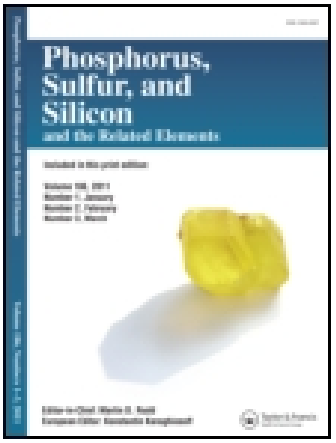

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The First Mitsunobu Protocol for Efficient Synthesis of α-Acyloxyphosphonates Using 4,4′-Azopyridine

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THE FIRST MITSUNOBU PROTOCOL FOR EFFICIENT SYNTHESIS OF α-ACYLOXYPHOSPHONATES USING 4,4′-AZOPYRIDINE

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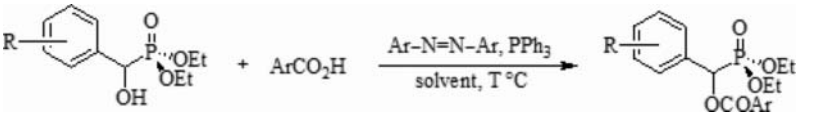
GRAPHICAL ABSTRACT



Abstract *This is the first report on applying the Mitsunobu protocol for the synthesis of various α-acyloxyphosphonates using 4,4′-azopyridine and PPh_3 with diverse aromatic and aliphatic carboxylic acids. Under these conditions, diethyl azodicarboxylate (DEAD) as the traditional reagent for Mitsunobu reaction is not efficient. The insoluble pyridine hydrazine byproduct can be simply isolated and recycled to its azopyridine by an oxidation reaction and reused again.*

[Supplemental materials are available for this article. Go to the publisher's online edition of Phosphorus, Sulfur, and Silicon and the Related Elements *for the following free supplemental resource*: *Characterization data of compounds 3a–3z2 and NMR spectra.]*

Keywords Mitsunobu reaction; esterification; α-hydroxyphosphonates; α-acyloxyphosphonates; azopyridine

INTRODUCTION

Organophosphorus compounds have found diverse applications in organic and inorganic chemistry.[1] Among these, α-acyloxyphosphonates are considered as pivotal and precious phosphorus compounds for the synthesis of optically active α-hydroxyphosphonates. α-hydroxyphosphonates are important compounds and some of them have been shown to possess enzyme inhibitor activity[2] such as inhibitor of renin,[3] human immunodeficiency virus (HIV) protease, and polymerase.[4] They also show anticancer[5] and antiviral[6] activities. In addition, α-hydroxyphosphonates are useful precursors for the preparation of α-functionalized phosphonates, such as amino, keto, and halophosphonates.[7–9] Biocatalysts such as enzymatic systems have been introduced for the enantioselective hydrolysis of racemic α-acyloxyphosphonates.[10] Surprisingly, given the extensive use of α-functionalized phosphonates in biological systems and organic synthesis, there are only

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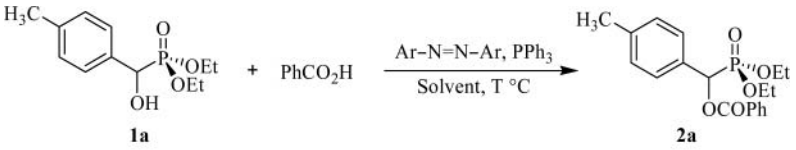
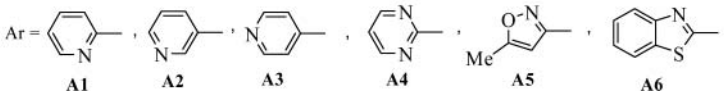
a few reports on the synthesis of α-acyloxyphosphonates in the literature. In an earlier report, Shingare and coworkers[11] have synthesized new α-acetoxyphosphonate derivatives of tetrazolo [1,5-a] quinoline using Ac_2O/DBU at room temperature and their antimicrobial activities were evaluated. In a reaction reported by Hammerschmidt, various α- and β-acyloxyphosphonates were synthesized by hydrolases with isopropenyl acetate as acyl donor in organic solvents.[12] Reaction of α-hydroxyphosphonates with Ac_2O under microwave irradiation,[13] aldehydes and ketones with acyl phosphites,[14] direct acetylation of α-hydroxyphosphonates with ketene catalyzed by $BF_3{\cdot}OEt_2$[15] or H_2SO_4,[16] and using of enzymatic systems[17] to preparation of α-acylphosphonates are the other reported procedures. Although the Mitsunobu reaction using diethyl azodicarboxylate (DEAD) and PPh_3 has been widely used for the acylation of alcohols, this potentially useful method has not been applied to α-hydroxyphosphonates.[18] Recently, we have reported efficient esterification of alcohols using 4,4′-azopyridine[19] and 5,5′-dimethyl-3,3′-azoisoxazole[20] as good alternatives for the traditional DEAD in Mitsunobu reaction. With the good results obtained by this protocol in mind and continuing our pursuit in transformation of α-hydroxyphosphonates to other derivatives,[21] we have decided to exploit the scope of this method for the synthesis of the α-acyloxyphosphonates.

RESULTS AND DISCUSSION

α-hydroxyphosphonates were synthesized according to the literature[22] and subjected to the Mitsunobu esterification with acids using different heterocyclic azo compounds (**A1**–**A6**) as well as DEAD and PPh_3. With the use of a model reaction based on diethyl α-hydroxy-4-methylbenzylphosphonate (**1a**) and benzoic acid, some different conditions have been screened. Among the studied azo reagents **A1**–**A6**, 4–4′-azopyridine (**A3**) was found to be the most efficient one for this reaction. Surprisingly, the use of DEAD and

Table 1 Optimization of conditions



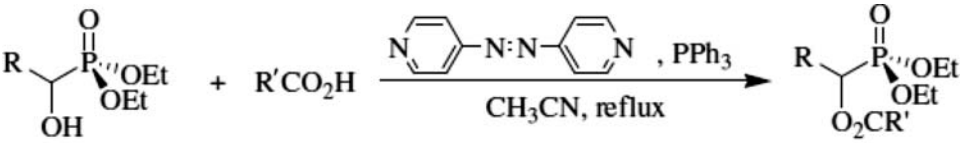


Entry	Azo (Solvent, T)	Time (h)	Yield of **2a** (%)
1	**A1** (CH_3CN, reflux)	17	55
2	**A2** (CH_3CN, reflux)	24	28
3	**A3** (CH_3CN, reflux)	12	82
4	**A3** (CH_3CN, r.t)	48	N.R
5	**A4** (CH_3CN, reflux)	72	N.R
6	**A5** (CH_3CN, reflux)	72	N.R
7	**A6** (CH_3CN, reflux)	72	N.R
8	DEAD (CH_3CN, reflux)	24	40
9	DIAD (CH_3CN, reflux)	24	34

DIAD was not suitable, and under similar reaction conditions, only 40% and 34% of **2a** were obtained, respectively (Table 1, entries 8 and 9). The results of the optimization are shown in Table 1.

Among the various solvents such as CH_2Cl_2, $CHCl_3$, THF, 1,4-dioxane, DMF, and acetone that were evaluated, refluxing CH_3CN gave the best results. Finally, the optimized mole ratio of the reactants was found to be: α-hydroxyphosphonate (2 equiv.): acid (1.3 equiv.): azo (1.8 equiv.): PPh_3 (1.8 equiv.). With the optimized reaction conditions in hand, the scope of the esterification of α-hydroxyphosphonates with different carboxylic acids was investigated. The results are summarized in Table 2.

Table 2 Conversion of α-hydroxyphosphonates **1a–d** to corresponding esters **3a–3z2** using **A3** and PPh_3[a]



1a–d **3a–3z2**

Entry	R	R′	Product	Time (h)	Yield (%)[b]
1	4-CH_3-C_6H_4-(**1a**)	4-NO_2-C_6H_4-(**2a**)	**3a**	9	88
2	4-CH_3-C_6H_4-	C_6H_5-(**2b**)	**3b**	12	82[23a]
3	4-CH_3-C_6H_4-	4-CH_3-C_6H_4-(**2c**)	**3c**	15	76
4	4-CH_3-C_6H_4-	2-Cl-C_6H_4-(**2d**)	**3d**	15	79
5	4-CH_3-C_6H_4-	3-Cl-C_6H_4-(**2e**)	**3e**	12	83
6	4-CH_3-C_6H_4-	4-Cl-C_6H_4-(**2f**)	**3f**	12	85
7	4-CH_3-C_6H_4-	CH_3CH=CH-(**2g**)	**3g**	14	77
8	C_6H_5-(**1b**)	4-NO_2-C_6H_4-(**2a**)	**3h**	10	83
9	C_6H_5-	C_6H_5-(**2b**)	**3i**	12	80[23a]
10	C_6H_5-	4-CH_3-C_6H_4-(**2c**)	**3j**	15	71[23b]
11	C_6H_5-	2-Cl-C_6H_4-(**2d**)	**3k**	15	75
12	C_6H_5-	3-Cl-C_6H_4-(**2e**)	**3l**	12	84
13	C_6H_5-	4-Cl-C_6H_4-(**2f**)	**3m**	12	85[23b]
14	C_6H_5-	CH_3CH_2-(**2h**)	**3n**	15	75
15	2,6-di-Cl-C_6H_3-(**1c**)	4-NO_2-C_6H_4-(**2a**)	**3o**	18	74
16	2,6-di-Cl-C_6H_3-	4-CH_3-C_6H_4-(**2c**)	**3p**	24	65
17	2,6-di-Cl-C_6H_3-	2-Cl-C_6H_4-(**2d**)	**3q**	24	72
18	2,6-di-Cl-C_6H_3-	3-Cl-C_6H_4-(**2e**)	**3r**	18	75
19	2,6-di-Cl-C_6H_3-	4-Cl-C_6H_4-(**2f**)	**3s**	18	78
20	2,6-di-Cl-C_6H_3-	CH_3CH=CH-(**2g**)	**3t**	24	69
21	4-Cl-C_6H_4-(**1d**)	4-NO_2-C_6H_4-(**2a**)	**3u**	12	76
22	4-Cl-C_6H_4-	C_6H_5-(**2b**)	**3v**	14	77[23a]
23	4-Cl-C_6H_4-	4-CH_3-C_6H_4-(**2c**)	**3w**	15	73
24	4-Cl-C_6H_4-	2-Cl-C_6H_4-(**2d**)	**3x**	15	77
25	4-Cl-C_6H_4-	3-Cl-C_6H_4-(**2e**)	**3y**	12	74
26	4-Cl-C_6H_4-	4-Cl-C_6H_4-(**2f**)	**3z**	12	79
27	4-Cl-C_6H_4-	CH_3CH=CH-(**2g**)	**3z1**	16	69
28	4-Cl-C_6H_4-	CH_3CH_2-(**2h**)	**3z2**	16	71

[a]Reaction conditions: **1** (2.0 mmol), acid (1.3 mmol), **A3** (1.8 mmol), PPh_3 (1.8 mmol) in acetonitrile (4 mL) at 80°C. [b]Isolated yields.

Substrates with either electron-donating or electron-withdrawing groups on the phenyl group of α-hydroxyphosphonate could be applied in this transformation. For example, diethyl α-hydroxy-4-methylbenzylphosphonate **1a** was examined as a substrate and it was found that the reaction of **1a** with various acids proceeded smoothly in good yields. In the cases of carboxylic acids **2a** and **2d**–**f** having $–NO_2$ and or –Cl substitutents, the reactions proceeded more cleanly and smoothly, affording the corresponding products **3a**, **3d**–**f** in higher yields (79%–88%) (Table 2, entries 1, 4–6). However, if an electron-donating group such as –Me was introduced on the benzene ring of the acid, the yield of **3c** decreased to 76% (Table 2, entry 3). Also, unsaturated and saturated aliphatic carboxylic acids such as crotonic and propionic acids **2g**, **h** were used in this reaction (Table 2, entries 7, 14, 20, 27, and 28). A key benefit associated with the use of 4,4′-azopyridine in the synthesis of α-acyloxyphosphonates is not only its ease of preparation but also its capacity to remove its hydrazine byproduct from the reaction mixture by simple filtration. In addition, the produced hydrazine byproduct can be simply recycled to its azo compound by oxidation with iodosobenzene diacetate in DMSO.[18]

CONCLUSION

This report describes the first application of the Mitsunobu method using 4,4′-azopyridine and PPh_3 for the efficient synthesis of various α-acyloxyphosphonates. The method is general and can be applied to wide range of aliphatic and aromatic carboxylic acids and also varieties of α-hydroxyphosphonates. Advantages of using 4,4′-azopyridine as an easily prepared azo reagent are (a) its more efficiency compared to DEAD and DIAD; (b) simplicity in separation of its hydrazine byproduct; and (c) its easy recyclability for further use.

EXPERIMENTAL SECTION

Typical procedure for conversion of 4-methylbenzaldehyde to its corresponding α-hydroxyphosphonate[22]: To a mixture of 4-methylbenzaldehyde (1.20 g, 10 mmol) and diethyl phosphite (1.3 mL, 10 mmol), CaO (560 mg, 10 mmol) was added. The reaction mixture was stirred at room temperature. After 30 min, a bulk white solid was obtained. EtOAc (10 mL) was then added to the reaction mixture, and the mixture was stirred for 30 min at room temperature. The obtained solution was filtered and the filtrate was evaporated. Purification of the crude product was achieved by crystallization using EtOAc/petroleum ether (3/7). The corresponding α-hydroxyphosphonate was obtained in 91% yield (235 mg).

Acylation of α-hydroxy-4-methylbenzylphosphonate using 4,4′-azopyridine in modified Mitsunobu protocol as a typical procedure: Triphenylphosphine (0.47 g, 1.8 mmol) was added to a solution of 4,4′-azopyridine (0.32 g, 1.5 mmol) and 4-nitrobenzoic acid (0.22 g, 1.3 mmol) in refluxing acetonitrile (5 mL), and the solution was stirred to dissolve the solids. Then, α-hydroxy-4-methylbenzylphosphonate (0.516 g, 2 mmol) was added. The resulting solution was stirred at 80°C (reflux) for 9 h. After the reaction was filtered off to remove the produced pyridine hydrazine (262 mg, isolated yield: 81%), the solvent was removed in vacuo. The so-formed α-(4-nitrobenzoate)-4-methylbenzylphosphonate was isolated by chromatography on a short column of silica gel (*n*-hexane:ethyl acetate = 2:1) in 88% yield (716 mg).

The Supplemental Materials contain the complete ^{1}H and ^{13}C NMR data for **3a–3z2**, in addition to elemental analysis information and sample NMR spectra.

Oxidation of 4,4′-pyridinehydrazine to 4,4′-azopyridine by iodosobenzene diacetate PhI(OAc)$_2$: Iodosobenzene diacetate (0.322 g, 1.0 mmol) was added in one portion to a stirred solution of 4,4′-pyridinehydrazine (0.186 g, 1.0 mmol) in 7 mL of DMSO and the reaction mixture was stirred at room temperature for 6 h. H_2O (20 mL) was then added and the reaction solution was extracted with EtOAc (3 × 20 mL). The organic extracts were combined together and dried over anhydrous $MgSO_4$. Upon concentrating the solution under vacuum, 4,4′-azopyridine **A3** was precipitated as orange crystals (127 mg, 69%).

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