three input combinatorial method for the synthesis of α-amino phosphonates and phosphonic acids on solid support. Either $Yb(OTf)_3$ catalysis or sonication provided the desired products in high yield and purity. The two methods are complementary and allow direct access to a highly diverse library of α-amino phosphonates and phosphonic acids.

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≠ Part of the present work was presented at the Western Biotechnology Conference (31st Annual American Chemical Society, Western Regional Meeting), San Diego, CA; October **1995**, presentation #105.

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14. All compounds gave satisfactory ^{1}H NMR and mass spectral data. Compound **6a**: ^{1}H NMR (400 MHz, CD_3OD) δ 0.84 (t, J = 7.2 Hz, 3 H), 1.24 (m, 2 H), 1.48-1.68 (m, 2 H), 2.78-2.84 (m, 1 H), 2.90-2.98 (m, 1 H), 3.76 (s, 3 H), 4.16 (d, *J* = 15.6 Hz, 1 H), 4.62-4.77 (m, 2 H), 6.91 (d, J = 8.0 Hz, 2 H), 7.18-7.29 (m, *J* = 6.0 Hz, 5 H), 7.43 (d, J= 8.0 Hz, 2 H); ESIMS, *m/z* for $C_{19}H_{26}O_4PN$ $[M-H]^-$: 362.
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