Phosphonate Ester Synthesis Using a Modified Mitsunobu Condensation

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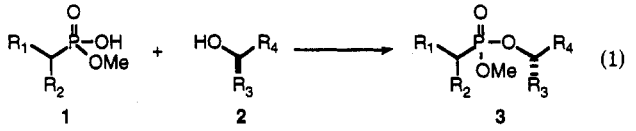
Introduction

We have previously reported the synthesis of phosphonate esters from phosphonic acids and alcohols utilizing standard Mitsunobu coupling conditions.[1] In these reactions, the alcohol and Mitsunobu reagents were present in excess relative to the phosphonic acid (acid-limiting conditions). Attempts to apply this methodology to the synthesis of phosphonate esters under conditions in which the alcohol was the limiting reagent resulted in a drastic increase in reaction times and lower yields of the phosphonate esters compared to our earlier work. Our interest in phosphonate ester synthesis under alcohol-limiting conditions results from our desire to perform solid-phase peptidylphosphonate synthesis where the resin supported alcohol is the limiting reagent, but the methodology would also be applicable when the alcohol component is expensive or is difficult to synthesize. In this article we describe the results of our investigation into the cause of these differences as well as a modified Mitsunobu coupling procedure that provides comparable yields and coupling times under alcohol-limiting conditions.

Phosphonate esters are recognized as an important class of enzyme inhibitors either as transition-state analogues,[2] or nonhydrolyzable phosphate surrogates.[3] Typical methods for the synthesis of phosphonic acid esters involve formation of a phosphoryl chloride followed by displacement with the appropriate alcohol,[4] Karenewsky's phosphonous acid coupling method,[5] or by the use of condensing reagents.[6] We have found that the Mitsunobu reaction,[7] which utilizes the redox chemistry of triphenylphosphine and a dialkyl azodicarboxylate to condense an acidic reagent with primary and secondary alcohols, provides a general and efficient route to phosphonic acid esters.

Standard Mitsunobu couplings are performed with an equimolar excess of alcohol, triphenylphosphine, and DIAD relative to the acidic component. By analogy, condensations under alcohol-limiting conditions, initially attempted using an equimolar excess of phosphonic acid, triphenylphosphine, and DIAD yielded unsatisfactory results. A systematic study of a model reaction (eq 1) by ^{1}H-NMR was performed, the results of which are discussed below.



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Results and Discussion

The model reaction (eq 1; R_1 = NH-Cbz, R_2 = CH_3, R_3 = $CH_2(C_6H_5)$, R_4 = CO_2CH_3) was complete within 1 h using the standard Mitsunobu procedure and phosphonic acid-limiting conditions (Table 1, entry 1). This is in contrast to alcohol-limiting conditions with an equimolar excess of phosphonic acid, triphenylphosphine, and DIAD which required greater than 72 h for completion (entry 2). This could be reduced to 12 h using a slight excess of DIAD and triphenylphosphine relative to phosphonic acid and alcohol (entry 3). However, when a larger excess of DIAD and triphenylphosphine were employed, minimal product formation was observed (entry 4).

The Mitsunobu reaction mechanism with carboxylic acids has been investigated by a number of workers[8] and the analogous mechanism for a phosphonic acid is shown in Scheme 1. A typical Mitsunobu coupling reaction proceeds via path A and it is generally recognized that the rate-determining step is reaction of the alcohol with the protonated betaine **5** to generate the alkoxyphosphonium salt **7** which then readily cascades to product.[8b] Path B is accessed only when there is no acidic component present to protonate the betaine **4**.[9]

The results in Table 1 are readily interpreted using this mechanism. When an equimolar excess of phosphonic acid, triphenylphosphine, and DIAD relative to the alcohol are used (entry 2), the protonated betaine **5** is formed and reacts sluggishly with the alcohol to form the alkoxyphosphonium salt **7** (path A). When a slight excess of unprotonated betaine **4** is present (entries 1 & 3), it assists formation of the alkoxyphosphonium salt **7** via general base catalysis. However, with a larger excess of **4** (entry 4) path B may be accessed and result in formation of the dialkoxyphosphorane **6** which could then undergo an E2 elimination instead of cascading to product.[9b,10]

Thus, alcohol-limiting conditions were sought that would favor path A over path B. The above mechanistic interpretation suggests a number of improvements that can be made to facilitate formation of the desired phosphonate ester **3**. First, addition of an exogenous base as a general base catalyst should increase the rate of reaction between the alcohol and **5** to form **7**. Second, increasing the electrophilicity of phosphorus in **5** should also increase the rate of formation of **7**. Additionally, to disfavor access to path B and potential elimination reactions, an equimolar excess of phosphonic acid, phosphine, and DIAD should be used.

These changes were incorporated into the model reaction (eq 1) and the results are summarized in Table 1 (entries 5–7). All couplings were performed with an equimolar excess of phosphonic acid, DIAD, and phosphine relative

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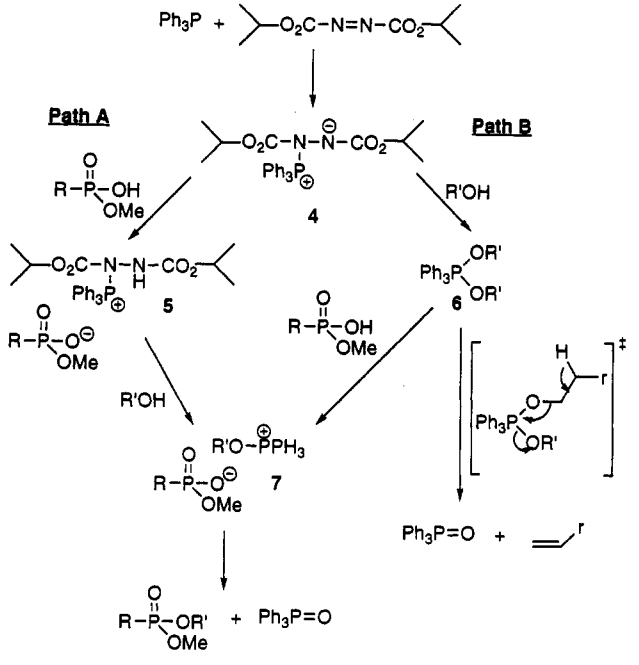
Table 1. Reaction Times for Phosphine/DIAD-Mediated Phosphonic Acid Couplings [eq 1: phosphonic acid 1, (*R*)-R_1 = NH-Cbz; R_2 = CH_3; alcohol 2, (D)-R_3 = $CH_2(C_6H_5)$; R_4 = CO_2CH_3]

	equivalents						
no.	phosphonic acid 1	alcohol 2	TPP	(4-Cl-Ph)$_3$P[a]	DIAD	TEA	coupling time (h)
1	1.0	1.5	1.5	–	1.5	–	1
2	2.0	1.0	2.0	–	2.0	–	>72[b]
3	1.5	1.0	2.0	–	2.0	–	12
4	1.5	1.0	3.0	–	3.0	–	*b*
5	2.0	1.0	2.0	–	2.0	5.0	8
6	2.0	1.0	–	2.0	2.0	–	6
7	2.0	1.0	–	2.0	2.0	5.0	0.5

[a] Tris(4-chlorophenyl)phosphine. [b] Negligible product formation.

Scheme 1



to the alcohol. Upon addition of triethylamine the reaction time was reduced to 8 h (entry 5). A number of commercially available phosphines with electron-withdrawing substituents on the phenyl rings were investigated. The most electron-deficient phosphine studied, tris(pentafluorophenyl)phosphine, was unable to form the betaine 4 as evidenced by ^{1}H-NMR. Relative to triphenylphosphine only a modest improvement in reaction time was observed with tris(4-fluorophenyl)phosphine while tris(4-chlorophenyl)phosphine reduced the reaction time to 6 h (entry 6). These results correlate with the σ values for the *p*-aryl substituents H, F, and Cl on the phosphines, 0, 0.06, and 0.23, respectively, a trend that has also been observed by groups studying Mitsunobu condensations with carboxylic acids.[8a] Combining the addition of an exogenous base with the substitution of tris(4-chlorophenyl)phosphine for TPP (entry 7) reduced the reaction time to 0.5 h, which is comparable to the standard Mitsunobu coupling results (entry 1). Additional improvements in rates and yields may be achievable with more electron-deficient phosphines, providing this does not result in an E2 elimination reaction of the alkoxyphosphonium salt 7.

The effect of additional steric encumbrance on the yields and reaction times was studied, and the results are summarized in Table 2. Satisfactory results were obtained even with the most sterically demanding couplings. The coupling times and isolated yields are comparable to the results we have previously reported for the standard Mitsunobu procedure under phosphonic acid-limiting conditions.

In conclusion, a mild and efficient method for the synthesis of phosphonic acid esters based on a modified Mitsunobu condensation has been described for the case in which the alcohol is the limiting reagent. The modifications include the use of exogenous base and electron-deficient phosphines and the reaction provides satisfactory results even with sterically hindered phosphonic acids and alcohols. This method compliments our previous work with Mitsunobu mediated phosphonic acid couplings and extends its usefulness to syntheses requiring alcohol-limiting conditions. Application of this work to solid-phase peptidylphosphonate synthesis is ongoing and will be reported in due course.

Experimental Section

^{1}H-NMR spectra were recorded at 300 MHz. Mass spectra and elemental analysis were performed at the University of California, Berkeley, CA. Benzylphosphonic acid, tris(pentafluorophenyl)-, tris(4-fluorophenyl)-, and tris(4-chlorophenyl)phosphine were purchased from Lancaster Synthesis Inc., glycolic acid, D-lactic acid, 3-D-phenyllactic acid, and α-D-hydroxyisovaleric acid from Fluka, and all remaining chemicals from Aldrich Chemical Co. THF was refluxed over potassium and distilled prior to use.

General Procedure for the Preparation of Alkylphosphonic Acid Esters. To the methyl alkylphosphonate (1.5 mmol), dissolved in THF (10 mL) was added tris(4-chlorophenyl)-phosphine (1.5 mmol), DIAD (1.5 mmol), and triethylamine (5 mmol) followed by the alcohol (1 mmol). Upon completion of the reaction the mixture was concentrated under vacuum and the crude product was then purified by flash chromatography (EtOAc/hexanes).

Methyl isopropyl benzylphosphonate (3a): ^{1}H-NMR ($CDCl_3$) δ 7.29 (m, 5H), 4.62 (m, 1H), 3.64 (d, J = 11 Hz, 3H), 3.14 (d, J = 22 Hz, 2H), 1.29 (d, J = 6 Hz, 3H), 1.17 (d, J = 6 Hz, 3H). ^{31}P-NMR δ 27.15. FAB MS (MH^+, m/z): 228. Anal. Calcd for $C_{11}H_{17}O_3P{\cdot}0.6H_2O$: C, 55.26; H, 7.69. Found: C, 55.05; H, 7.29.

Methyl 2-[(Methoxybenzylphosphoryl)oxy]acetate (3b): ^{1}H-NMR ($CDCl_3$) δ 7.32 (m, 5H), 4.49 (d, J = 11 Hz, 1H), 4.47 (d, J = 11 Hz, 1H); 3.77 (s, 3H), 3.73 (d, J = 11 Hz, 3H), 3.30 (d, J = 22 Hz, 1H), 3.28 (d, J = 22 Hz, 1H); ^{31}P-NMR δ 29.67; FAB MS (MH^+, m/z) 258. Anal. Calcd for $C_{11}H_{17}O_3P$: C, 51.13; H, 5.86; P, 12.00. Found: C, 50.88; H, 6.10; P, 11.63.

Methyl L-2-[(Methoxybenzylphosphoryl)oxy]propionate (3c): ^{1}H-NMR ($CDCl_3$) δ 7.31 (m, 5H), 4.95 (m, 0.5H), 4.76 (m, 0.5H), 3.78 (d, J = 11 Hz 1.5H), 3.75 (s, 3H), 3.65 (d, J = 11 Hz, 1.5H), 3.21 (m, 2H), 1.54 (d, J = 6 Hz, 1.5H), 1.28 (d, J = 6 Hz, 1.5H); ^{31}P-NMR δ 28.99, 28.44. FAB MS (MH^+, m/z: 272. Anal. Calcd for $C_{12}H_{17}O_5P{\cdot}0.5H_2O$: C, 51.24; H, 6.46. Found: C, 51.17; H, 6.46.

Methyl L-2-[(Methoxybenzylphosphoryl)oxy]-3-phenylpropionate (3d): ^{1}H-NMR ($CDCl_3$) δ 7.29 (m, 10H), 5.18 (m, 0.5H), 5.00 (m, 0.5H), 3.76 (s, 3H), 3.74 (d, J = 11 Hz, 1.5H), 3.70 (d, J = 11 Hz, 1.5H), 3.13 (m, 4H); ^{31}P-NMR δ 28.89; FAB MS (MH^+, m/z): 348. Anal. Calcd for $C_{11}H_{17}O_3P{\cdot}0.5H_2O$: C, 60.49; H, 6.22. Found: C, 60.49; H, 6.22.

Methyl L-2-[(Methoxybenzylphosphoryl)oxy]-3-methylbutyrate (3e): ^{1}H-NMR ($CDCl_3$) δ 7.31 (m, 5H), 4.78 (m, 0.5H), 4.59 (m, 0.5H), 3.77 (s, 3H), 3.73 (d, J = 11 Hz, 1.5H), 3.63 (d, J = 11 Hz, 1.5H), 3.28 (m, 2H), 2.26 (m, 0.5H), 2.09 (m, 0.5H), 1.02 (d, J = 7 Hz, 1.5H), 0.92 (d, J = 7 Hz, 1.5H), 0.87 (d, J = 7 Hz, 3H); ^{31}P-NMR δ 29.17, 28.47; FAB MS (MH^+, m/z): 300. Anal. Calcd for $C_{11}H_{17}O_3P{\cdot}0.35H_2O$: C, 54.84; H, 7.15; P, 10.10. Found: C, 54.83; H, 7.14; P, 10.14.

Methyl L-2-[[Methoxy-[1-[*N*-(Benzyloxycarbonyl)amino]-methyl]-phosphoryl]oxy]propionate (3f): ^{1}H-NMR ($CDCl_3$) δ 7.37 (m, 5H), 5.68 (m, 0.5H), 5.40 (m, 0.5H), 5.15 (s, 2H), 5.06 (m, 0.5H), 4.94 (m, 0.5H), 3.87 (d, J = 11 Hz, 1.5H), 3.80 (s, 3H),

Table 2. Unsymmetrical Diester Syntheses via Modified Mitsunobu Condensations of Methyl Alkylphosphonates with Alcohols

no.	phosphonate 1	alcohol 2	coupling time (h)	isolated yield (%)
3a	R_1 = H; R_2 = $CH_2(C_6H_5)$	R_3 = R_4 = CH_3	0.5	91
3b		R_3 = H; R_4 = CO_2CH_3	0.3	81
3c		(D)-R_3 = CH_3; R_4 = CO_2CH_3	0.3	88
3d		(D)-R_3 = $CH_2(C_6H_5)$; R_4 = CO_2CH_3	0.5	79
3e		(D)-R_3 = $CH(CH_3)_2$; R_4 = CO_2CH_3	3.0	61
3f	R_1 = NH-Cbz; R_2 = H	(D)-R_3 = CH_3; R_4 = CO_2CH_3	0.5	81
3g		(D)-R_3 = $CH_2(C_6H_5)$; R_4 = CO_2CH_3	0.5	72
3h		(D)-R_3 = $CH(CH_3)_2$; R_4 = CO_2CH_3	4.0	50
3i	R_1 = NH-Cbz; R_2 = CH_3	(D)-R_3 = CH_3; R_4 = CO_2CH_3	0.5	86
3j		(D)-R_3 = $CH_2(C_6H_5)$; R_4 = CO_2CH_3	0.5	84
3k		(D)-R_3 = $CH(CH_3)_2$; R_4 = CO_2CH_3	3.5	43
3l	R_1 = NH-Cbz; R_2 = $CH(CH_3)_2$	(D)-R_3 = CH_3; R_4 = CO_2CH_3	0.5	88
3m		(D)-R_3 = $CH_2(C_6H_5)$; R_4 = CO_2CH_3	0.5	80
3n		(D)-R_3 = $CH(CH_3)_2$; R_4 = CO_2CH_3	7.0	50

3.75 (d, J = 11 Hz, 1.5H), 3.68 (m, 2H), 1.58 (d, J = 6 Hz, 1.5H), 1.50 (d, J = 6 Hz, 1.5H); ^{31}P-NMR δ 25.51, 24.01; FAB MS (MH^+, m/z) 346. Anal. Calcd for $C_{11}H_{17}O_3P$: C, 48.70; H, 5.84; N, 4.06; P, 8.97. Found: C, 48.88; H, 6.08; N, 3.94; P, 8.87.

Methyl L-2-[[Methoxy-[1-[*N*(Benzyloxycarbonyl)amino]-methyl]phosphoryl]oxy]-3-phenylpropionate (3g): ^{1}H-NMR ($CDCl_3$) δ 7.31 (m, 10H), 5.49 (m, 0.5H), 5.12 (m, 3H), 4.47 (m, 0.5H), 3.79 (m, 6H), 3.61 (m, 2H), 3.26 (m, 1H), 3.00 (m, 1H); ^{31}P-NMR δ 25.24, 24.45; FAB MS (MH^+, m/z) 422. Anal. Calcd for $C_{11}H_{17}O_3P$: C, 57.00; H, 5.75; N, 3.32. Found: C, 56.65; H, 6.07; N, 3.41.

Methyl L-2-[[Methoxy[1-[*N*-(Benzyloxycarbonyl)amino]-methyl]phosphoryl]oxy]-3-methylbutyrate (3h): ^{1}H-NMR ($CDCl_3$) δ 7.35 (m, 5H), 5.71 (m, 0.5H), 5.39 (m, 0.5H), 5.14 (s, 1H), 5.13 (s, 1H), 4.85 (m, 0.5H), 4.71 (m, 0.5H), 3.75 (m, 8H), 2.28 (m, 1H), 1.07 (d, J = 7 Hz, 1.5H), 1.00 (d, J = 7 Hz, 1.5H), 0.93 (d, J = 7 Hz, 1.5H), 0.92 (d, J = 7 Hz, 1.5H). ^{31}P-NMR δ 25.88, 24.31. FAB MS (MH^+, m/z): 374. Anal. Calcd for $C_{11}H_{17}O_3P$: C, 50.73; H, 6.56; N, 3.70; P, 8.18. Found: C, 50.77; H, 6.68; N, 3.53; P, 8.00.

Methyl L-2-[[Methoxy-[(*R*)-1-[*N*-(Benzyloxycarbonyl)-amino]ethyl]phosphoryl]oxy]propionate (3i): ^{1}H-NMR ($CDCl_3$) δ 7.37 (m, 5H), 5.69 (m, 0.5H), 5.32 (m, 0.5H), 5.10 (m, 2.5H), 4.92 (m, 0.5H), 4.26 (m, 1H), 3.84 (d, J = 11 Hz, 1.5H), 3.77 (s, 3H), 3.73 (d, J = 11 Hz, 1.5H), 1.58 (d, J = 7 Hz, 1.5H), 1.41 (m 4.5H); ^{31}P-NMR δ 27.76, 26.96; FAB MS (MH^+, m/z): 360. Anal. Calcd for $C_{11}H_{17}O_3P$: C, 50.13; H, 6.18; N, 3.90; P, 8.62. Found: C, 49.79; H, 6.23; N, 4.14; P, 8.62.

Methyl L-2-[[Methoxy-[(*R*)-1-[*N*-(Benzyloxycarbonyl)-amino]ethyl]phosphoryl]oxy]-3-phenylpropionate (3j): ^{1}H-NMR ($CDCl_3$) δ 7.29 (m, 10H), 5.10 (m, 3H), 4.29 (m, 0.5H), 4.00 (m, 0.5H), 3.78 (m, 6H), 3.28 (m, 1H), 3.02 (m, 1H), 1.37 (d, J = 7 Hz, 0.75H), 1.31 (d, J = 7 Hz, 0.75H), 1.09 (d, J = 7 Hz, 0.75H), 1.03 (d, J = 7 Hz, 0.75H). ^{31}P-NMR δ 27.51, 26.77; FAB MS (MH^+, m/z) 436. Anal. Calcd for $C_{11}H_{17}O_3P{\cdot}0.\ 2H_2O$: C, 57.44; H, 6.07; N, 3.19. Found: C, 57.44; H, 6.30; N, 3.19.

Methyl L-2-[[Methoxy-[(*R*)-1-[*N*-(Benzyloxycarbonyl)-amino]ethyl]phosphoryl]oxy]-3-methylbutyrate (3k): ^{1}H-NMR ($CDCl_3$) δ 7.38 (m, 5H), 5.80 (m, 0.5H), 5.35 (m, 0.5H), 5.16 (s, 1H), 5.15 (s, 1H), 4.82 (m, 0.5H), 4.68 (m, 0.5H), 4.29 (m, 1H), 3.81 (m, 6H), 2.26 (m, 1H), 1.44 (m, 3H), 1.00 (m, 6H); ^{31}P-NMR δ 28.07, 27.10; FAB MS (MH^+, m/z) 388. Anal. Calcd for $C_{11}H_{17}O_3P$: C, 52.71; H, 6.77; N, 3.62. Found: C, 52.33; H, 6.84; N, 3.71.

Methyl L-2-[[Methoxy-[(*R,S*)-1-[*N*-(Benzyloxycarbonyl)-amino]-2-methylpropyl]phosphoryl]oxy]propionate (3l): ^{1}H-NMR ($CDCl_3$) δ 7.38 (m, 5H), 5.15 (m, 2H), 4.97 (m, 1H), 4.10 (m, 1H), 3.78 (m, 6H), 2.22 (m, 1H), 1.49 (m, 3H), 1.01 (m, 6H). ^{31}P-NMR δ 27.08, 26.13, 26.03; FAB MS (MH^+, m/z) 388. Anal. Calcd for $C_{11}H_{17}O_3P$: C, 52.71; H, 6.77; N, 3.62; P, 8.00. Found: C, 52.73; H, 7.01; N, 3.52; P, 7.80.

Methyl L-2-[[Methoxy-[(*R,S*)-1-[*N*-(Benzyloxycarbonyl)-amino]-2-methylpropyl]phosphoryl]oxy]-3-phenylpropionate (3m): ^{1}H-NMR ($CDCl_3$) δ 7.38 (m, 10H), 5.10 (m, 3H), 4.02 (m, 1H), 3.71 (m, 6H), 3.12 (m, 2H), 2.04 (m, 1H), 0.97 (m, 3H), 0.81 (m, 3H); ^{31}P-NMR δ 27.09, 26.85, 26.15, 26.00; FAB MS (MH^+, m/z) 464. Anal. Calcd for $C_{11}H_{17}O_3P{\cdot}0.\ 3H_2O$: C, 58.91; H, 6.59; N, 2.99; P, 6.60. Found: C, 58.89; H, 6.98; N, 2.93; P, 6.55.

Methyl L-2-[[Methoxy-[(*R,S*)-1-[*N*-(Benzyloxycarbonyl)-amino]-2-methylpropyl]phosphoryl]oxy]-3-methylbutyrate (3n): ^{1}H-NMR ($CDCl_3$) δ 7.34 (m, 5H), 5.57 (m, 0.5H), 5.45 (m, 0.5H), 5.15 (m, 2H), 4.70 (m, 1H), 4.12 (m, 1H), 3.75 (m, 6H), 2.22 (m, 2H), 0.97 (m, 12H); ^{31}P-NMR δ 27.64, 27.24, 26.48, 26.08; FAB MS (MH^+, m/z): 416. Anal. Calcd for $C_{11}H_{17}O_3P$: C, 54.93; H, 7.28; N, 3.37. Found: C, 55.19; H, 7.24; N, 3.36.