Studies on Organophosphorus Compounds 55. A New and Facile Synthetic Route to 1-Alkyl(Aryl)-2-amino-1-hydroxyalkylphosphonic Acids

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Nucleophilic addition of dimethyl phosphite to acylamino ketones prepared conveniently by the Dakin–West reaction involving reaction of the corresponding α-amino acids and acid anhydrides, followed by subsequent hydrolysis affords 1-alkyl(aryl)-2-amino-1-hydroxyalkylphosphonic acids in satisfactory yield.

Successful isolation of 2-amino-1-hydroxyethylphosphonic acid from a living organism[1] has awakened increasing interest in the synthesis of its derivatives for structure–activity studies of this multifunctional phosphorus compound bearing a P–C bond. Among numerous synthetic methods studied,[2-6] that of Tone et al., based on the reaction of *N*-(2-oxoethyl)phthalimide and dimethyl phosphite in the presence of a base followed by hydrazinolysis and subsequent hydrolysis,[6] attracted our attention since it can be developed as a general method for the preparation of various derivatives of 2-amino-1-hydroxyethylphosphonic acid based on the nucleophilic addition of dialkyl phosphite to a carbonyl group in the α-position to a substituted amino function. Herein we wish to report a new and facile synthetic route leading to 1-alkyl(aryl)-2-amino-1-hydroxyalkylphosphonic acids using acylamino ketones as key intermediates.

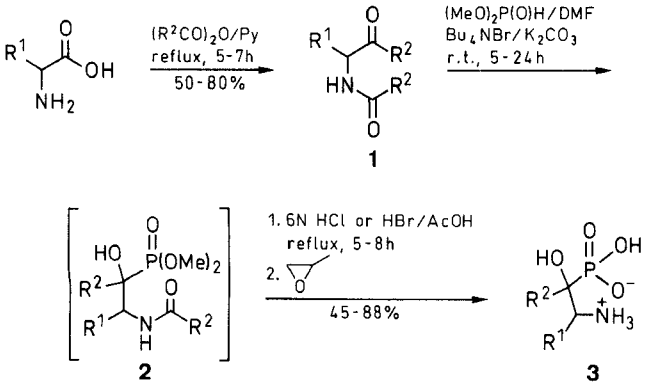

Table 1. Compounds **1** Prepared

Product	R^1	R^2	Yield (%)	bp (°C)/mbar or mp (°C) (solvent)	Molecular Formula[a] or Lit data
1a	H	Me	76	110–113/0.7	120–123/1[12]
1b	H	Et	59	88–90/0.3	$C_7H_{13}NO_2$ (143.2)
1c	H	Pr	56	137–140/1.5	$C_9H_{17}NO_2$ (171.2)
1d	H	*n*-C_5H_{11}	62	82–85 (ligroin)	$C_{13}H_{25}NO_2$ (227.3)
1e	H	Ph	50	122–123 (xylene)	123–124[7]
1f	Me	Me	80	102–106/2	102–106/2[7]
1g	Me	Et	73	116–118/0.9	$C_8H_{15}NO_2$ (157.2)
1h	Me	Pr	78	110–111/0.2	$C_{10}H_{19}NO_2$ (185.3)
1i	Bn	Me	76	96.5–98 (ligroin)	98–99[8]

[a] Satisfactory microanalyses obtained: C ±0.35, H ±0.10, N ±0.12.

Table 2. Spectroscopic Data of Compounds **1**

Product	IR (film), (ν, cm^{-1}) NH	NHC=O	C=O	^1H NMR (CCl_4) δ, J_{HH} (Hz)
1a	3410	1740	1700	7.4 (m, 1H, NH), 4.6 (d, 2H, J = 6, NCH_2), 2.1 (s, 3H, $COCH_3$), 1.9 (s, 3H, $NCOCH_3$)
1b	3340	1720	1675	7.4 (m, 1H, NH), 4.4 (d, 2H, J = 5.5, NCH_2), 2.1–2.5 (m, 4H, 2 $COCH_2CH_3$), 1.0–1.3 (m, 6H, 2 CH_2CH_3)
1c	3380	1720	1675	7.1 (m, 1H, NH), 4.1 (d, 2H, J = 5, NCH_2), 2.2–2.6 (m, 4H, 2 $COCH_2$), 1.6–1.9 (m, 4H, 2 $COCH_2CH_2$), 1.0 (t, 6H, J = 6.5, 2 $COCH_2CH_2CH_3$)
1d	3310	1690	1650	7.2 (m, 1H, NH), 4.3 (d, 2H, J = 5, NCH_2), 2.3–2.7 (m, 4H, 2 $COCH_2$), 0.9–1.7 (m, 18H, 2 $C_4H_9CH_2$)
1e	3280	1720	1690	7.7 (m, 5H, C_6H_5), 7.3 (m, 6H, C_6H_5 + NH), 4.7 (d, 2H, J = 5, NCH_2)
1f	3290	1720	1660	7.5 (m 1H, NH), 3.8–4.3 (m, 1H, NHCH), 2.0 (s, 3H, $COCH_3$), 1.9 (s, 3H, $NCOCH_3$), 1.0 (d, 3H, J = 5, $CHCH_3$)
1g	3290	1720	1660	7.6 (m, 1H, NH), 4.3 (m, 1H, NHCH), 2.0–2.6 (m, 4H, 2 CH_2CO), 0.9–1.3 (m, 9H, 3 CH_3)
1h	3290	1715	1665	7.6 (m, 1H, NH), 4.3 (m, 1H, NHCH), 2.0–2.4 (m, 8H, 2 CH_2CH_2CO), 1.0–1.2 (m, 9H, 3 CH_3)
1i	3280	1720	1690	7.3 (s, 5H, C_6H_5), 7.1 (m, 1H, NH), 4.8 (m, 1H, CHNH), 3.1 (d, 2H, J = 6.5, $C_6H_5CH_2$), 2.2 (s, 3H, $CCOCH_3$), 2.0 (s, 3H, $NCOCH_3$)

Table 3. Compounds **3** Prepared

Product	R^1	R^2	Yield (%)	mp (°C)	Molecular Formula[a] or Lit. mp (°C)
3a	H	Me	86	239–242	239–240[3]
3b	H	Et	71	235–236	235–236[3]
3c	H	Pr	65	231–232	230–231[3]
3d	H	*n*-C_5H_{11}	38	227–229	226–227[3]
3e	H	Ph	62	228–230	226–227[3]
3f	Me	Me	81	233–234	233–234[3]
3g	Me	Et	52	226–227	$C_5H_{14}NO_4P$ (183.2)
3h	Me	Pr	41	220–221	$C_6H_{16}NO_4P$ (197.2)
3i	Bn	Me	88	235–236	$C_{10}H_{16}NO_4P$ (245.2)

[a] Satisfactory microanalyses obtained: C ±0.46, H ±0.22, P ±0.38.

The acylamino-substituted ketones **1** are obtained by heating α-amino acids with anhydrides, such as acetic, propionic, butyric, hexanoic and benzoic, in the presence of pyridine. In this well-known Dakin–West reaction,

Table 4. Spectroscopic Data of Compounds **3**

Product	IR (film), ν (cm^{-1})				^1H NMR (D_2O/NaOD) δ, J (Hz)
	NH_3^+	P–OH	$PO_3^=$	P=O–H	
3a	3450, 1630	3200–2100	1540	1140	2.8–3.3 (m, 2H, $C\underline{H}_2NH$), 1.3 (d, 3H, $J_{PH} = 11$, CH_3)
3b	3250, 1620	3400–2000	1510	1120	2.9–3.3 (m, 2H, $C\underline{H}_2NH$), 1.6 (m, 2H, $CH_3C\underline{H}_2P$), 0.9 (t, 3H, $J_{PH} = 6$, $C\underline{H}_3CH_2$)
3d	3210, 1610	3500–2000	1540	1140	2.9 (d, 2H, $J_{PH} = 11.5$, $C\underline{H}_2NH$), 0.9–1.7 (m, 11H, C_5H_{11})
3e	3150, 1595	3400–2000	1500	1140	7.5 (s, 5H, C_6H_5), 3.6 (d, 2H, $J_{PH} = 10$, $C\underline{H}_2NH$)
3f	3350, 1520	3400–2000	1520	1160	3.2–3.7 (m, 1H, $C\underline{H}NH$), 1.35 (3H, $J_{PH} = 11$, $PCCH_3$), 1.2 (d, 3H, $J_{HH} = 6$, $C\underline{H}_3CHNH$)
3g	3300, 1610	3400–2000	1520	1160	3.5–4.0 (m, 1H, $C\underline{H}NH$), 1.2–2.0 (m, 5H, $CH_3C\underline{H}_2$, $C\underline{H}_3CHN$), 1.1 (t, 3H, $J_{HH} = 5.5$, $C\underline{H}_3CH_2$)
3h	3250, 1600	3500–2000	1550	1120	3.5–4.0 (m, 1H, $C\underline{H}N$), 1.2–1.8 (m, 5H, $CH_3C\underline{H}_2$, $C\underline{H}_3CH_2CH_2N$), 1.1 (t, 3H, $J_{HH} = 5.5$, $C\underline{H}_3CH_2$)
3i	3200, 1625	3500–2000	1530	1160	3.2–3.7 (m, 1H, CHN), 3.1 (d, 2H, $C_6H_5C\underline{H}_2$), 1.2 (d, 3H, $J_{HH} = 6$, $C\underline{H}_3CHN$)

formation of **1** is believed to involve a base-catalyzed acylation of an oxazolone, which is similar to the Erlenmeyer reaction.[7–10] Addition of dimethyl phosphite to **1** proceeds under mild conditions in the presence of potassium carbonate and tetrabutylammonium bromide in dimethylformamide. This addition reaction can be considered as a process involving a nucleophilic addition of phosphite to the sp^2 carbon atom.[11] The addition product **2** thus obtained is directly hydrolyzed without isolation. The hydrolytic conditions are determined by the nature of the acylamine structure, in other words, by the stability of the amide linkage in **2**. Either hydrochloric acid or hydrogen bromide in acetic acid can be used. Treatment of the hydrolyzed products with propylene oxide in the usual manner affords 1-alkyl(aryl)-2-amino-1-hydroxyalkylphosphonic acids **3** in satisfactory yield. The purity of the compounds synthesized is examined by spectroscopic investigation in addition to elemental analyses.

Melting points are not corrected. IR spectra were obtained on a Shimadzu 440 spectrometer. ^1H NMR spectra were recorded on a Varian EM-360A (60 MHz) spectrometer using TMS as external standard.

Acylamino Ketones (1); General Procedure:
A mixture of amino acid (0.1 mol), acid anhydride (0.5 mol) and pyridine (0.5 mole) was heated under reflux for 5–7 h with vigorous stirring. After that, excess pyridine, acid anhydride and acid formed were taken off under reduced pressure. The residue thus obtained was treated with aq $NaHCO_3$ to remove acidic components and then extracted with $CHCl_3$ (5 × 50 mL). After removal of solvent from dried $CHCl_3$ extract, the residue was fractionally distilled under reduced pressure or recrystallized from petroleum ether (60–90 °C) or xylene.

1-Alkyl(Aryl)-2-amino-1-hydroxyalkylphosphonic and 1-Aminomethyl-1-hydroxyalkylphosphonic Acids 3; General Procedure:
To a mixture of dimethyl phosphite (15 mmol) and **2** (10 mmol) in DMF (2 mL) was added a catalytic amount of K_2CO_3 and Bu_4NBr and then stirred at r.t. for 5–24 h. The reaction was monitored by TLC. Upon completion of the reaction the mixture was extracted with CH_2Cl_2 (15 mL). The solid was filtered off, the solvent and volatile components were removed on a rotatory evaporator. The residue was washed with petroleum ether (3 mL) and then hydrolyzed either by 6N HCl (30 mL) or by a mixture of equal volume (10 mL) of 40% HBr in AcOH under reflux for 5–8 h. After cooling down, the solvents were removed under reduced pressure and the residue thus obtained was dissolved in a minimum amount of EtOH and treated with excess propylene oxide. Recrystallization from aq EtOH afforded **3** as fine colorless crystalline solid.

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