The mild synthesis of oxime phosphates by Atherton–Todd reaction

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The oximes (**1a–i**) on reaction with diethyl phosphonates (**2**) in the presence of triethylamine using chlorocarbons as solvents mildly provide oxime phosphates (**3a–i**) in good yields and have no the Beckmann rearrangement.

Keywords: oxime phosphates, Atherton–Todd reaction

The phosphorylation and dephosphorylation of proteins plays an important role in regulating biochemical processes.[1] Moreover, phosphorylated biomolecules have many unique activities.[2] Phosphate prodrugs are widely used to increase the aqueous solubility of poorly water-soluble drugs and to improve their oral bioavailability, which would otherwise reduce the clinical usefulness of these drugs.[3] The phosphate units which are attached either directly or via a spacer group to a hydroxyl or an amine group of the parent drug, are hydrolysed by alkaline phosphatase to the parent drug.[4] Recently a study of ketoxime phosphates using as phosphate prodrug structures has been reported.[5] Therefore the development of a facile and efficient method for synthesis of the oxime phosphates is required.

The phosphorylation of alcohols and/or phenols by reaction with phosphorus trichloride to give phosphotriesters is common practice in organic synthesis. However, the preparation of unsymmetrical phosphotriesters which possess three distinct alkyl groups in the phosphotriester molecules is more difficult. Accordingly efforts to construct these compounds have been made, providing many approaches to the unsymmetrical phosphoric acids derivatives.[6] These important methods for the conversion of hydroxy groups of alcohols or phenols to unsymmetrical phosphotriesters include reactions of a target alcohols or phenols with dialkyl chlorophosphate,[7] with triester phosphite in the presence of I_2,[8] with diester phosphite in the presence of I_2,[9] by the reaction of Mitsunobu reaction,[10] as well as Atherton–Todd reaction.[11] In contrast to the reaction of the hydroxyl groups of alcohols or phenols, that of oximes is rather unstable. Oximes readily undergo the Beckmann rearrangement to the corresponding amides under acidic conditions.[12] Deoximation reactions to the corresponding carbonyl compounds occurs in the presence of the oxidative reagents[13] such as halogens. Therefore, we wish to report herein an effective, straightforward strategy to prepare oxime phosphates from oximes including ketoximes and aldoximes, by the Atherton–Todd reaction in good yields (Scheme 1). Note that Beckmann rearrangement of ketoximes and deoximation reaction of oximes was not observed in this procedure.

In summary, a facile and straightforward synthesis of oxime phosphates under Atherton–Todd reaction conditions is described in the presence of triethylamine using chlorocarbons as solvents and an oxime and diethyl phosphite as starting materials in good yields. This method is simple in operation and gives good yields of oxime phosphates (Table 1).

General procedure

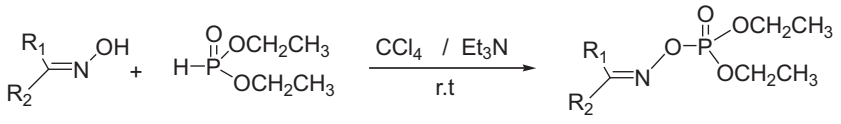
All melting points were determined on a Yanaco apparatus and are uncorrected. NMR spectra were measured on a Brucker 300 MHz NMR instrument in $CDCl_3$, chemical shifts are expressed as δ units, TMS was used as an internal standard for ^{1}H NMR, and ^{13}C NMR. IR spectra were determined as liquid films on Avatar360FT-IR spectrophotometer.

Elemental analysis was carried out with a Yanaco CHNcorder MT-3 Analyser. All the ketones and aldehydes were redistilled before being used.

To the mixture of diethyl phosphite **2** (3.45 g, 0.025 mol) and triethylamine(20 ml) was added dropwise a solution of oximes **1** (0.025 mol) dissolved in carbon tetrachloride(20 ml) at such rate that the internal temperature did not rise above 5°C under ice-cooling with vigorous stirring. After completion of the addition, the ice-bath was removed, and the temperature of the reaction mixture rose spontaneously to room temperature for 0.5 h. The mixture was stirred at room temperature for 5 h. The solid of reaction mixture was Then separated by suction filtration through celite and washed with ether(2 × 10 ml). Evaporation of the solvent gave crude product. The product was purified by column chromatography on silica gel using a mixture of ethylacetate and hexane as eluent(10: 90) to give oil liquid compounds **3**.

Phenylmethaniminyl diethyl phosphate (**3a**): Oil,^{1}H NMR ($CDCl_3$) 7.07–7.65 (m, 5H, C_6H_5), 8.12 (s, 1H, H-C=N), 4.15–4.27 (m, 4H, OCH_2), 1.15–1.28 (m, 6H, CH_3); ^{13}C NMR ($CDCl_3$) 16.21, 16.31, 62.7, 62.9, 166.5, 142.3, 130.7, 125.7, 121.6, 120.6, 118.6; IR (film, cm^{-1}) 1656 (C=N), 1040 (P–O–C), 990 (N-O), 1211 (P = O); Anal. Calcd. for $C_{11}H_{16}NO_4P$: C, 51.36; H, 6.27; N, 5.45. Found: C, 51.37; H, 6.61; N, 5.72.

Cyclohexaniminyl diethyl phosphate (**3b**): Oil, ^{1}H NMR ($CDCl_3$) 4.05–4.17 (m, 4H, OCH_2), 1.15–1.28 (m, 6H, CH_3), 1.29–1.31 (m, 6H, $3CH_2$), 1.52–1.59 (m, 4H, $2CH_2$); ^{13}C NMR ($CDCl_3$) 16.51, 16.61, 61.7, 61.9, 160.5, 40.2, 38.2, 25.7, 25.8, 30.6; IR (film, cm^{-1})



1 **2** **3**

a: $R^1 = C_6H_5$, R^2 = H b: $R^1 = R^2 = -(CH_2)_5-$
c: R^1 = n-Pr, R^2 = Me d: R^1 = 4-ClC_6H_4, R^2 = Me
e: R^1 = 4-$CH_3OC_6H_4$, R^2 = Me f: R^1 = i-Bu, R^2 = Me
g: R^1 = Et, R^2 = Me h: $R^1 = R^2 = -(CH2)_6-$
i: R^1 = 4-$CH_3C_6H_4$, R^2 = Me

Scheme 1

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Table 1 Synthesis of compounds (**3a–i**)

Compounds	R_1	R_2	Yield/%
3a	C_6H_5	H	90
3b	$-(CH_2)_5-$	$R^1 = R^2$	92
3c	n-Pr	Me	95
3d	4-ClC_5H_4	Me	94
3e	4-$CH_3OC_5H_4$	Me	90
3f	i-Bu	Me	92
3g	Et	Me	94
3h	$-(CH_2)_6-$	$R^1 = R^2$	93
3i	4-$CH_3C_5H_4$	Me	95

1653 (C=N), 1043 (P–O–C), 956 (N–O), 1218 (P = O); Anal. Calcd. for $C_{10}H_{20}NO_4P$: C, 48.19; H, 8.09; N, 5.62. Found: C, 48.36; H, 8.31; N, 5.72.

Pentan-2-iminyl diethyl phosphate (**3c**): Oil, ^{1}H NMR ($CDCl_3$) 1.33 (t, 2H, J = 8,24 Hz, CH_2), 1.55 (m, 2H, CH_2), 2.01 (s, 3H, CH_3), 0.865 (t, 3H, J = 7.12 Hz, CH_3), 4.15–4.18 (m, 4H, OCH_2), 1.05–1.18 (m, 6H, CH_3); ^{13}C NMR ($CDCl_3$) 16.52, 16.41, 60.7, 61.5, 163.5, 15.2, 16.2, 38.7, 25.6; IR (film, cm^{-1}) 1643 (C=N), 1043 (P–O–C), 976 (N-O), 1216 (P = O); Anal. Calcd. for $C_9H_{20}NO_4P$: C, 45.57; H, 8.50; N, 5.90. Found: C, 45.36; H, 8.31; N, 5.70.

1-(4-chlorophenyl)ethaniminyl diethyl phosphate (**3d**): Oil, ^{1}H NMR ($CDCl_3$) 7.19–7.34 (m, 4H, C_6H_4), 1.90 (s, 3H, CH_3), 4.12–4.15 (m, 4H, OCH_2), 1.15–1.20 (m, 6H, CH_3); ^{13}C NMR ($CDCl_3$) 16.51, 16.31, 59.7, 61.5, 17.5, 155.3, 136.3, 130.7, 129.7, 132.6; IR (film, cm^{-1}) 1650 (C=N), 1051 (P–O–C), 956 (N-O), 1211 (P = O); Anal. Calcd. for $C_{12}H_{17}ClNO_4P$: C, 47.15; H, 5.61; N, 4.58. Found: C, 47.36; H, 5.31; N, 4.70.

1-(4-methoxyphenyl)ethaniminyl diethyl phosphate (**3e**): Oil, ^{1}H NMR ($CDCl_3$) 6.97–7.45 (m, 4H, C_6H_4), 3.78 (s, 3H, CH_3O), 1.93 (s, 3H, CH_3), 4.07–4.11 (m, 4H, OCH_2), 1.11–1.16 (m, 6H, CH_3); ^{13}C NMR ($CDCl_3$) 16.31, 16.41, 59.7, 60.3, 55.9, 23.6, 155.3, 126.3 163.3, 130.7, 114.7; IR (Film, cm^{-1}) 1652 (C=N), 1050 (P–O–C), 966 (N-O), 1221 (P = O); Anal. Calcd. for $C_{13}H_{20}NO_5P$: C, 51.83; H, 6.69; N, 4.65. Found: C, 51.46; H, 6.51; N, 4.70.

3-methylpentan-2-iminyl diethyl phosphate (**3f**): Oil, ^{1}H NMR ($CDCl_3$) 1.90 (s, 3H, CH_3), 1.82–1.86 (m, 1H, CH), 1.34 (d, 2H, J = 6.3 Hz, CH_2), 4.07–4.11 (m, 4H, OCH_2), 1.11–1.16 (m, 12H, CH_3); ^{13}C NMR ($CDCl_3$) 14.81, 14.41, 59.7, 58.3, 18.6, 47.9, 23.6, 24.0, 158.3; IR (film, cm^{-1}) 1622 (C=N), 1050 (P–O–C), 986 (N-O), 1220 (P = O); Anal. Calcd. for $C_{10}H_{22}NO_4P$: C, 47.80; H, 8.83; N, 5.57. Found: C, 47.56; H, 8.51; N, 5.71.

Butan-2-iminyl diethyl phosphate (**3g**):Oil, ^{1}H NMR ($CDCl_3$) 4.07 (m, 4H, OCH_2), 1.04–1.11 (m, 9H, CH_3), 1.43 (q, 2H, J = 6.2 Hz, CH_2), 1.90 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) 14.8, 58.3, 158.5, 18.0, 7.2, 31.1; IR (film, cm^{-1}) 1620 (C=N), 1040 (P–O–C), 967 (N-O), 1220 (P = O); Anal. Calcd. for $C_8H_{18}NO_4P$: C, 43.05; H, 8.13; N, 6.28. Found: C, 43.06; H, 8.21; N, 6.51.

Cycloheptaniminyl diethyl phosphate (**3h**): Oil, ^{1}H NMR ($CDCl_3$) 4.07–4.11 (m, 4H, OCH_2), 1.11–1.16 (m, 6H, CH_3), 1.29–1.30 (m, 8H, CH_2), 1.51 (m, 4H, CH_2); ^{13}C NMR ($CDCl_3$) 14.8, 14.0, 58.3, 59.1, 164.4, 30.0, 37.0, 23.6, 32.2; IR (film, cm^{-1}) 1625 (C=N), 1060 (P–O–C), 967 (N-O), 1220 (P = O); Anal. Calcd. for $C_{11}H_{22}NO_4P$: C, 50.18; H, 8.42; N, 5.32. Found: C, 50.06; H, 8.21; N, 5.41.

1-(4-methylphenyl)ethaniminyl diethyl phosphate (**3i**): Oil, ^{1}H NMR ($CDCl_3$) 7.13–7.55 (m, 4H, C_6H_4), 4.15–4.27 (m, 4H, OCH_2), 1.11 (t, 3H, J = 6.5 Hz, CH_3), 1.01 (t, 3H, J = 6.3 Hz, CH_3), 2.38 (s, 3H, CH_3), 1.97 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) 14.3, 14.0, 58.3, 59.1, 155.4, 17.6.0, 24.4, 131.6, 140.2, 129.1; IR (film, cm^{-1}) 1625 (C=N), 1050 (P–O–C), 968 (N-O), 1220 (P = O); Anal. Calcd. for $C_{13}H_{20}NO_4P$: C, 54.73; H, 7.07; N, 4.91. Found: C, 54.66; H, 7.22; N, 4.61.

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