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Reaction of the Salt of N-Phosphoryl-N′-methylimidazole and Its Application to the Synthesis of Monoalkyl Dihydrogen Phosphates[1]

Hiroshi Takaku, Yoshifusa Shimada, and Katsuharu Aoshima

Department of Chemistry, Chiba Institute of Technology[2]

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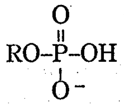
Numerous methods[3] have been reported for the phosphorylation of alcohols but there are only a few[4] which are well suited to the preparation of monoalkyl dihydrogen phosphates. Recently, Mukaiyama, *et al.*[5] reported the formation of several alkyl dihydrogen phosphates from the reaction of alcohols with inorganic phosphorous acid and mercury compounds.

We found that the oxidation of inorganic phosphorous acid with mercuric chloride in N-methylimidazole gives the salt of N-phosphoryl-N′-methylimidazole[6] (**3**) in a quantitative yield and **3** can react with a slight excess of alcohol, producing monoalkyl dihydrogen phosphate (**4**) in a good yield. Phosphorylation can also be effected without isolating the intermediate **3**.

When a mixture of phosphorous acid (**1**) and mercuric chloride in N-methylimidazole (**2**) was allowed to stand at 80° for 1 hr and then treated with a slight excess of ethanol at

Table I. Alkyl Dihydrogen Phosphates[a] (4)



$$RO-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O^-}{|}}{P}}-OH$$

Compd. No.	R	Yield (%)	mp (°C)	Rf[b]	Formula	Analysis (%)					
						Calcd.			Found		
						C	H	N	C	H	N
4a	methyl	76	167—169	0.26	$C_7H_{12}O_4NP$	40.98	5.90	6.83	40.85	6.05	6.88
4b	ethyl	78	163—165	0.37	$C_8H_{14}O_4NP$	43.84	6.49	6.39	44.08	6.69	6.59
4c	propyl	86	138—139	0.45	$C_9H_{16}O_4NP$	46.35	6.92	6.01	46.96	7.19	6.12
4d	iso-propyl	70	158—159	0.43	$C_9H_{16}O_4NP$	46.35	6.92	6.01	46.28	6.95	6.05
4e	butyl	75	138—140	0.54	$C_{10}H_{18}O_4NP$	48.58	7.34	5.66	48.61	7.54	5.61
4f	iso-butyl	67	156—158	0.51	$C_{10}H_{18}O_4NP$	48.58	7.34	5.66	48.73	7.61	5.75
4g	amyl	70	135—136	0.63	$C_{11}H_{20}O_4NP$	50.56	7.72	5.36	50.68	7.75	5.78
4h	iso-amyl	71	149—151	0.59	$C_{11}H_{20}O_4NP$	50.56	7.72	5.36	50.48	7.38	5.84

[a] The compounds were isolated as their monoanilinium salts.
[b] Paper chromatography was carried out by the ascending technique using Toyo Roshi No. 50 paper. Solvent system used was *n*-propanol–conc. ammonium hydroxide–water (6:3:1, v/v).

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[1] Part of this work was presented at the 92nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1972.

[2] Location: *Narashino-shi, Chiba.*

[3] D.M. Brown, "Advances in Organic Chemistry: Methods and Results," Vol. 3, Interscience Publishers, Inc., New York, 1963, p. 75.

[4] F. Cramer and G. Weimann, *Chem. Ber.*, **94**, 996 (1961).

[5] T. Obata and T. Mukaiyama, *J. Org. Chem.*, **32**, 1063 (1967).

[6] E. Jampel, M. Wakselman, and M. Vilkas, *Tetrahedron Letters*, **1968**, 3553.

80° for 4 hr, monoethyl dihydrogen phosphate (**4b**) was obtained as the monoanilinium salt in 78% yield. In a similar manner, various alkyl dihydrogen phosphates (**4**) were obtained in high yields and these results are listed in Table I. The analytically pure salts given in Table I were easily isolated by chromatography over acidic ion-exchange resin, followed by treatment with aniline and recrystallization from ethanol.

This reaction seems to proceed through an intermediate, inner salt of N-phosphoryl-N′-methylimidazole (**3**), formed from **1** and mercuric chloride in N-methylimidazole. The inner salt (**3**) in turn reacts with the alcohol to give monoalkyl dihydrogen phosphate (**4**) as shown in Chart 1. The salt (**3**) can be isolated as a barium salt by adding barium hydroxide. This structure was confirmed by elemental analysis and from infrared and nuclear magnetic resonance (in D_2O) spectra.

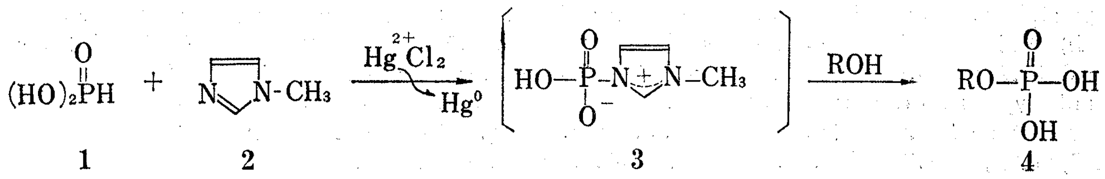

Chart 1

Monoalkyl dihydrogen phosphate (**4**) could not be isolated as pure anilinium salt when a small excess of alcohol was to be phosphorylated by this method; at the same time, several uncharacterized phosphorus compounds were also produced, thus making the purification much more difficult. However, when acetonitrile as a solvent and a slight excess of mercuric chloride were used, the formation of by-products decreased and **4** was obtained in a fairy good yield. According to this method, benzyl (**4i**) and bornyl (**4j**) dihydrogen phosphates were obtained from the corresponding alcohols as the anilinium salts in 83 and 72% yields respectively.

Of various oxidizing agents examined, mercuric chloride and mercurous chloride were found to be effective for this type of reaction while halogens were ineffective.

Experimental

Alcohols and solvents used were purified and dried by the conventional procedures. H_3PO_3 and mercury compounds were ground and dried over P_2O_5 *in vacuo* before use. Paper chromatography was carried out the ascending technique using Toyo Roshi No. 50 paper. Phosphorus compounds were made visible on paper chromatograms after spraying the chromatograms with the Isherwood Reagent.[7]

Ethyl Dihydrogen Phosphate (4b)——A mixture of 0.82 g (0.01 mole) of H_3PO_3 and 2.72 g (0.01 mole) of $HgCl_2$ in 3.28 g (0.04 mole) of N-methylimidazole was heated on a water bath at 80° for 1 hr with vigorous stirring, and then 2.30 g (0.05 mole) of dry EtOH was added to the reaction mixture. Stirring was continued at 80° for 4 hr. After removal of metallic Hg by filtration, the filtrate was concentrated and the residue was dissolved in 50 ml of acetone. The acetone solution was passed through a column (12 × 200 mm) of Amberlite IR-120 resin (H^+ form) already prepared in H_2O, and eluted with EtOH (50%). The combined eluate and washing were evaporated to dryness under a reduced pressure. The pale yellow syrupy residue was dissolved in 5 ml of 95% EtOH, 1.5 ml of aniline was added to the solution, and the mixture was kept standing in a refrigerator overnight. A white precipitate was separated and collected by filteration. The precipitate was recrystallized from EtOH. Monoanilinium salt of **4b** (1.71 g, 78%) was obtained as white crystals, mp 163—165°. *Rf* 0.37. *Anal.* Calcd. for $C_8H_{14}O_4NP$: C, 43.84; H, 6.49; N, 6.39. Found: C, 44.08; H, 6.69; N, 6.59.

By a similar procedure, alkyl dihydrogen phosphates (**4a**, **4c**, **4d**, **4e**, **4f**, **4g**, and **4h**) were prepared and their results are listed in Table I.

N-Phosphoryl-N′-methylimidazole (3)——A mixture of 1.64 g (0.02 mole) of H_3PO_3 and 5.44 g (0.02 mole) of $HgCl_2$ in 6.56 g (0.08 mole) of N-methylimidazole was heated on a water bath at 80° for 1 hr with vigorous stirring. The mixture was poured into 20 ml of water and metallic Hg was removed by filtration. The filtrate was adjusted to pH 9 with $Ba(OH)_2$ and the precipitate which occurred was centrifuged off.

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7) C.S. Hanes and F.A. Isherwood, *Nature*, **164**, 1107 (1949).

The supernatant was saturated with CO_2 to remove excess $Ba(OH)_2$ and centrifuged. After removal of excess $Ba(OH)_2$, the aqueous solution was concentrated *in vacuo* on a water bath. The dried residue was triturated with acetone to give a white powder, this powder was dissolved in water, and precipitated again with acetone. The sample for analysis was dried over P_2O_5 *in vacuo* at 100—110° to constant weight. *Anal.* Calcd. for $(C_4H_6O_3N_2P)_2Ba$: C, 20.84; H, 3.07; N, 12.15. Found: C, 20.97; H, 3.09; N, 12.63. IR ν_{max}^{KBr} cm^{-1}: 1170, and 1140 (phosphoryl groups). NMR (in D_2O) τ: 6.65 (3H, s, N-CH_3), 2.85 (2H, m, CH=CH) and 2.25 (1H, m, N-CH=N).

Benzyl (4i) and Bornyl (4j) Dihydrogen Phosphate——A solution of 0.82 g (0.01 mole) of H_3PO_3, 3.00 g (0.01 mole) of $HgCl_2$, and 3.28 g (0.04 mole) of N-methylimidazole in dry acetonitrile (2 ml) was warmed rapidly to 80°. After additional stirring for 1 hr, 1.40 g (0.013 mole) of benzyl alcohol was added. Stirring was continued at 80° for 4 hr. Precipitated metallic Hg was filtered off, the filtrate was evaporated under a reduced pressure, and the oil was desalted through a column (12 × 200 mm) of Amberlite IR-120 resin (H^+ form) prepared in 50% EtOH, followed by elution with the same solvent. The collected eluate (between 40 and 120 ml fractions) was concentrated, the oily residue was dissolved in 5 ml of 95% EtOH, and then 1.5 ml of aniline was added to the solution. The mixture was kept standing in a refrigerator overnight. A white precipitate separated and was collected by filtration. Dianilinium salt of benzyl dihydrogen phosphate (**4i**) (2.97 g, 81%) was obtained as white crystals, mp 151—153°. *Rf* 0.55. *Anal.* Calcd. for $C_{19}H_{23}O_4N_2P$: C, 61.79; H, 4.97; N, 7.48. Found: C, 61.36; H, 5.06; N, 4.31.

Similarly, bornyl dihydrogen phosphate (**4j**) was synthesized from 0.013 molar equivalent of borneol, and it was obtained in 2.46 g (75%) as monoanilinium salt, mp 194—196°. *Rf* 0.64. *Anal.* Calcd. for $C_{16}H_{26}O_2NP$: C, 58.72; H, 8.02; N, 4.28. Found: C, 57.99; H, 8.11; N, 4.31.

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Studies on Thiophene Derivatives. IX. Decarboxylation of 3-(5-Substituted 2-thienyl)malonic Acids[1]

Yôichi Taniguchi and Hidefumi Katô

Department of Chemistry, Kurume Technical College[2]

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In our previous papers,[3,4] a number of 2-heteroaryl-3-(5-substituted 2-thienyl)acrylic acid derivatives have been reported, and the *cis* and *trans* configurations of these acrylic acids were determined by the measurement of dipole moment. Although quite a few 3-(5-substituted 2-thienyl)acrylic acids were prepared by base catalized condensations, such as Perkin reaction, Knoevenagel reaction, Reformatskiy reaction, and Wittig reaction, relatively few attempts have been made to specify the configurations of these thienyl acrylic acids.[5]

We now report the preparation and specification of the *cis*- and *trans*-3-(5-substituted 2-thienyl)acrylic acids (**3a**—**c**) and (**4a**—**c**).

Knoevenagel reactions of 5-substituted 2-thiophenecarbaldehydes (**1a**: R=H, **1b**: R=Br, and **1c**: R=NO_2) with malonic acid afforded the corresponding dicarboxylic acids (**2a**—**c**), which were decarboxylated in acetic anhydride at 140° to give a mixture of *cis* and *trans* acrylic acids (**3a**—**c** and **4a**—**c**). The structures and spectral data nuclear magnetic resonance (NMR), ultraviolet (UV) and infrared (IR) of these acrylic, acids which were separated by column

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[1] Part VIII: H. Saikachi and Y. Taniguchi, *Yakugaku Zasshi*, **88**, 1566 (1968).
[2] Location: *1232 Komorino, Kurume, Fukuoka.*
[3] H. Saikachi and Y. Taniguchi, *Yakugaku Zasshi*, **88**, 1256 (1968).
[4] H. Saikachi and Y. Taniguchi, *Yakugaku Zasshi*, **88**, 1559 (1968).
[5] *a*) E.B. Robert and A.C. John, *J. Org. Chem.*, **30**, 1588 (1965); *b*) L. Rand, D. Haidukewych, and R.J. Dolinski, *ibid.*, **31**, 1272 (1966); *c*) H. Dresser and J.E. Graham, *ibid.*, **32**, 985 (1967); *d*) N.N. Girotra and N.L. Wendler, *ibid.*, **34**, 3192 (1969).