Tetrahedron Vol. 49, No. 2, pp. 363-368, 1993
Printed in Great Britain

0040-4020/93 $5.00+.00

TETRAZOLE CATALYZED SYNTHESIS OF PHOSPHONATE ESTERS

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(*Received in USA* 24 *September* 1992)

Abstract : 1*H*-tetrazole selectively catalyzed mono addition of alcohols to phosphonic dichlorides such that mixed phosphonate diesters could be synthesized in high yields and under mild conditions.

Phosphonate monoesters, long employed as analogs of natural phosphates[1] and more recently as transition-state analogs of ester hydrolysis[2], are usually protected during synthesis in the form of mixed diesters and revealed by selective dealkylation in the final stages. The simplest preparation of the mixed diesters would employ sequential addition of different alcohols to the phosphonic dichloride but mixtures of products obtain for unhindered alcohols[3]. Additionally, hindered alcohols such as menthol[4] react with phosphonic dichlorides very poorly, yielding only about 5% menthyl phosphonochloridate with the corresponding alkyl halide as the major product[5]. Alkoxides of secondary alcohols will react with phosphonic dichlorides[6] or phosphonochloridates[7-11] but yields are variable (15-55%). More circuitous routes to the mixed diesters include multi-step procedures *via* phosphite intermediates[12,13]. None of these methods worked well in our effort to synthesize a phosphonate monoester transition-state analog for cholesteryl ester and we opted to reexplore direct synthesis of the mixed diesters from phosphonic dichlorides.

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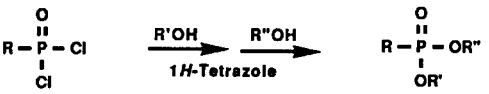
In order to alter the nature of the reacting species and potentially minimize side reactions, we investigated the effect of catalysts similar to those used for acyl chloride esterification[14]. Neither imidazole or pyridine had an effect on the ease or course of reaction. However, a catalytic amount of 1*H*-tetrazole was found to increase the rate of phosphonylation and eliminate conversion of alcohol to alkyl halide for hindered alcohols such as menthol or testosterone (table 1, entries 4-9). In the absence of tetrazole but under otherwise identical conditions we obtained only trace amounts of the desired diesters and the major product was the alkyl halide of the hindered alcohol.

The sequential addition of one equivalent of cyclohexanol and one equivalent of methanol to phenylphosphonic dichloride produced substantial amounts of all three phosphonate diesters, confirming that alkyl phosphonochloridates of unhindered alcohols are not adequately less reactive than the starting phosphonic dichlorides[3]. However, in the presence of 1*H*-tetrazole but again under otherwise identical conditions, we obtained the mixed diester exclusively (table 1, entry 3). Even if

Table 1 Catalyzed Synthesis of Mixed Diesters of Phosphonic Acids



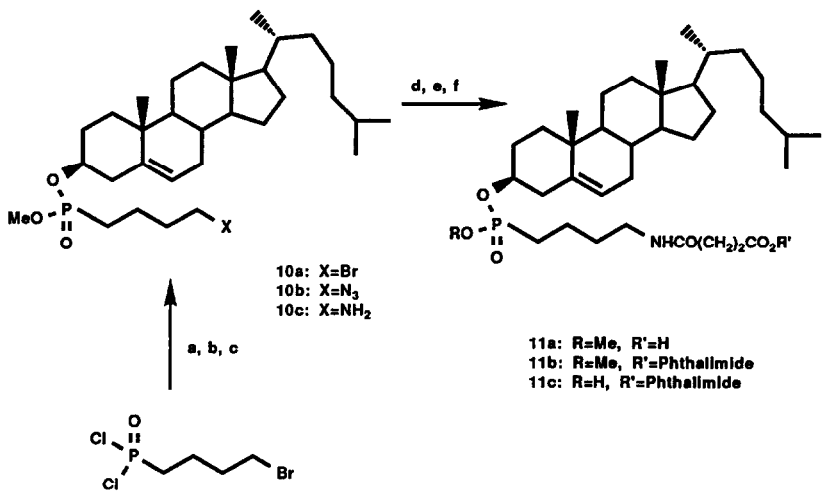
Entry	$RP(O)Cl_2$	R'OH[a]	R"OH[b]	Yield (%)[c]
1.	Ph	$PhCH_2OH$	MeOH (1.1)	82[d]
2.	Ph	$PhCH(CH_3)OH$	MeOH (1.3)	91[e]
3.	Ph	Cyclohexanol	MeOH (1,4)	90
4.	Ph	Menthol	$PhCH_2OH$ (1.1)	98[f]
5.	Ph	Testosterone	$PhCH_2OH$ (3.4)	78[g]
6.	Ph	Menthol	*i*-PrOH (1.1)	97
7.	Ph	Menthol	MeOH (excess)	93
8.	Et	Menthol	MeOH (1.1)	99
9.	Pr	Menthol	MeOH (1.1)	99

a) 1 equivalent of alcohol was used. b) the amount of alcohol used is in parenthesis. c) isolated yield; assignment by ^{1}H-nmr, high-resolution mass spec. d) Dibenzyl and dimethyl phosphonates isolated in 4% and 7% yields respectively. e) Hydrogenolysis generated methyl phenylphosphonic acid in 94% yield. f) Hydrogenolysis generated menthyl phosphonate in 93% yield. g) Debenzylated by catalytic hydrogenation in a solution of methanol and cyclohexene (1:2, vol. ratio) in 92% yield.

both alcohols were primary, the symmetrical diesters were reduced to negligible amounts (entry 1). The mechanism whereby tetrazole enhances selective displacement of a single chlorine from phosphonic dichlorides remains to be elucidated. 1*H*-tetrazole enhances the reactivity of the phosphonic dichloride, probably by nucleophilic catalysis, but apparently less effectively catalyzes reaction of the alkyl phosphonochloridate, perhaps due to increased steric requirements.

Phenol reacted as avidly as methanol in the presence tetrazole and α-methylbenzylphenyl phenylphosphonate was obtained in >90% yield (not shown). Aryl and alkylphosphonic dichlorides reacted equally well with hindered alcohols (entries 7-9). The tetrazole catalysis method provided high yields of mixed diesters across a broad spectrum of alcohols but defining the limits of the method, the highly hindered secondary alcohol of testosterone required an extended reaction time (entry 8). Despite forcing conditions, *t*-butanol failed to react.

Illustrating this method, cholesterol was added to 4-bromo-butylphosphonic dichloride[15] (1 eq) under the standard catalysis conditions, and the reaction was quenched with methanol to yield the



Synthesis of cholesteryl phosphonate 11c. a) Cholesterol, 1*H*-tetrazole (cat.), $EtNPr_2$, PhH, overnight, then MeOH, 95%; b) NaN_3, H_2O, aliquat (cat.) 65°C, 2 days, 79%; c) Ph_3P, tetrahydrofuran, H_2O; d) succinic anhydride (0.7 eq, CH_3CN: CH_2Cl_2/1:7 vol rt, overnight, 93%; e) dicyclohexylcarbodiimide, dimethylformamide, hydroxyphthalimide, 4°C, overnight, 82%; f) bromotrimethylsilane $CDCl_3$, rt, 1h

mixed diester **10a** in 95% yield. The terminal portion of the acid moiety was elaborated for coupling to carrier protein and selective dealkylation with bromotrimethylsilane[16] yielded the desired phosphonate monoester **11c**.

As an alternative general method for preparing the phosphonate monoester of a hindered alcohol, methanol can be replaced by benzyl alcohol and deprotection carried out by catalytic hydrogenation (Table 1, entry 5)[17] For the phosphonate monoester of a less hindered alcohol, a selectively removable secondary alcohol avoids the minor symmetrical products obtained from the catalyzed synthesis of mixed diesters of two primary alcohols. Thus monomethyl phenylphosphonate was prepared by esterification with α-methylbenzyl alcohol, followed by addition of methanol and hydrogenolysis of the diester product, in 86% overall yield. (Table 1, entry 2).

Phosphonate monoester transition-state analogs are typically modeled closely to the structure of the target ester to maximize non-covalent binding, and presumably catalytic activity, in the elicited antibodies[2] but a potentially large series of phosphonate monoester analogs may be required for optimization of kinetics[18]. The strategy discussed here provides a simple solution for their synthesis with mild conditions and high yields.

EXPERIMENTAL SECTION

Anhydrous benzene was obtained by distillation from calcium hydride. Merck silica gel was employed for column chromatography. Infrared absorption maxima are reported in wave numbers (cm^{-1}). Chemical shifts are reported downfield of tetramethylsilane in parts per million (ppm) of the applied field. Coupling constants are reported in hertz (Hz). Infrared spectra were recorded on a Jasco IR A-1 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a 200 MHz Varian Forrier-Transform Spectrometer in the deuterated solvent noted. Mass spectra were measured on a Riber mag R10-10 instrument.

General procedure:

To a solution of 1*H*-tetrazole (12 mg, 0.17 mmole), menthol (0.28 g, 1.8 mmole), diisopropyl ethyl amine (0.68 ml, 3.9 mmole), and benzene (18 ml) was added phenyl phosphonic dichloride (0.25 ml, 1.8 mmole) at 5°C. After stirring overnight at room temperature, excess of MeOH was added and stirring was continued for 10 min. Evaporation of solvent and purification by column chromatography on silica gel gave the desired phosphonate (0.51 g, 1.6 mmole) in 93% yield. Diester products are numbered to correspond to the entries in Table 1. Diesters 3 and 7 were previously reported[3,5]

Spectral and Analytic Data:

1: IR ($CHCl_3$) 3418, 3066, 3005, 2954, 2852, 1595, 1498, 1456, 1440, 1380, 1248, 1132, 1011 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.03 ~ 7.94 (m, 10 H), 5.11 (m, 2 H), 3.72 (dd, J = 1.2, 7.6 Hz, 3 H); ^{13}C (75 MHz, $CDCl_3$) δ 136.2, 132.7, 132.6, 131.9, 131.8, 128.8, 128.6, 128.4, 128.3, 127.9, 67.6, 67.5, 52.7, 52.6; MS Calcd for $C_{14}H_{15}O_3P$ 262.0759, found 262.0761.

2: IR ($CHCl_3$) 3417, 3017, 2953, 2851, 1595, 1496, 1440, 1378, 1247, 1198, 1132, 1047, 995 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.22 - 7.85 (m, 10 H), 5.59 (m, 2 H), 3.72 (dd, J = 0.6, 7.6 Hz, 3/2 H), 3.52 (dd, J = 0.6, 7.6 Hz, 3/2 H), 1.67 (d, J = 4.4 Hz, 3/2 H), 1.57 (d, J = 4.4 Hz, 3/2 H); ^{13}C (75 MHz,

$CDCl_3$) δ 132.5, 132.4, 132.3, 132.2, 131.8, 131.7, 131.6, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 125.9, 75.3, 75.2, 52.0, 24.5, 24.4; MS Calcd for $C_{15}H_{17}O_3P$ 276.0915, found 276.0941.

4: IR ($CHCl_3$) 3423, 3016, 2959, 2872, 1456, 1379, 1226, 1203, 1131, 992 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.80 (m, 2 H), 7.25 - 7.54 (m, 8 H), 5.01 (m, 2 H), 4.26 (m, 1 H), 0.51 ~ 2.30 (m, 18 H); ^{13}C (75 MHz, $CDCl_3$) δ 136.4, 132.3, 132.2, 131.9, 131.8, 131.7, 131.6, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.5, 126.9, 78.4, 78.3, 78.0, 77.9, 67.5, 67.4, 67.3, 67.2, 48.6, 48.5, 43.3, 43.0, 34.1, 31.6, 31.5, 25.6, 25.5, 22.8, 22.7, 22.0, 21.9, 21.0, 20.9, 15.6, 15.3; MS calcd for $C_{23}H_{31}O_3P$ 386.2011, found 386.2027.

5: IR ($CHCl_3$) 3422, 3012, 2948, 1662, 1616, 1440, 1376, 1240, 1198, 1009 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.82 (m, 2 H), 7.27 ~ 7.56 (m, 8 H), 5.71 (s, 1 H), 5.02 (m, 2 H), 4.28 (m, 1 H), 0.78 - 2.48 (m, 19 H), 1.16 (d, J = 4.6 Hz, 3 H), 0.82 (d, J = 9.0 Hz, 3H); MS Calcd for $C_{32}H_{39}O_4P$ 518.2586, found 518.2595.

6: IR ($CHCl_3$) 3423, 3022, 2961, 1440, 1387, 1228, 1201, 1132, 989 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.81 (m, 2 H), 7.39 (m, 3 H), 4.52 (m, 1 H), 4.08 ~ 4.24 (m, 1 H), 0.40 ~ 2.38 (m, 24 H); ^{13}C (75 MHz, $CDCl_3$) δ 132.0, 131.9, 131.8, 131.7, 131.6, 131.5, 128.3, 128.1, 128.0, 77.8, 77.7, 77.5, 77.4, 48.6, 48.5, 43.4, 43.1, 34.1, 34.0, 31.6, 31.5, 25.5, 25.4, 23.7, 23.8, 23.7, 22.8, 22.8, 22.7, 22.0, 21.9, 21.1, 15.7, 15.2; MS Calced for $C_{19}H_{31}O_3P + H^+$ 339.2089, found 339.2071.

8: IR ($CHCl_3$) 3421, 2958, 2872, 1458, 1248, 1213, 1061, 997 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.20 (m, 1 H), 3.69 (m, 3 H), 0.87 ~ 2.17 (m, 14 H), 0.88 (d, J = 4.6 Hz, 6 H), 0.79 (d, J = 4.4 Hz, 3 H); ^{13}C (75 MHz, $CDCl_3$) δ 77.0, 76.9, 48.5, 48.4, 43.5, 43.2, 34.1, 31.5, 25.7, 25.5, 22.8, 22.0, 21.9, 21.0, 19.8, 18.9, 15.6, 15.5, 6.7; MS Calcd for $C_{13}H_{27}O_3P + H^+$ 263.1776 found 263.1785.

9: IR ($CHCl_3$) 3416, 2962, 2873, 1456, 1253, 1202, 996 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.18 (m, 1 H), 3.67 (m, 3 H), 0.76 - 2.22 (M, 25 H); ^{13}C (75 MHz, $CDCl_3$) δ 77.1, 76.9, 48.5, 48.4, 43.5, 43.2, 34.1, 31.5, 29.5, 28.7, 27.6, 26.8, 25.9, 25.5, 22.8, 22.0, 21.9, 21.0, 16.3, 16.2, 16.1, 15.6, 15.5, 15.4, 15.2; MS Calcd for $C_{14}H_{29}O_3P + H^+$ 277.1932, found 277.1917.

10b: IR ($CHCl_3$) 3422, 2947, 2869, 2100, 1638, 1466, 1382, 1253, 1193, 1060, 1016 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.38 (brd.s, 1 H) 4.23 (m, 1 H), 3.68 (dd, J = 2.0, 7.2 Hz, 3 H), 3.25 (t, J = 4.6 Hz, 2 H), 2.35 (m, 2 H); ^{13}C (75 MHz, $CDCl_3$) δ 139.5, 122.9, 76.2, 76.1, 56.6, 56.1, 51.3, 49.9, 42.3, 40.4, 39.7, 36.9, 35.8, 31.8, 30.2, 30.1, 29.9, 28.6, 28.2, 28.0, 26.7, 24.7, 23.9, 22.5, 22.3, 21.0, 19.3, 18.7, 11.9; MS (CI) Calcd for $C_{34}H_{60}N_3O_3P + H^+$ 590.4529. Found 590.4459

11a: IR ($CHCl_3$) 3443, 2949, 2869, 1717, 1662, 1532, 1467, 1383, 1236, 1198, 1059, 1017 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.54 (brd.s, 1H), 5.36 (brd.s, 1 H), 4.19 (m, 1 H), 3.69 (dd, J = 1.8, 7.2 Hz, 3H), 3.23 (m, 2 H), 2.63 (m, 2 H), 2.47 (t, J = 4.2 Hz, 2 H), 2.38 (m. 2 H); ^{13}C (75 MHz, $CDCl_3$) δ 175.3, 172.6, 139.4, 123.0, 76.6, 56.6, 56.1, 52.3, 52.2, 50.0, 42.3, 40.4, 40.3, 40.2, 39.8, 39.6, 39.4, 39.2, 36.9, 36.4, 36.2, 35.8, 31.9, 31.3, 30.4, 30.1, 30.0, 29.3, 28.9, 28.0, 25.9, 25.7, 24.3, 24.0, 23.8, 22.8, 21.8, 21.0, 19.2, 18.7, 11.9; MS calced for $C_{38}H_{66}NO_6P + Na^+$ 686.4526, found 686.4485.

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