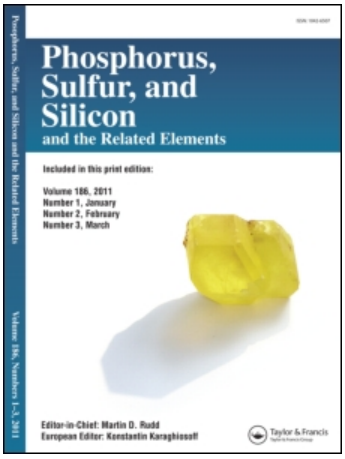

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Synthesis of α-Hydroxy Phosphonates Using a Solid Supported Base

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SYNTHESIS OF α-HYDROXY PHOSPHONATES USING A SOLID SUPPORTED BASE

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A mild, efficient synthesis of α-hydroxy phosphonates is described where a quaternary ammonium hydroxide ion exchange resin is used as a base to promote the addition of diethyl phosphite to aryl aldehydes for a Pudikov type reaction.

Keywords: α-hydroxy phosphonate; ion exchange resin; quaternary ammonium hydroxide; diethyl phosphite

INTRODUCTION

α-Hydroxy phosphonates[1–3] are of synthetic interest because they are precursors to α-hydroxy phosphonic acids which have demonstrated biological activity. In particular, α-hydroxy phosphonic acids and derivatives are inhibitors of enzymes such as HIV protease[4], renin[5], EPSP synthase[6], a tyrosine-specific protein kinase[7], insulin receptor tyrosine kinase[8], and other proteases[9]. The use of reagents supported on solid surfaces, such as alumina[10], alumina/potassium fluoride[11], and polymer-supported 1,5,7-triazabicyclo-[4.4.0]dec-5-ene (TBD)[12] for the synthesis of the α-hydroxy phosphonates has been reported as effective procedures for the synthesis of α-hydroxy phosphonates[13]. We report here a new, easy and effective method for the synthesis of α-hydroxy phosphonates (**1**, Scheme) in good

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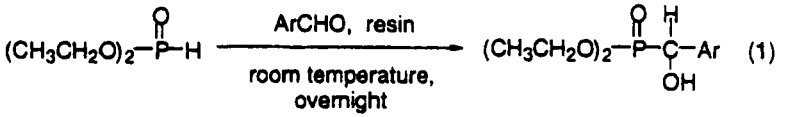
yields using diethyl phosphite, an aryl aldehyde and a solid supported base without the use of solvent.



SCHEME

RESULTS AND DISCUSSION

In our efforts to develop new methods for preparing α-hydroxy phosphonates, we examined the use of solid potassium carbonate as a base under microwave oven conditions; however, this method gave capricious results. In searching for milder reaction conditions and an alternate base, we employed a polystyrene tetraalkylammonium hydroxide ion exchange resin [Rexyn® 201(OH)] as a solid supported base for this reaction. The reaction setup was straightforward and required only that the resin, phosphite, and aldehyde be stirred together overnight at room temperature followed by simple purification to give good yields of products (Table I). No solvent was used in the reaction setup, and the reaction outcome was not adversely affected. The phosphite, aided by sufficient stirring, appeared to adequately dissolve the solid aldehydes (entries 8, 10) for complete reaction. In some cases (entries 1, 2, 4–6), the reaction product solidified after a period of time without loss in yield as compared to ones that did not solidify. After stirring for approximately 24 hours, the reaction mixture was diluted with methylene chloride, followed by simple filtration to remove the resin, and then concentrated under vacuum. NMR (^{1}H and ^{31}P) analysis of unpurified material indicated relatively clean products, showing product and trace amounts of starting materials with no discernible by-products. Purification of the α-hydroxy phosphonate products was straightforward. The compounds solidified after concentration or by a cooling the sample in pentane with a dry ice/acetone bath. The solid product could be recrystallized or simply washed with pentane to remove residual starting materials and filtered by vacuum to give pure product. In the case of an oil (entry 7), it was purified by Kugelrohr distillation. Currently

this method has been performed on 1 and 5 mmol scales (entries 1 vs. 2 and 5 vs. 6) to prepare α-hydroxy phosphonates. All compounds were characterized by ^{1}H, ^{13}C and ^{31}P NMR, and melting point and compared to available literature data.

The use of a basic ion exchange resin to promote the phosphite addition to a variety of aryl aldehydes (Pudikov reaction) appears to be an effective means for the synthesis of α-hydroxy phosphonates that is comparable to existing methods. Advantages to this method include: 1) simple reaction setup, work-up and purification, 2) no reaction solvent employed (greener chemistry), 3) technical grade phosphite used, 4) mild reaction conditions (reaction run at ambient temperature), 5) good yields (64–89%) without by-products, and 6) potential application in combinatorial synthesis.

TABLE I α-Hydroxy phosphonates (**1**) synthesized according to the Scheme[1-4]

Entry	*ArCHO (Ar)*	*Yield[a,b]* (%)	*^{31}P NMR[c]*	*Melting Point (°C)[d,e]*
1	C_6H_5-	76	22.0	81–82 (78–80)
2		82[f]	22.0	81–82 (78–80)
3		0[g]		
4	*p*-MeC_6H_4-	89	22.1	99–101 (98–100)
5	*p*-$MeOC_6H_4$-	73	22.2	121–122 (118–120)
6		74[f]	21.9	121–122 (118–120)
7	*m*-$MeOC_6H_4$-	64	21.9	Oil[h]
8	*p*-ClC_6H_4-	78[i]	21.4	69–72 (70–72)
9	*o*-ClC_6H_4-	87	21.6	75.5–77 (76–78)
10	*p*-$NO_2C_6H_4$-	69[j]	20.2	88–90 (82–84)

a. Based on purified material using pentane wash method unless otherwise noted; reaction conditions are not necessarily optimized.
b. 1 mmol reaction scale unless otherwise noted.
c. 85% H_3PO_4 external reference; at 121.4 Hz (300 MHz NMR) in $CDCl_3$.
d. Uncorrected.
e. Literature MP data (in parentheses) taken from Reference 2b.
f. 5 mmol reaction scale.
g. Control, no resin used.
h. Kugelrohr distillation at 107–158°C at 0.68–0.70 mm Hg.
i. Recrystallized from cyclohexane.
j. Recrystallized from cyclohexane and ethyl acetate.

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(d) See reference 2c for the use of solid K_2CO_3 in ethanol.

[14] A typical experiment: The resin [101 mg, Rexyn® 201 (OH), Fisher Scientific] was added to a round bottomed flask with a stirring bar and fitted with a rubber septum. Diethyl phosphite (0.14 mL, 1 mmol, 94%, technical grade) was added, followed by tolualdehyde (0.12 mL, 1 mmol), by syringe. The mixture was stirred at room temperature under argon for 24 hours. The mixture was diluted with CH_2Cl_2, filtered through a cotton plug, and concentrated under reduced vacuum. Upon solidification, the product was washed with pentane, isolated by vacuum filtration and further dried under reduced pressure to afford the phosphonate (230 mg, 89%) as a white solid: mp 99–101 °C (lit. 98–100[2b]); IR (neat solid/ATR) 3247, 1228, 1205, 1052, 1018, 960, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36 (dd, 2H, J = 9.0, 2.1), 7.17 (d, 2H, J = 7.2), 4.97 (d, 1H, J = 10.5), 4.12–3.90 (m, 4H), 3.02 (br s, 1H), 2.35 (d, 3H, J = 2.1), 1.27 (t, 3H, J = 7.0), 1.22 (t, 3H, J = 6.9); ^{13}C NMR (75.4 MHz) δ 16.4 (d, J_{CP} = 2.3), 16.5 (d, J_{CP} = 2.9), 21.3, 63.0 (d, J_{CP}= 7.5), 63.3 (d, J_{CP} = 6.9), 70.7 (d, J_{CP} = 159.0), 126.9 (d, J_{CP} = 5.7), 128.9 (d, J_{CP} = 2.9), 133.2, 137.8 (d, J_{CP} = 2.9); ^{31}P NMR (121.4 MHz) δ 22.1.