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SYNTHESIS OF PHOSPHONIC MONOESTERS FROM PHOSPHONOUS ACIDS

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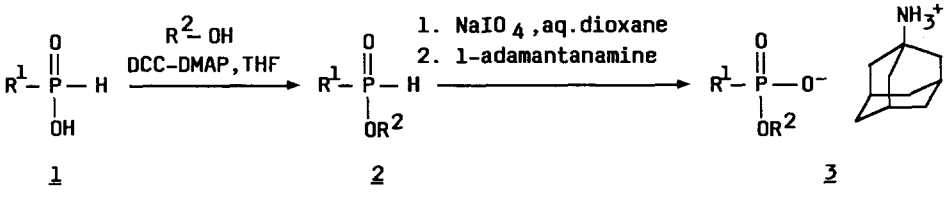
ABSTRACT: Phosphonic monoesters are prepared in a two-step procedure by DCC-DMAP mediated esterification of phosphonous acids and oxidation of the resulting phosphonous monoester.

The preparation of phosphonic monoesters usually involves either the direct hydrolysis of symmetrical phosphonic diesters[1] or hydrolysis of the corresponding phosphonochloridates[2a,b]. The latter must be prepared either from a symmetrical diester by treatment with phosphorus pentachloride[2a-c] or by treatment of a phosphonyl dichloride with one equivalent of the appropriate alcohol[3]. Neither of these methods is very efficient with respect to the alcohol component and both are somewhat limited in the variety and complexity of the kind of esters that one can prepare. The direct monoesterification of phosphonic acids requires rather forcing conditions (large excess of the alcohol component and either dicyclohexylcarbodiimide (DCC), triethylamine, THF, reflux[4] or trichloroacetonitrile, pyridine, 50-80°C[5]) and fails for hindered alcohols such as t-butanol[4b].

We wish to report a general, efficient synthesis of phosphonic monoesters 3 from phosphonous acids 1 which are readily available by hydrophosphorylation of olefins[6] and imines[7]. In contrast to phosphonic acids, phosphonous acids 1 undergo rapid esterification at room temperature in the presence of DCC (1.05 equiv.), N,N-dimethylaminopyridine (0.1 equiv.) and a slight excess of alcohol (1.1 equiv.) in THF to give the corresponding phosphonous monoesters 2 in excellent yield. Oxidation of the phosphonous monoesters 2 proceeds smoothly with sodium metaperiodate to afford the phosphonic monoesters 3, convienently isolated as their 1-adamantanamine salts, in high overall yield.

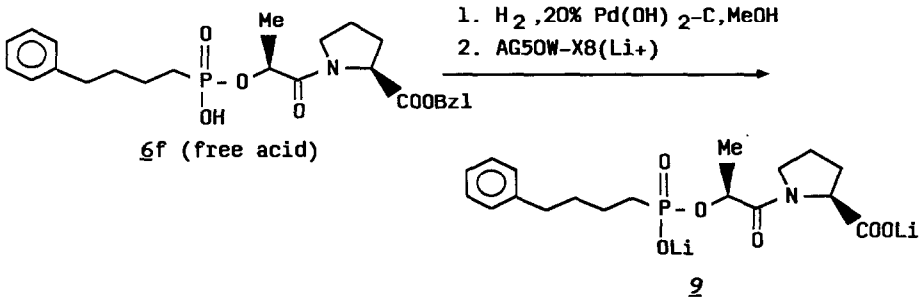


1 2 3

We have applied this procedure to a wide variety of alcohols and phosphonous acids. Table 1 illustrates the generality of this method with respect to the alcohol component for a series of esters 6a-f of 4-phenylbutyl phosphonic acid. This procedure works well even with sterically hindered alcohols such as t-butanol (5d) and with alcohols containing *alpha* electron withdrawing substituents such as ethyl lactate

(5c) and lactoylproline benzyl ester (5f). We have also utilized this methodology for the preparation of the monobenzyl esters 8a−d of a series of structurally diverse phosphonic acids. As shown in Table 2, aromatic (7a), branched aliphatic (7b) and *alpha* benzyloxycarbonylamino alkyl (7cd) phosphonous acids can all be converted to the corresponding phosphonic monobenzyl esters 8a−d by this procedure.

The utility of this method is demonstrated by the synthesis of the phosphonate angiotensin converting enzyme (ACE) inhibitor 9. Phosphonate 9 was obtained previously as a diastereomeric mixture by a lengthy synthesis from 4−phenylbutyl phosphonyl dichloride in 19% overall yield[8]. Attempted direct esterification of 4−phenylbutyl phosphonic acid with lactoylproline benzyl ester (5f) (DCC, pyridine, 80°C, 1.5 hrs.), gave the desired phosphonic monoester 6f contaminated with the corresponding benzyl ester 6b which proved difficult to separate. Benzyl ester 6b was apparently formed from benzyl alcohol generated by lactonization of 5f under the reaction conditions. Using the present method, 6f was prepared free of benzyl ester 6b in 84% yield from 4−phenylbutyl phosphonous acid (4). Deprotection of 6f as the free acid (H_2, 20% $Pd(OH)_2$−C, MeOH) gave phosphonate 9 isolated as its dilithium salt (AG50W−X8, lithium form) in 90% yield. Phosphonate 9 had an I_{50} of 56nM against rabbit lung ACE using hippuryl histidyl leucine as a substrate[9].



6f (free acid)

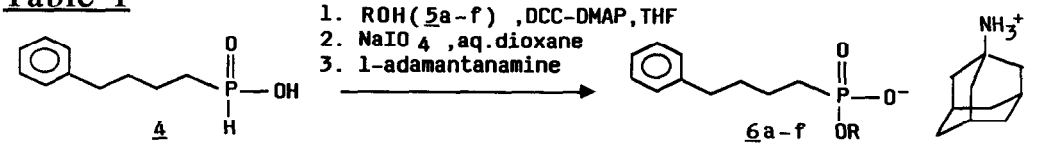
9

The following example is representive of this procedure.

To a solution of 4−phenylbutyl phosphonous acid[10] (4, 1.224 g, 6.18 mmole) and lactoylproline benzyl ester[11] (5f, 1.80 g, 6.49 mmole) in dry THF (15 ml) at room temperature under argon was added DCC (1.40 g, 6.80 mmole) and DMAP (0.076 g, 0.62 mmole). After stirring at room temperature for 2 hrs., the mixture was diluted with EtOAc (50 ml), filtered and washed successively with 5% $KHSO_4$, saturated $NaHCO_3$ and saturated NaCl solutions, dried over Na_2SO_4 and evaporated to give the crude phosphonous monoester as a colorless oil. TLC(silica gel, 1:1 acetone−hexane) Rf=0.25 (Rf of 5f=0.37).

The crude phosphonous monoester was taken up in dioxane (10 ml) and treated with a solution of $NaIO_4$ (1.52 g, 7.11 mmole) in water (4.0 ml). After stirring at room temperature for 16 hrs., the mixture was filtered then partitioned between EtOAc−2% $KHSO_4$ (75 ml each). The organic phase was washed successively with water, dilute $NaHSO_3$ and saturated NaCl solutions, dried over Na_2SO_4 and

Table 1



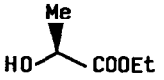
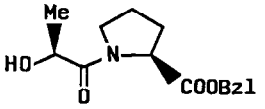
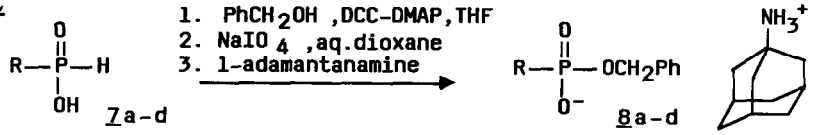
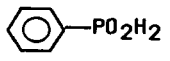
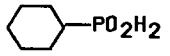
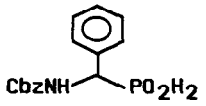
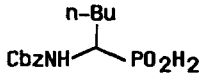
Example	ROH	m.p. of 6	Yield of 6
a	EtOH	183-184 °C	89%
b	$PhCH_2OH$	181-184 °C	76%
c	i-PrOH	188-190 °C	79%
d	t-BuOH	188-191 °C	88%
e		142-143 °C	65%
f		172-174 °C	84%

Table 2



Example	$R-PO_2H_2$	m.p. of 8	Yield of 8
a		257-259°C	64%
b		215-217°C	76%
c		163-164°C	82%
d		(154-156°C)*	82%

All compounds gave satisfactory microanalysis (C,H,N,P)

* m.p. of free acid

evaporated to give the crude phosphonic monoester (3.089 g) as a colorless, viscous oil. TLC(silica gel, 20:1:1 CH_2Cl_2–MeOH–AcOH) Rf=0.31.

The crude phosphonic monoester (3.089 g) was taken up in Et_2O (20 ml) and treated with a solution of 1–adamantanamine (1.00 g) in Et_2O (5 ml). The resulting white precipitate was collected and washed with Et_2O to give analytically pure adamantanamine salt **6f** (3.256 g, 84% overall yield from **4**) as a white solid, m.p. 172–174°C.

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10. 4–Phenylbutyl phosphonous acid (**4**) was prepared from 4–phenylbutene (50 g, 0.38 mole), $NaH_2PO_2 \cdot H_2O$ (120 g, 1.13 mole), H_2SO_4 (30 ml) and AIBN (5.0 g) in absolute EtOH (1200 ml), reflux, 16 hrs. and isolated as its 1–adamantanamine salt (115.1 g, 87%), m.p. 192–200°C. TLC(silica gel, 7:2:1 i–PrOH–conc.NH_4OH–H_2O) Rf=0.69.

11. Lactoylproline benzyl ester (**5f**) was prepared by the reaction of L–sodium lactate (1.70 g, 15.0 mmole), diphenylphosphoryl azide (4.60 g, 16.7 mmole), proline benzyl ester HCl (3.60 g, 15.0 mmole) and triethylamine (2.1 ml, 15.2 mmole) in DMF (30 ml) at room temperature for 24 hrs. (60% yield), m.p. 86–88°C (i–Pr_2O). TLC(silica gel, EtOAc) Rf=0.40.

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