Selective Preparation of (*E*)-3-Oxo-1-alkenylphosphonates by Insertion of Acyl Chlorides and Nitriles into Zirconacycles

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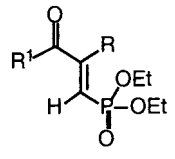
Received December 23, 2001

Zirconacycles **1**, obtained from diethyl 1-alkynylphosphonates, insert either acyl chlorides or nitriles to provide, after acidic workup, (*E*)-3-oxo-1-alkenylphosphonates, **2**, in isolated yields of 55−83%. Insertion produces only one regio- and stereoisomer. The reaction is quite general and proceeds well with both aliphatic and aromatic acyl chlorides. Acetonitrile and *p*-methoxybenzonitrile also inserted efficiently. Insertion of isobutyl chloroformate produced the vinylphosphonocarboxylate, **2c,** the first representative of this class of compounds.

While the synthesis,[1] chemistry,[2] and applications[3] of vinylphosphonates has been and is currently being amply explored, a potentially very interesting group of compounds, 3-oxo-1-alkenylphosphonates, **2**, has received



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much less attention. This is somewhat surprising, since it has been shown that compounds **2** are potentially very attractive synthetic intermediates. For instance, they readily undergo Diels−Alder reactions.[4] They have been used in the synthesis of thiazolehydroxyphosphonates and other heterocycles.[5] Enantioselective reduction of **2** by baker's yeast provided 3-hydroxy-1-alkenylphosphonates with up to 95% ee.[7] The latter compounds have been found useful in the synthesis of biologically active compounds.[8] However, the preparation of **2** is restricted

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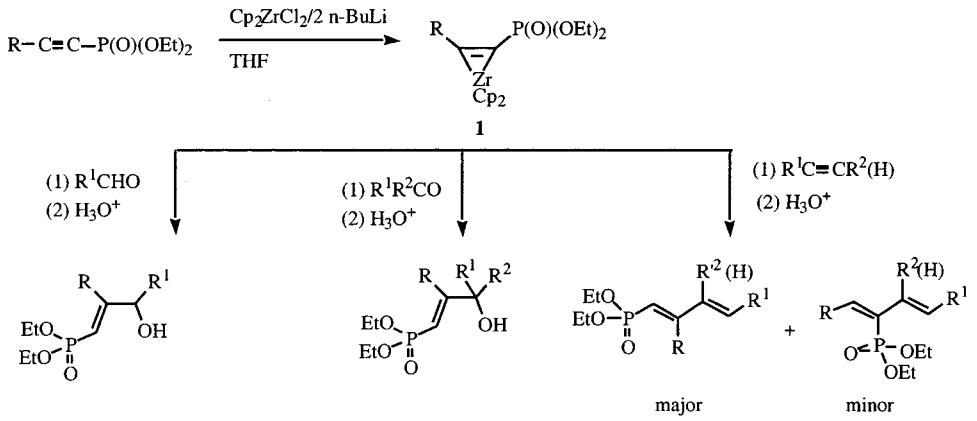
10.1021/jo016403e CCC: $22.00
Published on Web 05/01/2002

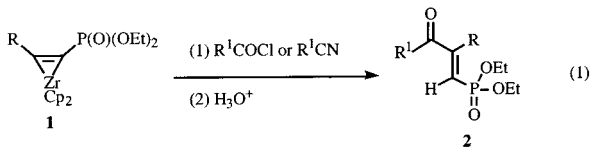
Scheme 1



to several procedures that provide access to a limited number of structures. Compounds **2** were initially prepared as mixtures in low yield by Michaelis−Arbusov or Michaelis−Becker reactions of 2-chlorovinyl ketones.[9] McClure prepared one derivative of **2** (R=CH_3, R^1=H,) by reacting NBS with 2,2,2-triethoxy-1,2λ^5-oxaphospholene.[10] Maffei[7] prepared cyclic dialkyl(3-oxo-1-alkenylphosphonates) by oxidation of the corresponding hydroxyl derivatives according to Ölher's method.[11] Thus, though proven to be useful, no general synthesis of substituted **2** has been reported to date.

We have recently been investigating the formation of zirconacycles from 1-alkynylphosphonates.[12] We have shown that the three-membered zirconacycles, **1**, obtained from 1-alkynylphosphonates and Negishi's reagent, Cp_2ZrCl_2/2-*n*-BuLi,[13] react with alkynes,[14] ketones,[15] and aldehydes[16] to produce substituted vinylphosphonates in a highly stereo- and regioselective manner (Scheme 1).

In continuation of our studies of insertion reactions of 1, we now report on the reaction of **1** with acyl chlorides and nitriles to provide in high yield the title compounds, **2** (eq 1).



(1)

The acyl chlorides and nitriles were freshly distilled or recrystallized before use, and 10% excess was introduced to the reaction in order to reach the maximum conversion. The reaction was general and proceeded with aromatic and aliphatic nitriles (Table 1). Also, satisfactory results were obtained with aliphatic, substituted, and nonsubstituted aromatic acyl chlorides. Addition of 7 mol % of $CuBr{\cdot}SMe_2$ was necessary for the reactions of acyl chlorides to proceed.[17] In the absence of the above catalyst, only 5% of (*E*)-3-oxo-1-alkenylphosphonates was produced, the major products being *cis*-alkenylphosphonates, i.e., only reduction of the triple bond occurred. Unlike the acyl chlorides reactions, the reaction with nitriles proceeded smoothly in the absence of a catalyst.[18]

Table 1. (*E*) 3-Oxo-1-alkenylphosphonates Obtained by Insertion of Acyl Chlorides and Nitriles into Zirconacycles

entry	R	R_1	yield, % isolated (^{31}P NMR)[c]
2a	*n*-Bu	Et[a]	78 (95)
2b	*n*-Bu	*t*-Bu[a]	81 (97)
2c	*n*-Bu	*i*-BuO[a]	83 (97)
2d	*n*-Bu	Ph[a]	65 (91)
2e	*n*-Bu	2-FC_6H_4[a]	60 (85)
2f	*n*-Bu	C_6H_5CH=CH[a]	60 (87)
2g	*n*-Bu	Np[a]	55 (85)
2h	*n*-Bu	4-$MeOC_6H_4$[b]	70 (94)
2i	Ph	CH_3[a]	65 (91)
2j	Ph	CH_3[b]	68 (93)

[a] Obtained from the acyl chloride. [b] Obtained from the nitrile. [c] Conversion % estimated by ^{31}P NMR of the reaction mixture.

The conversion of starting materials was followed by ^{31}P NMR of the reaction mixture. The starting alkynylphosphonates absorb at ca. −6 ppm.[19] These were not expected to be recovered since hydrolysis of the zirconacycles **1** produces 1-alkenylphosphonates, which absorb at ∼17.2 ppm[1g] if no coupling with acyl chlorides or nitriles occurred. In the reaction of 2-naphthanoyl chloride and cinnamoyl chloride (Table 1, entries g and f, respectively) lower yields were obtained compared to the other acyl chlorides and nitriles, apparently due to sterics. Reaction of **1** with isobutyl chloroformate (Table 1, entry c) is particularly interesting. The vinylphosphonocarboxylate, **2c**, was obtained (eq 2). Compounds of this kind have not been previously reported.[20]

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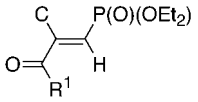
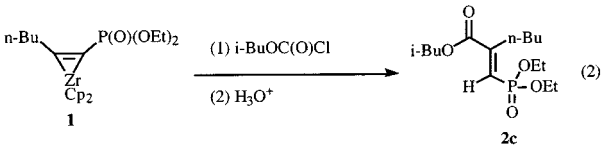
Table 2. Selected NMR Data for Compounds 2



	$^3J_{PC}$ (Hz)				
entry	allylic carbon	carbonyl carbon	^{31}P NMR δ ppm	$^2J_{PH}$ (Hz)	^{1}H NMR, C1 δ ppm
2a	7.7	23.8	18.81	18.6	5.31
2b	7.7	23.8	15.86	15.6	5.38
2c	6.0	29.5	15.51	16.5	6.48
2d	6.3	21.8	15.51	16.2	5.83
2e	6.3	20.8	16.2	15.4	5.98
2f	6.3	21.6	16.86	17.7	5.70
2g	6.3	20.8	15.41	16.2	5.98
2h	6.8	26.3	15.65	16.5	5.76
2i	7.4	22.7	14.24	15.6	6.65



The (*E*)-3-oxo-1-alkenylphosphonates are stable oils. The purification of the products was achieved by silica gel chromatography, and satisfactory spectral and analytical results were obtained.

The reaction of both acyl chlorides and nitriles produced only one isomer, with coupling taking place on C2. This regioselectivity was determined by the ^{1}H NMR spectroscopy. The doublet in the region 5.3−6.7 ppm (Table 2), due to phosphorus splitting of the vinylic hydrogen on C1 ($^2J_{PH}$ = 5.3−6.6 Hz), is diagnostic of coupling occurring on C2. No coupling on C1 was observed, otherwise a doublet of triplets in the double bond region would have been observed. This regioselectivity is apparently due to steric factors. The stereochemistry of the double bond was determined by carbon phosphorus coupling constants. The large $^3J_{PC}$ coupling constants of the carbonyl carbon (20.8−29.5 ppm, Table 2) are consistent with a trans configuration of the substituent with respect to phosphorus, whereas the small $^3J_{PC}$ of the allylic carbon (6.0−7.5 ppm) indicates that the allylic carbon is in the cis position to phosphorus. Thus, only (*E*)-3-oxo-1-alkenylphosphonates were produced. The ^{31}P NMR absorption of products **2** was in the region (18.8−14.2 ppm) that is (ca. 1−5 ppm) upfield compared to the reactions of the zirconacycle **1** with aldehydes[16] and ketones.[15]

This one-pot, direct, and selective synthesis of compounds **2** is superior to other methods. First, the other methods have not been shown to be general, and the yields are variable, generally low, and accompanied by many side products. Second, the reaction works equally well with either acyl chlorides or nitriles, with the use of one or the other, depending on which is more readily available, making available novel ketones and esters.

Experimental Section

All reactions were carried out under dry conditions in a nitrogen atmosphere using vacuum line and glovebox techniques. Staring materials were purchased from commercial suppliers and used without further purification. GCMS spectra were obtained in EI mode on a 30 m methylsilicone column.

General Procedure for Acyl Chlorides. To 0.292 g (1 mmol) of zirconocene dichloride dissolved in 5 mL of dry THF at −78 °C was added 1.25 mL of 1.6 M *n*-BuLi (2 mmol) dropwise in a 25 mL round-bottom flask. After stirring for 3 h at −78 °C, 0.39 g (0.9 mmol) of 1-hexynylphosphonate was added, and the mixture was warmed gradually to room temperature and stirred overnight, after which 7 mol % CuBr·SMe_2 was added, followed by 1.1 mmol of freshly distilled acyl chloride, and the mixture was stirred for additional 24 h. The reaction mixture was worked up with diluted HCl, and the product was extracted with ether (2 × 15 mL), separated on a silica gel column (85% petroleum ether:15% ethyl acetate), and analyzed by NMR spectroscopy.

General Procedure for Nitriles. To 0.292 g (1 mmol) of zirconocene dichloride dissolved in 5 mL of dry THF at −78 °C was added 1.25 mL of 1.6 M *n*-BuLi (2 mmol) dropwise into a 25 mL round-bottom flask. After stirring for 3 h at −78 °C, 0.39 g (0.9 mmol) of 1-alkynylphosphonate was added and the mixture was warmed gradually to room temperature and stirred overnight. Then 1.1 mmol of freshly distilled nitrile was added and the mixture was stirred for additional 24 h. The reaction mixture was worked up with diluted HCl, and the product was extracted with ether (2 × 15 mL), separated on a silica gel column (85% petroleum ether: 15% ethyl acetate), and analyzed by NMR spectroscopy.

2a: Obtained from propionyl chloride. ^{1}H NMR (300 MHz): δ 0.89 (t, 6H, J_{HH} = 8.5 Hz), 0.90 (t, 3 H, J_{HH} = 8.6 Hz), 1.29 (t, 6H, J_{HH} = 7.1 Hz), 1.12−1.58 (overlap, 4H), 2.12 (t, 2H), 2.45 (m, 2H), 4.02 (m, 4H), 5.31 (d, 1H, $^2J_{PH}$ =18.6 Hz). ^{31}P NMR (121 MHz): δ 18.81. ^{13}C NMR (75.5 MHz): δ 211.9 (d, $^3J_{pc}$ = 23.8 Hz, trans), 162.8 (d, $^2J_{pc}$ = 4.1 Hz), 114.5 (d, $^1J_{pc}$ = 186.6 Hz), 61.4 (d, $^2J_{pc}$ = 5.7 Hz), 31.4 (d, $^3J_{PC}$ = 7.7 Hz), 30.7, 22.3, 16.1 (d, $^3J_{pc}$ = 6.3 Hz), 13.8. MS (EI): *m*/*z* (%) 276 (15.7), 247(47.1), 219 (18.1), 205 (14.2), 192 (53.9), 138 (18.6), 110 (17.6), 81 (35.3), 67 (22.5), 55 (23.5), 28 (54.9), 18 (100). Anal. Calcd for $C_{13}H_{25}O_4P$: C, 56.19; H, 9.12; P, 11.21. Found: C, 56.47; H, 9.03; P, 11.30.

2b: Obtained from pivaloyl choride. ^{1}H NMR (300 MHz): δ 0.71 (t, 6H, J_{HH} = 8.6 Hz), 1.08 (s, 9H), 1.29 (t, 6H, J_{HH} = 7.2 Hz), 1.15−1.50 (overlap, 4H), 2.57 (m, 2H), 3.95 (m, 4H), 5.38 (d, 1H, $^2J_{PH}$ = 15.6 Hz). ^{31}P NMR (300 MHz): δ 15.21. ^{13}C NMR (75.5 MHz): δ 211.9 (d, $^3J_{pc}$ = 23.8 Hz, trans), 162.9 (d, $^2J_{pc}$ = 4.1 Hz), 114.5 (d, $^1J_{pc}$ = 186.6 Hz), 61.4 (d, $^2J_{pc}$ = 5.7 Hz), 31.4 (d, $^3J_{PC}$ = 7.7 Hz), 30.7, 27.2, 22.2, 16.1 (d, $^3J_{pc}$ = 6.5 Hz), 13.8. MS (EI): *m*/*z* (%) 304 (1.0), 289 (1.1), 275 (1.1), 261 (3.9), 247 (42.6), 219 (68.3), 191 (32.7), 177 (9.9), 163 (50.5), 138 (23.3), 110 (27.7), 81 (100), 57 (82.2), 41 (68.3), 29 (56.4), 18 (46.5). Anal. Calcd for $C_{15}H_{29}O_4P$: C, 59.19; H, 9.60; P, 10.17. Found: C, 59.05; H, 9.69; P, 10.11.

2c: Obtained from isobutylchloroformate.^{1}H NMR (300 MHz): δ 0.80 (t, 3H, J_{HH} = 6.9 Hz), 0.84 (d, 6H, J_{HH} = 6.6 Hz), 1.25 (t, 6H, J_{HH} = 7.2 Hz), 1.12−1.38 (overlap, 4H), 1.88 (m, 1H), 2.60 (m, 2H), 3.85 (d, 2H, J_{HH} = 6.6 Hz), 4.00 (m, 4H), 6.48 (d, 1H, $^2J_{PH}$ = 16.5 Hz). ^{31}P NMR (300 MHz): δ 15.51. ^{13}C NMR (75.5 MHz): δ 166.1 (d, $^3J_{pc}$ = 29.5 Hz, trans), 152.0 (d, $^2J_{pc}$ = 9.7 Hz), 124.0 (d, $^1J_{pc}$ = 187.1 Hz), 71.3, 61.6 (d, $^2J_{pc}$ = 5.7 Hz), 31.2, 29.3 (d, $^3J_{PC}$ = 6.0 Hz), 27.3, 22.4, 18.8, 16.0 (d, $^3J_{pc}$ = 6.6 Hz), 13.6. MS (EI): *m*/*z* (%) 320 (7.3), 292 (11.7), 246 (9.2), 218 (82.9), 190 (69.3), 160 (96.1), 109 (50.7), 81 (100), 65 (33.1), 41 (62.9), 29 (57.5), 18 (20.5). Anal. Calcd for $C_{15}H_{29}O_5P$: C, 56.24; H, 9.12; P, 9.67. Found: C, 56.31; H, 9.09; P, 9.69.

2d: Obtained from benzoyl chloride. ^{1}H NMR (300 MHz): δ 0.79 (t, 3H, J_{HH} = 8.6 Hz), 1.33 (t, 6H, J_{HH} = 7.2 Hz), 1.18−1.63 (overlap, 4H), 2.88 (m, 2H), 4.08 (m, 4H), 5.83 (d, 1H, $^2J_{PH}$ = 16.2 Hz), 7.25−7.80 (overlap, 5H). ^{31}P NMR (300 MHz): δ 15.51. ^{13}C NMR (75.5 MHz): δ 197.4 (d, $^3J_{pc}$ = 21.8 Hz, trans), 160.2 (d, $^2J_{pc}$ = 4.6 Hz), 133.3, 129.7, 128.5, 121.4 (d, $^1J_{pc}$ = 186.0 Hz), 61.9 (d, $^2J_{pc}$ = 5.7 Hz), 30.6 (d, $^3J_{PC}$ = 6.3 Hz), 29.5, 24.8, 16.2 (d, $^3J_{pc}$ = 6.5 Hz), 13.7. MS (EI): *m*/*z* (%) 324 (4.5), 323 (7.0), 295 (10.0), 267 (5.6), 239 (3.9), 219 (10.1), 187 (17.5), 105 (100), 77 (73.1), 51 (12.5), 29 (15.6). Anal. Calcd

(20) These compounds, their isomers, or transformation products may be potential inhibitors of sodium−phosphate cotransport: (a) Loghman-Adham, M. *Gen. Pharmacol.* 1996, *27*, 305. (b) Ullrich, K. J.; Rumrich, G.; Burke, T. R.; Shirazi-Beechey, S. P.; Lang, H.-J. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 1223.

for $C_{17}H_{25}O_4P$: C, 62.95; H, 7.77; P, 9.55. Found: C, 63.01; H, 7.83; P, 9.49.

2e: Obtained from 2-fluorobenzoyl chloride. ^{1}H NMR (300 MHz): δ 0.91 (t, 3H, J_{HH} = 7.2 Hz), 1.32 (t, 6H, J_{HH} = 7.2 Hz), 1.20−1.50 (overlap, 4H), 2.86 (m, 2H), 4.06 (m, 4H), 5.98 (d, 1H, $^2J_{PH}$ = 16.2 Hz), 7.05−7.53 (overlap, 4H). ^{31}P NMR (300 MHz): δ 15.41. ^{13}C NMR (75.5 MHz): δ 194.5 (d, $^3J_{pc}$ = 20.8 Hz, trans), 160.5 (d, $^2J_{pc}$ = 4.6 Hz), 134.0, 131.5,124.2 123.8 (d, $^1J_{pc}$ = 186.5 Hz), 116.2, 61.9 (d, $^2J_{pc}$ = 5.7 Hz), 30.8, 29.2 (d, $^3J_{PC}$ = 6.3 Hz), 22.8, 16.3 (d, $^3J_{pc}$ = 6.5 Hz), 13.5. MS (EI): *m*/*z* (%) 343 (0.5), 242 (3.4), 341 (1.5), 313 (6.9), 285 (6.9), 219 (12.8), 205 (19.7), 123 (100), 95 (28.6), 28 (6.6). Anal. Calcd for $C_{17}H_{24}FO_4P$: C, 59.64; H, 7.06; P, 9.05; F, 5.55. Found: C, 59.59; H, 6.98; P, 8.97; 5.60.

2f: Obtained from cinnamoyl chloride. ^{1}H NMR (300 MHz): δ 0.84 (t, 3H, J_{HH} = 6.9 Hz), 1.32 (t, 6H, J_{HH} = 7.2 Hz), 1.20−1.80 (overlap, 4H), 2.46 (t, 2H), 4.08 (m, 4H), 5.82 (d, 1H, $^2J_{PH}$ = 17.7 Hz), 7.05−7.67(m, 7H). ^{31}P NMR (300 MHz): δ 16.86. ^{13}C NMR (75.5 MHz): δ 197.8 (d, $^3J_{pc}$ = 21.6 Hz, trans), 160.1 (d, $^2J_{pc}$ = 4.6 Hz), 154.3, 136.2, 133.4, 130.2, 128.7, 122.1 (d, $^1J_{pc}$ = 191.7 Hz), 119.7, 61.5 (d, $^2J_{pc}$ = 6.0 Hz) 30.3 (d, $^3J_{PC}$ = 6.3 Hz), 29.6, 24.3, 16.3 (d, $^3J_{pc}$ = 6.6 Hz), 14.0. MS (EI): *m*/*z* (%) 350 (5.1), 335 (3.5), 321 (29.4), 273 (25.1), 247 (39.1), 239 (3.9), 219 (10.1), 187 (17.5), 105 (100), 103 (16.3), 77 (73.1), 51 (12.5), 29 (15.6). Anal. Calcd for $C_{19}H_{27}O_4P$: C, 65.13; H, 7.76; P, 8.84. Found: C, 64.98; H7.65; P, 8.75.

2g: Obtained from 1-naphthoyl chloride. ^{1}H NMR (300 MHz): δ 0.81 (t, 3H, J_{HH} = 7.2 Hz), 1.32 (t, 6H, J_{HH} = 7.2 Hz), 1.10−1.50 (overlap, 4H), 2.86 (m, 2H), 4.06 (m, 4H), 5.82 (d, 1H, $^2J_{PH}$ = 16.2 Hz), 7.35−7.73 (overlap, 4H). ^{31}P NMR (300 MHz): δ 15.41. ^{13}C NMR (75.5 MHz): δ 190.5 (d, $^3J_{pc}$ = 20.8 Hz, trans), 160.5 (d, $^2J_{pc}$ = 4.6 Hz), 136.0−123.0, 122.2 (d, $^1J_{pc}$ = 186.5 Hz), 61.9 (d, $^2J_{pc}$ = 5.7 Hz), 30.8, 29.2 24.8 (d, $^3J_{PC}$ = 6.3 Hz), 16.3 (d, $^3J_{pc}$ = 6.5 Hz), 14.5. MS (EI): *m*/*z* (%) 374 (2.1), 359 (3.6), 245 (13.1), 331 (19.3), 317 (31.3), 285 (6.9), 247 (13.3), 219 (12.8), 205 (19.7), 127 (100), 95 (28.6), 28 (6.6). Anal. Calcd for $C_{21}H_{27}O_4P$: C, 67.37; H, 7.27; P, 8.27. Found: C, 67.19; H, 7.18; P, 8.29.

2h: Obtained form 4-methoxybenzonitrile. ^{1}H NMR (300 MHz): δ 0.87 (t, 3H, J_{HH} = 8.6 Hz), 1.35 (t, 6H, J_{HH} = 7.2 Hz), 1.18−1.50 (overlap, 4H), 2.87 (m, 2H), 3.85 (s, 3H), 4.10 (m, 4H), 5.76 (d, 1H, $^2J_{PH}$ = 16.5 Hz), 6.93 (d, 2H), 7.82 (d, 2H). ^{31}P NMR (300 MHz): δ 15.74. ^{13}C NMR (75.5 MHz): δ 196.1 (d, $^3J_{pc}$ = 26.3 Hz, trans), 160.8 (d, $^2J_{pc}$ = 5.4 Hz), 132.2, 128.3, 119.7 (d, $^1J_{pc}$ = 185.4 Hz), 113.8, 111.9, 61.8 (d, $^2J_{pc}$ = 5.7 Hz), 55.5, 31.2 (d, $^3J_{PC}$ = 6.8 Hz), 30.3, 22.8, 16.4 (d, $^3J_{pc}$ = 6.5 Hz), 13.9. MS (EI): *m*/*z* (%) 354 (5.9), 324 (4.5), 225 (10.8), 217 (21.6), 189 (6.9), 135 (100), 77 (20.6), 57 (10.8), 28 (58.6), 18 (65.7). Anal. Calcd for $C_{18}H_{27}O_5P$: C, 61.01; H, 7.68; P, 8.74. Found: C, 60.89; H, 7.77; P, 8.63.

2i: Obtained from acetyl chloride. ^{1}H NMR (300 MHz): δ 1.09 (t, 6H, J_{HH} = 7.2 Hz) 2.26 (s, 3H), 3.70−3.92 (m, 4H), 6.65 (d, 1H, $^2J_{PH}$ = 15.6 Hz). 7.29−7.40 (overlap, 5H). ^{31}P NMR (300 MHz): δ 14.24. ^{13}C NMR (75.5 MHz): δ 199.0 (d, $^3J_{pc}$ = 22.7 Hz, trans), 155.7 (d, $^2J_{pc}$ = 4.0 Hz), 135.1, 129.9, 128.8, 125.3 (d, $^1J_{pc}$ = 189.1 Hz), 62.2 (d, $^2J_{pc}$ = 6.0 Hz), 28.2 (d, J_{pc} = 7.4 Hz, cis), 16.3 (d, $^3J_{pc}$ = 6.6 Hz). MS (EI): *m*/*z* (%) 282 (0.6), 267 (0.5), 209 (2.7), 183 (8.4), 167 (14.0), 131 (100), 102 (20.7), 81 (15.3), 77 (6.4), 43 (17.4), (28.6), 29 (5.7). Anal. Calcd for $C_{14}H_{19}O_4P$: C, 59.57; H, 6.78; P, 10.97. Found: C, 59.50; H,6.71; P, 10.99. **2j** obtained from acetonitrile was identical in every aspect to **2i** obtained from acetyl chloride.

Acknowledgment. We thank the Israeli Science Foundation, the MECC, the Horowitz Foundation, and the Grass Center for Drug Development at the School of Pharmacy for support of this work.

Supporting Information Available: ^{1}H, ^{13}C, and ^{31}P NMR spectra for compounds **2a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO016403E