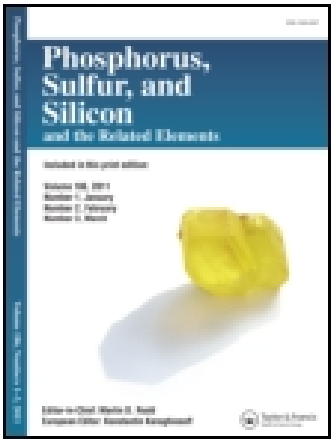

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N-(Diphenoxyphosphoryl)Succinimide: Synthesis and Reaction with Alkoxides

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N-(DIPHENOXYPHOSPHORYL)SUCCINIMIDE: SYNTHESIS AND REACTION WITH ALKOXIDES

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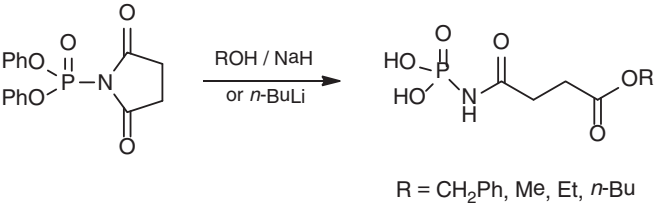
GRAPHICAL ABSTRACT



Abstract *Reaction of succinimide with diphenylchlorophosphate in the presence of lithium bis(trimethylsilyl)amide followed by aqueous work-up led to the formation of amidophosphate 3. The same reaction performed in the presence of sodium hydride yield N-(diphenylphosphoryl)succinimde 4, which undergoes nucleophilic ring opening with sodium alkoxides resulted in the formation of phosphoroamidate analogues 5 a-d in good yields.*

Keywords Phosphorylated succinimide; nucleophilic ring opening; phosphoramidates

INTRODUCTION

Recently, *N*-phosphoryl oxazolidinones[1,2] as well as *N*-phosphoryl thiazolidine derivatives[3] have been proposed as useful and stable reagents for phosphorylation of alcohols. Lal et al. applied diphenyl phosphoryl azide (DPPA) – the known acyl azide forming reagent[4] – also for the conversion of alcohols into azides through the formation of phosphate. This shows that *N*-phosphorylated compounds containing a cleavable P—N bond may be used as an alternative of phosphorochloridates, in which a reactive P—Cl bond is present. Moreover, other compounds containing labile P—N bonds, e.g., diethylphosphorosuccinimidate, have been used for the phosphorylation of alcohols under acidic or neutral conditions.[5] Hydrolysis of di(*n*-butyl)phosphorosuccinimidate in the presence of sodium borohydride in aqueous ethanol gives *O*,*O*-di(*n*-butyl)phosphoramidate.[6] In the course of our investigations on phosphorylation reactions,[7] the synthesis of diphenylphosphoro-succinimidate has been attempted with the aim of using this reagent for reaction with alcohols.

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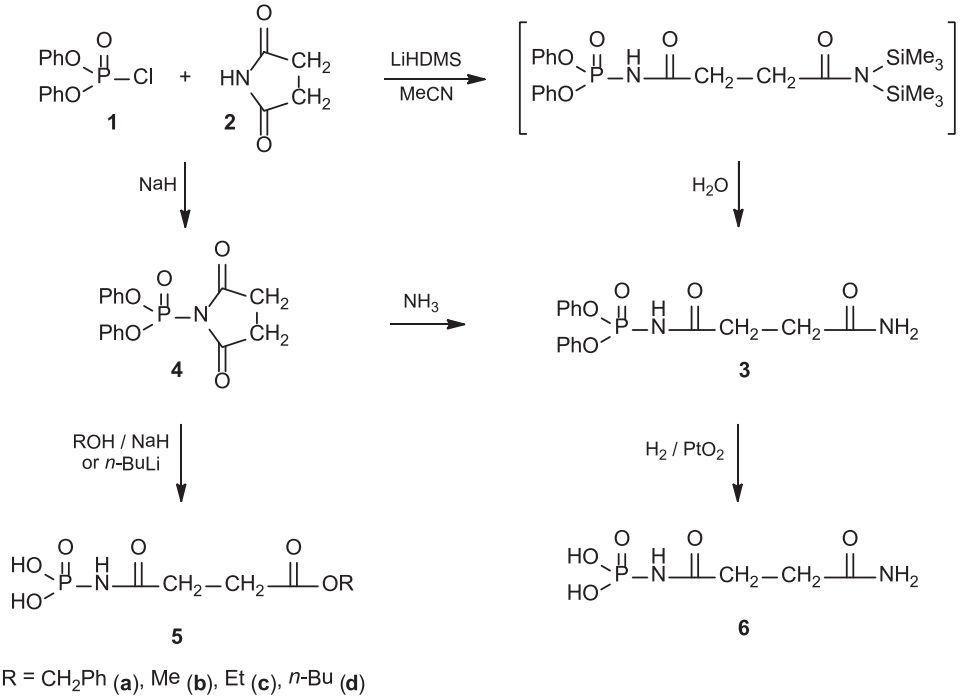
RESULTS AND DISCUSSION

Reaction of diphenyl chlorophosphate **1** with succinimide **2** and lithium bis(trimethylsilyl)amide (LiHMDS) in acetonitrile or tetrahydrofurane (THF) solution followed by aqueous workup surprisingly yielded not the succinimide derivative but the amidophosphate **3**, suggesting that the succinimide ring is cleaved in the course of the reaction (Scheme 1). However, treatment of succinimide with 1 equivalent of either *n*-butyl lithium (*n*-BuLI) or sodium hydride in acetonitrile or THF followed by the addition of diphenyl chlorophosphate yielded the expected *N*-(diphenoxyphosphoryl)succinimide **4** in good yield. Although compound **4** is a low melting reagent, it can be stored for months and is easily handled.



Scheme 1 Synthetic route to the substituted phosphoroamidates **5** and **6**.

Chlorophosphates usually react with alcohols in the presence of triethylamine as a hydrochloric acid scavenger. Interaction of alcohols with compound **4** in the presence of triethylamine did not result in the formation of products. As the leaving-group ability of the succinimide anion is worse than that of chloride, the nucleophilicity of the alcohol was increased by formation of the corresponding alkoxide. In our study, lithium and sodium alkoxides were prepared. Unexpectedly, when lithium benzyloxide was reacted with *N*-(diphenoxyphosphoryl)succinimide **4**, the benzyl ester of succinic amide derivative **5a** was obtained, together with only traces of the corresponding phosphate triester. The same was observed when methyl, ethyl, or *n*-butyl alcohols were used. Methyl, ethyl, or *n*-butyl esters of succinic amide derivatives **5b**, **5c**, and **5d** were thus prepared; the products contained as impurity only a small amount of the corresponding monoalkyl phosphates. The results presented clearly indicate that nucleophilic ring opening is the driving force leading to the formation of esters of succinic acid. Moreover, reaction of **4** with 1 equivalent of aqueous

ammonia also led to ring opening and resulted in the formation of compound **3**, the same compound formed in the reaction of diphenyl chlorophosphate with succinimide in the presence of LiHMDS, confirming presumably the same reaction pathway. This clearly shows that the P—N—C=O bond system makes the carbonyl carbon atom more susceptible to the attack by nucleophilic species as compared with the pentavalent phosphorus atom. Moreover, catalytic reduction (H_2/PtO_2) of phenyl ester **3** resulted in the formation of the acid **6**.

In conclusion, we have developed a simple method for functionalization of succinic acid. This method makes it possible to prepare its monoesters or monoamides, together with the phosphorylated amide, starting from *N*-(diphenoxyphosphoryl)succinimide. Since phosphoroamidates containing a modified succinic acid have been shown to be putative inhibitors of the enzyme aspartate-semi-aldehyde dehydrogenase,[8] this method may also be useful for the preparation of these compounds.

EXPERIMENTAL

All chemicals were commercially available and used without further purification. Thin layer chromatography (TLC) was performed using Merck aluminum-backed plates (Kieselgel 60 F_{254}), and visualization was achieved by ultraviolet (UV) light. Separations by column chromatography were performed using silica gel (0.063–0.200 mm). MALDI-TOF-MS spectra were recorded with a Biflex III apparatus. FTIR spectra were measured for crystalline compounds with a Momentum microscope (IR detector) attached to a Mattson Genesis II Gold spectrometer (IR source). ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded with a Varian Unity Plus spectrometer (500 MHz) operating at 500 MHz, 125 MHz, and 200 MHz, respectively. Chemical shifts are given in parts per million (ppm) relative to tetramethylsilane as internal or 85% H_3PO_4 as external standard.

Synthesis of Diphenyl (4-Amino-4-Oxobutanoyl)Amidophosphate (3)

To a solution of succinimide **1** (0,99 g, 10 mmol) in anhydrous acetonitrile (50 mL), LiHMDS (10 mL of 1 M solution in THF) was added portionwise with stirring, while the temperature was kept at $-10^{\circ}C$. After 20 min, diphenyl chlorophosphate (2.06 mL, 10 mmol) was added by means of a syringe and the reaction mixture was stirred for additional 20 min. The solvent was evaporated; the residue was dissolved in ethyl acetate (20 mL), washed with water (three times × 10 mL), and dried over $MgSO_4$. The solvent was evaporated again. The residue was dissolved in diethyl ether (20 mL) and kept in a refrigerator. The precipitated product was collected. Yield: 2.57 g (74%). mp. 141–142°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.45–2.55 (m, 2H, CH_2), 2.60–2.70 (m, 2H, CH_2), 5.55–5.75 (br s, 2H, $CONH_2$), 7.15–7.45 (br s, 10H, C_6H_5), 8.25 (br s, 1H, NH); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 29.0, 31.3, 120.5, 125.5, 130.0, 150.0, 172.9, 173.9; ^{31}P NMR (200 MHz, DMSO-d_6): $\delta = -8.8$. IR (solid, cm^{-1}): ν = 1024, 1161, 1229, 1295, 1599, 1664. Anal. Calcd. for $C_{16}H_{17}N_2O_5P$ (348.29): C, 55.18; H, 4.92; N, 8.04. Found: C, 55.32; H, 5.05; N, 7.86. MS: m/z = 349 (MH^+).

Synthesis of *N*-(Diphenoxyphosphoryl)-Succinimide (4)

To a solution of succinimide **1** (0.99 g, 10 mmol) in anhydrous acetonitrile (20 mL), NaH (0.4 g as 60% suspension in mineral oil, 10 mmol) was added at $-10^{\circ}C$ with stirring under argon. After 10 min, diphenyl chlorophosphate (2.06 mL, 10 mmol) was added

and the reaction mixture was kept for 4 h. The solvent was evaporated; the residue was dissolved in ethyl acetate, the organic layer was washed with water, dried (over $MgSO_4$), and chromatographed on silica gel using ethyl acetate/hexane 2:1 v/v as eluent. Yield: 2.45 g (75%), low melting product, which solidified upon standing at low temperatures. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.35$ (s, 4H, $-CH_2\ -CH_2-$), 7.25–7.45 (br s, 10H, C_6H_5), ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 29.0, 120.5, 125.5, 130.0, 150.0, 173.9$; ^{31}P NMR (200 MHz, DMSO-d_6): $\delta = -10.2$. IR (solid, cm^{-1}): $\nu = 1034, 1275, 1688$. Anal. Calcd. for $C_{16}H_{14}NO_5P$ (331.25): C, 58.01; H, 4.26; N, 4.23. Found: C, 57.89; H, 4.21; N, 4.12. MS: m/z = 332 (MH^+).

Synthesis of Substituted Phosphoroamidates: General Procedure

To a solution of the respective alcohol (5 mmol) in dry acetonitrile (10 mL), an equimolar amount of sodium hydride or *n*-butyl lithium (2.5 M solution in hexane) was added and the solution was kept at -10°C for 10 min. Then, compound **4** (5 mmol) was added under argon and the reaction mixture was allowed to stand for 2 h. Subsequently, the reaction mixture was quenched with 1 N HCl (6 mL), the solvent was evaporated, and the residue was extracted with ethyl acetate. The organic layers were dried (over $MgSO_4$) and the solvent was evaporated. In the case of **5a**, the product was purified by column chromatography using ethyl acetate/hexane 2:1 v/v as eluent.

Benzyl 4-[(Diphenoxyphosphoryl)Amino]-4-Oxobutanoate (5a)

Oil. Yield: 1.53 g (70%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.55$–2.80 (m, 4H, $-CH_2-CH_2-$), 5.20 (s, 2H, CH_2–C_6H_5), 7.10–7.45 (br s, 15H, C_6H_5), 8.80 (br s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 28.9, 31.8, 67.8, 121.5, 125.6, 127.3, 127.9, 129.3, 130.0, 141.3, 150.0, 172.9, 173.9$; ^{31}P NMR (200 MHz, DMSO-d_6): $\delta = -8.6$. IR (solid, cm^{-1}): $\nu = 1025, 1164, 1239, 1285, 1655, 1724$. Anal. Calcd. for $C_{23}H_{22}NO_6P$ (439.39): C, 62.85; H, 5.05; N, 3.19. Found: C, 62.72; H, 4.97; N, 3.27. MS: m/z = 440 (MH^+).

Methyl 4-[(Diphenoxyphosphoryl)Amino]-4-Oxobutanoate (5b)

Oil. Yield: 1.65 g (92%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 2.45$–2.55 (m, 2H, CH_2), 2.60–2.70 (m, 2H, CH_2), 3.65 (s, 3H, CH_3), 7.10–7.35 (br s, 10H, C_6H_5), 8.75 (br s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 29.0, 31.3, 52.0, 121.9, 125.4, 129.8, 149.8, 172.68, 173.6$. ^{31}P NMR (200 MHz, DMSO-d_6): $\delta = -8.5$. IR(solid, cm^{-1}): $\nu = 1027, 1162, 1244, 1284, 1639, 1714$. Anal. Calcd. for $C_{17}H_{18}NO_6P$ (363.30): C, 56.20; H, 4.99; N, 3.86; P, 8.53. Found: C, 56.15; H, 4.91; N, 3.75. MS: m/z = 364 (MH^+).

Ethyl 4-[(Diphenoxyphosphoryl)Amino]-4-Oxobutanoate (5c)

Oil. Yield: 1.69 g (90%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.3$ (t, $J = 7.0$ Hz, 3H, CH_3), 2.45–2.55 (m, 2H, CH_2), 2.60–2.70 (m, 2H, CH_2), 4.12 (q, $J = 7.0$ Hz, 2H, CH_2), 7.10–7.45 (br s, 10H, C_6H_5), 8.65 (br s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 16.3, 29.3, 32.5, 63.9, 121.5, 125.7, 130.0, 149.5, 172.5, 173.5$. ^{31}P NMR (200 MHz, DMSO-d_6): $\delta = -8.5$. IR (solid, cm^{-1}): $\nu = 1032, 1155, 1229, 1291, 1629, 1684$. Anal.

Calcd. for $C_{18}H_{20}NO_6P$ (377.32): C, 57.30; H, 5.34; N, 3.71. Found: C. 57.10; H, 5.21; N, 3.55. MS: m/z = 378 (MH^+).

n-Butyl 4-[(Diphenoxyphosphoryl)Amino]-4-Oxobutanoate (5d)

Oil. Yield: 1.88 g (93%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.1$ (t, $J = 7.0$ Hz, 3H, CH_3), 1.35–1.55 (m 4H, $-CH_2-CH_2$), 2.45–2.55 (m, 2H, CH_2), 2.60–2.70 (m, 2H, CH_2), 4.10 (m, 2H, CH_2), 7.10–7.45 (br s, 10H, C_6H_5), 8.65 (br s, 1H, NH). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 16.0, 18.3, 29.6, 31.4, 32.3, 51.8, 121.6, 125.3, 129.7, 149.7, 172.6, 173.7$. ^{31}P NMR (200 MHz, DMSO-d_6): $\delta = -8.6$. IR (solid, cm^{-1}): $\nu = 1028, 1165, 1232, 1295, 1621, 1678$. Anal. Calcd. for $C_{20}H_{24}NO_6P$ (405.39): C, 59.26; H, 5.97; N, 3.46. Found: C, 59.10; H, 6.02; N, 3.34. MS: m/z = 406 (MH^+).

Synthesis of (4-Amino-4-Oxobutanoyl)-Phosphoramidic Acid (6)

Compound **3** (0.35 g, 1 mmol) was dissolved in methanol (20 mL), PtO_2 (50 mg) was added, and the mixture was stirred under a hydrogen-rich atmosphere (1 bar) for 4 h. Filtration and evaporation of the solvent afforded a hygroscopic white powder. Yield: 0.18 g (93%). ^{1}H NMR (500 MHz, D_2O): $\delta = 2.45$–2.55 (m, 2H, CH_2), 2.60–2.70 (m, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 29.4, 32.8, 172.4, 174.0$. ^{31}P NMR (200 MHz, DMSO-d_6): $\delta = -8.2$. IR (solid, cm^{-1}): $\nu = 1042, 1152, 1220, 1292, 1589, 1662$. Anal. Calcd. for $C_4H_9N_2O_6P$ (196.09): C, 24.50; H, 4.63; N, 14.29. Found: C, 24.55; H, 4.51; N, 14.17.

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