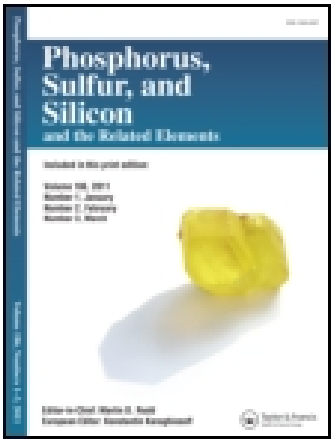

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis of the Phosphonoanalogue of Benzo[c]pyroglutamic Acid

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SYNTHESIS OF THE PHOSPHONOANALOGUE OF BENZO[C]PYROGLUTAMIC ACID

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Phosphonic analogue 1 of benzo[c]pyroglutamic acid was synthesized by three-step synthesis starting from N-tert-butylphtalimide and triethylphosphite. The acid-catalyzed, oxidative cascade conversion of phosphonate 11 to phthalimide and phosphoric acid diethyl ester was observed. A mechanism for this transformation was proposed.

Keywords Autoxidation; isoindolin-1-ones; phosphonic acids

INTRODUCTION

The isoindolin-1-one fragment is present in synthetic (e.g., indoprofen–anti-inflammatory agent) as well as in naturally occurring compounds, in particular in alkaloids (e.g., lennoxamine, nuevamine).[1–5] Isoindolin-1-one-3-yl-carboxylic acid, which is a benzanullated analogue of pyroglutamic acid, shows interesting and manifold biological activities.[6,7] Since phosphonic acid derivatives exhibit very high potency in inhibiting enzymes,[8–10] we have recently reported the synthesis of phosphonic acids possessing isoindolin-1-one moiety by dehydrative aromatization of epoxyisoindolylphosphonates.[11,12] These compounds showed biological activity as inhibitors of phosphodiesterase. Therefore, continuing our studies on the synthesis and biological properties of phosphonic analogues of natural compounds,[13,14] we have prepared a new isoindolin-1-one-3-yl-phosphonic acid **1**, which is a basic representative of this type of phosphonic acid.

RESULTS AND DISCUSSION

We have proposed two approaches to the synthesis of phosphonic acids **1**, which are shown in the retrosynthetic Scheme 1. The first route **A** is based on the reductive amination and cyclization of acylphosphonate **2**, while the second route **B** is based on the use of *N*-protected 3-hydroxy-isoindolin-1-one **3** as a key intermediate and a substrate for phosphonylation.

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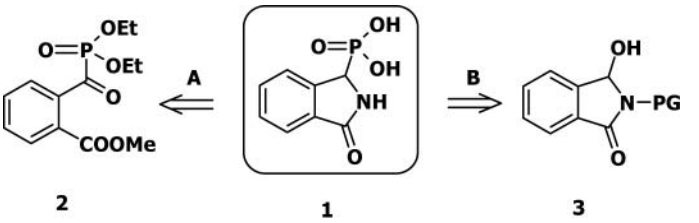
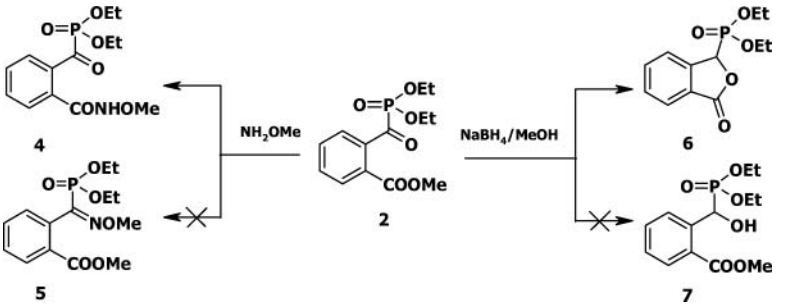


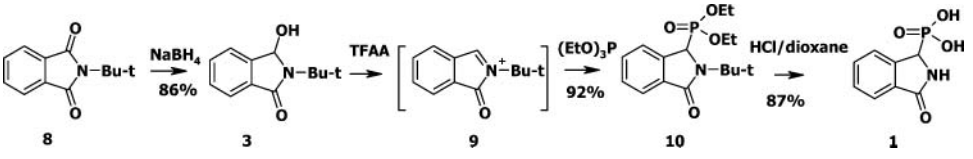
Scheme 1 Retrosynthetic analysis of isoindolin-1-one-3-yl phosphonic acid **1**.

A key compound of route **A**, the acylphosphonate **2**, has been synthesized by the reaction of triethylphosphite with chloride of monomethyl ester of phthalic acid.[15] For the reductive amination of acylphosphonate **2**, we used a well-known method, i.e., the transformation of **2** into oxime and its reduction to the corresponding amine.[16–18] However, under standard reaction conditions,[19] we have obtained only the hydroxamic acid derivative **4** (Scheme 2). The analysis of the reaction mixture by means of ^{31}P NMR spectroscopy does not detect even traces of compound **5**. Change of the reaction sequence, i.e., first reduction of acylphosphonate **2** by sodium borohydride with formation of α-hydroxyphosphonate **7** and its subsequent Mitsunobu amination,[20,21] was also unsuccessful, because under the reaction conditions (MeOH, 0–2°C), the hydroxyphosphonate **7** underwent intramolecular cyclization with formation of phosphonate **6** in 65% yield (Scheme 2).



Scheme 2 Attempts to prepare phosphonic acid **1** via route **A**.

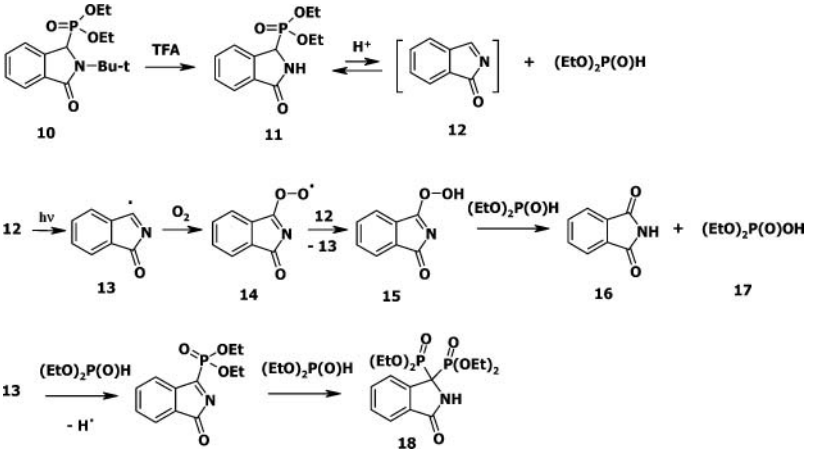
On the other hand, route **B** turned out to be the most suitable for the preparation of isoindolin-1-one-3-yl-phosphonic acid **1**, which was obtained by three-step synthesis as shown in Scheme 3. The reduction of *N-tert*-butylphthalimide **8** with sodium borohydride in methanol at 0–5°C afforded the 3-hydroxyisoindolone **3** in 86% yield. Treatment of compound **3** with trifluoroacetic anhydride generated a highly reactive acyliminium salt **9,** which reacted with triethylphosphite to give the phosphonate **10**.[22] Finally, acid hydrolysis



Scheme 3 Synthesis of phosphonic acid **1** via route **B**.

of phosphonate **10** led to the formation of isoindolin-1-one-3-yl-phosphonic acid **1** in 69% total yield. Acid **1** is a solid substance with a high melting point; it is soluble in water at pH > 8 and insoluble in organic solvents.

It was found that the phosphonate **10** could be selectively *N*-deprotected by refluxing for 1 h in trifluoroacetic acid and thus converted into the phosphonate **11** in almost quantitative yield (Scheme 4). After evaporation of the solvent and treatment of the residue with aqueous $NaHCO_3$, the phosphonate **11** was isolated as a crystalline substance. Without treatment with $NaHCO_3$, the product was isolated as viscous oil, which slowly crystallized over several weeks. The ^1H, ^{31}P NMR, and LCMS spectra showed that the mixture (oil + solid) consists of phosphonate **11**, phthalimide **16**, diethylphosphate **17**, and *bis*-phosphonate **18**. We assume that in the presence of traces of acid, which were not neutralized by $NaHCO_3$, retro-Michael reaction of phosphonate **11** occurred with formation of diethylphosphite and imine **12,** which underwent autooxidation,[23] and via the formation of radicals **13** and **14** (initiation stage) converted into the hydroperoxide **15** (chain growth stage). Reaction of the latter with diethylphosphite led to the formation of phosphoric acid diethyl ester **17** and phthalimide **16**. Formation of *bis*-phosphonate **18** can be explained by reaction of the radical **13** with two molecules of diethylphosphite, which confirms the proposed mechanism.



Scheme 4 Synthesis and oxidative transformations of phosphonate **11**.

In summary, the phosphonic analogue of benzo[c]pyroglutamic acid—the isoindolin-1-one-3-yl-phosphonic acid **1—**was prepared with 69% overall yield by a three-step synthesis starting from the *N*-*tert*-butylphtalimide (route **B**). Route **A**, starting from the acylphosphonate **2**, led to the formation of hydroxamic acid **4** and diethyl phthalid-3-yl-phosphonate **6** without the formation of isoindolin-1-one-3-yl-phosphonic acid **1**. The acid-catalyzed, oxidative cascade conversion of phosphonate **11** to phthalimide and diethylphosphate was observed. A mechanism for this conversion was proposed.

Now, using the elaborated method, we are going to synthesize various 2-substituted isoindolin-1-one-3-yl-phosphonic acids, which are cyclic analogues of α-(*N*-benzylamino)benzyl-phosphonic acid, a well known strong inhibitor of acid phosphatase.[8]

EXPERIMENTAL

All commercially available reagents were used without further purification. Melting points are uncorrected. IR spectra were obtained in KBr pellets and recorded with a Vertex 70 IR Fourier spectrophotometer. ^{1}H, ^{13}C, and ^{31}P NMR spectra were measured at 300, 100, and 80 MHz, respectively, in DMSO-d_6 and $CDCl_3$ solution with TMS as internal or 85% H_3PO_4 as external standard with Varian VXR-300 and Gemini 2000 (400 MHz) spectrometers. Chemical shifts (δ) are reported in parts per million. Coupling constants (J) are reported in Hz. Elemental analyses were performed in the analytical laboratory of the Institute. All solvents were distilled and purified by standard procedures. TLC was performed on plates coated with silica gel 60 with an F_{254} indicator; column chromatography was carried out on silica gel 60 (230–240 mesh). *N-tert*-butylphtalimide **8** was prepared according to the published method.[24]

Synthesis of Diethyl 2-(Methoxycarbonyl)benzoylphosphonate (2)

A mixture of monomethyl ester of phthalic acid (3.77 g, 20.93 mmol) and thionyl chloride (3.05 mL, 41.85 mmol) in anhydrous dichloromethane (15 mL) was refluxed for 40 min, cooled, and the solvent evaporated. The oily residue obtained was mixed with triethylphosphite (7.26 mL, 41.85 mmol) and heated under reflux for 16 h. Compound **2** was isolated as a colorless oil after vacuum distillation. Yield: 4.80 g (76%); bp 148–152°C/0.08 mm Hg. IR (CCl_4, cm^{-1}), ν_{max}: 929, 970, 1025, 1056, 1088, 1128, 1139, 1164, 1209, 1258, 1291, 1369, 1393, 1437, 1484, 1576, 1597, 1680, 1716, 1737, 2910, 2954, 2984. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.33$ (t, $J = 7.2$ Hz, 6H, $CH_2\underline{CH_3}$), 3.94 (s, 3H, OCH_3), 4.23 (m, 4H, OCH_2), 7.50 (d, $J = 7.3$ Hz, 1H, arom-H), 7.62 (m, 2H, arom-H), 7.97 (d, $J = 7.3$ Hz, 1H, arom-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 16.7$ (d, $J = 5.6$ Hz), 53.1, 64.3 (d, $J = 7.2$ Hz), 127.3 (d, $J = 1.4$ Hz), 129.6 (d, $J = 0.8$ Hz), 129.9, 131.3, 132.7, 140.6 (d, $J = 60$ Hz), 166.8, 204.8 (d, $J = 189$ Hz). ^{31}P NMR (80 MHz, $CDCl_3$): $\delta = -2.6$. Anal. Calcd. for $C_{13}H_{17}O_6P$ (300.25): C, 52.00; H, 5.71; P, 10.32. Found: C, 51.95; H, 5.75; P, 10.38%.

Synthesis of Diethyl 2-(Methoxyaminocarbonyl)benzoylphosphonate (4)

To a solution of **2** (1.27 g, 4.23 mmol) and *O*-methylhydroxylamine hydrochloride (0.39 g, 4.65 mmol) in anhydrous methanol (5 mL), pyridine (0.41 mL, 5.08 mmol) was added. After standing at ambient temperature for 72 h, the reaction mixture was evaporated, treated with 1N HCl (5 mL), extracted with chloroform (3 × 10 mL), washed with water (20 mL), and dried over Na_2SO_4, and the solvent was evaporated again. The residue was dissolved in diethyl ether (10 mL) and left at ambient temperature. The product precipitated as white crystals in the course of 3 days. Yield: 0.40 g (29%); mp 97–98°C. IR (KBr, cm^{-1}), ν_{max}: 565, 597, 645, 695, 726, 758, 802, 896, 980, 1022, 1071, 1097, 1143, 1213, 1445, 1576, 1716, 2627, 2942, 2987. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.20$ (t, $J = 7.0$ Hz, 6H, $CH_2\underline{CH_3}$), 3.84 (s, 3H, OCH_3), 4.08 (m, 4H, OCH_2), 7.23 (d, $J = 7.8$ Hz, 1H, arom-H), 7.52 (d, $J = 7.8$ Hz, 1H, arom-H), 7.64 (d, $J = 7.8$ Hz, 1H, arom-H), 7.93 (d, $J = 7.8$ Hz, 1H, arom-H), 13.08 (br. s, 1H, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 16.0$ (d, $J = 6.0$ Hz), 62.3 (d, $J = 1.0$ Hz), 62.7 (d, $J = 6.0$ Hz), 128.3 (d, $J = 3.1$ Hz), 128.8, 129.7, 130.4 (d, $J = 4.4$ Hz), 131.7, 131.8 (d, $J = 16.3$ Hz), 152.7 (d, $J = 216$ Hz), 166.6. ^{31}P

NMR (80 MHz, DMSO-d_6): $\delta = 7.0$. Anal. Calcd. for $C_{13}H_{18}NO_6P$ (315.27): C, 49.53; H, 5.75; P, 9.82. Found: C, 49.52; H, 5.75; P, 9.80%.

Synthesis of Diethyl Phtalide-3-yl-phosphonate (6)[25]

To a solution of **2** (0.57 g, 1.90 mmol) in anhydrous methanol (5 mL), $NaBH_4$ (72 mg, 1.90 mmol) was added portionwise while maintaining the temperature at 0–2°C. After additional stirring at ambient temperature for 30 min, the reaction mixture was quenched with 10% NH_4Cl solution (25 mL), extracted with dichloromethane (3 × 20 mL), washed with brine (20 mL), and dried over Na_2SO_4, and the solvent was evaporated. Compound **6** was obtained after crystallization of the residue from benzene/hexane as colorless crystals. Yield: 0.37 g (65%); mp 67–68°C. IR (KBr, cm^{-1}), ν_{max}: 525, 535, 704, 716, 756, 772, 790, 830, 891, 959, 982, 1042, 1158, 1204, 1259, 1288, 1476, 1774, 2915, 2991. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.05$ (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 1.28 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 3.96 (m, 2H, OCH_2), 4.17 (m, 2H, OCH_2), 6.29 (d, $J = 11.0$ Hz, 1H, OCHP), 7.69 (m, 2H, arom-H), 7.87 (t, $J = 7.7$ Hz, 1H, arom-H), 7.94 (d, $J = 7.7$ Hz, 1H, arom-H). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 16.7$ (d, $J = 5.3$ Hz), 16.9 (d, $J = 5.3$ Hz), 63.7 (d, $J = 6.8$ Hz), 64.1 (d, $J = 6.8$ Hz), 75.8 (d, $J = 163$ Hz), 124.1 (d, $J = 2.9$ Hz), 125.1 (d, $J = 4.4$ Hz), 125.9 (d, $J = 1.7$ Hz), 130.4 (d, $J = 2.5$ Hz), 135.2 (d, $J = 2.4$ Hz), 144.8 (d, $J = 4.5$ Hz), 169.9 (d, $J = 2.6$ Hz). ^{31}P NMR (80 MHz, DMSO-d_6): $\delta = 15.3$. Anal. Calcd. for $C_{15}H_{15}O_5P$ (270.22): C, 53.34; H, 5.60; P, 11.46. Found: C, 53.38; H, 5.69; P, 11.41%.

Synthesis of 2-tert-Buthyl-3-hydroxyisoindolin-1-one (3)[26]

To a solution of **8** (7.57 g, 37.25 mmol) in anhydrous methanol (100 mL), $NaBH_4$ (1.55 g, 40.97 mmol) was added portionwise while maintaining the temperature at 0–5°C. After additional stirring at ambient temperature for 45 min, the reaction mixture was quenched with acetic acid (10 mL), and the solvent was evaporated. The residue was treated with water (150 mL), and after 1 h stirring, compound **3** was filtered off, washed, and dried to give a white solid. Yield: 6.55 g (86%); mp 139–140°C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.57$ (s, 9H, *t*-Bu), 3.25 (d, $J = 11.2$ Hz, 1H, OH), 5.96 (d, $J = 11.2$ Hz, 2H, OCHN), 7.38–760 (m, 4H, arom-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 28.3$, 54.7, 82.3, 122.7, 122.9, 129.6, 131.9, 132.6, 143.6, 168.0. Anal. Calcd. for $C_{12}H_{15}NO_2$ (205.26): C, 70.22; H, 7.37. Found: C, 70.30; H, 7.39%.

Synthesis of Diethyl (2-tert-Buthylisoindoline-1-one-3-yl) phosphonates (10)

A mixture of **3** (1.00 g, 4.87 mmol) and trifluoroacetic anhydride (5 mL) was stirred for 30 min under argon. After the excess of trifluoroacetic anhydride and the resulting trifluoroacetic acid were removed under reduced pressure, triethylphosphite (1.69 mL, 9.74 mmol) in anhydrous chloroform (20 mL) was added to the residue, and the resulting mixture was stirred for 4 h. The reaction mixture was quenched with aqueous $NaHCO_3$ (saturated, 60 mL). The organic layer was washed with water (50 mL), dried over Na_2SO_4, and the solvent was evaporated. The residue obtained was purified using column chromatography (ethylacetate:hexane = 2 : 1, R_f 0.33) to give compound **10** as an oil. Yield: 1.46 g (92%). IR (CCl_4, cm^{-1}), ν_{max}: 803, 810, 970, 1026, 1100, 1128, 1142, 1164, 1193, 1211, 1259,

1317, 1326, 1347, 1368, 1395, 1468, 1697, 2931, 2980. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 0.97$ (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 1.24 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 1.60 (s, 9H, *t*-Bu), 3.81 (m, 2H, OCH_2), 4.03 (m, 2H, OCH_2), 5.49 (d, $J = 10.2$ Hz, 1H, OCHP), 7.50 (m, 1H, arom-H), 7.58 (d, $J = 4.3$ Hz, arom-H), 7.64 (d, $J = 4.3$ Hz, arom-H). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 15.7$ (d, $J = 5.4$ Hz), 15.9 (d, $J = 5.4$ Hz), 27.6, 55.4, 57.7 (d, $J = 150$ Hz), 62.3 (d, $J = 7.2$ Hz), 62.6 (d, $J = 7.2$ Hz), 122.0 (d, $J = 1.8$ Hz), 124.0 (d, $J = 2.8$ Hz), 127.9 (d, $J = 2.3$ Hz), 130.4 (d, $J = 2.5$ Hz), 133.4 (d, $J = 3.2$ Hz), 139.8 (d, $J = 7.0$ Hz), 168.0 (d, $J = 1.3$ Hz). ^{31}P NMR (80 MHz, DMSO-d_6): $\delta = 20.4$. Anal. Calcd. for $C_{16}H_{24}NO_4P$ (325.35): C, 59.07; H, 7.44; P, 9.52. Found: C, 59.08; H, 5.39; P, 9.43%.

Synthesis of Isoindoline-1-one-3-yl Phosphonic Acid (1)

A solution of **10** (0.98 g, 3.01 mmol) in a mixture of HCl_{conc} and dioxane (1:1) (100 mL) was heated at 80°C for 72 h, cooled, and the solvent was evaporated. The crystalline residue was treated with ethanol (10 mL), filtered off, washed, and dried to give compound **1** as a solid. Yield: 0.56 g (87%); mp > 270°C (dec.). IR (KBr, cm^{-1}), ν_{max}: 459, 544, 690, 715, 730, 797, 960, 1033, 1090, 1142, 1191, 1242, 1321, 1363, 1472, 1611, 1673, 2829, 3057, 3186, 3293. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 4.81$ (d, $J = 16.2$ Hz, 1H, NCHP), 7.49 (t, $J = 7.7$ Hz, 1H, arom-H), 7.61 (t, $J = 7.7$ Hz, 1H, arom-H), 7.66 (m, 2H, arom-H), 8.92 (s, 1H, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 54.9$ (d, $J = 149$ Hz), 122.5 (d, $J = 0.9$ Hz), 123.9 (d, $J = 2.4$ Hz), 127.5 (d, $J = 1.9$ Hz), 130.8 (d, $J = 2.4$ Hz), 132.2 (d, $J = 4.4$ Hz), 142.0 (d, $J = 5.8$ Hz), 169.4 (d, $J = 3.2$ Hz). ^{31}P NMR (80 MHz, DMSO-d_6): $\delta = 15.2$. Anal. Calcd. for $C_8H_8NO_4P$ (213.13): C, 45.08; H, 3.78; P, 14.53. Found: C, 45.12; H, 3.85; P, 14.69%.

Synthesis of Diethyl Isoindoline-1-one-3-yl-phosphonate (11)

A solution of **10** (0.71 g, 2.18 mmol) in trifluoroacetic acid (7 mL) was refluxed for 1.5 h, cooled, and the solvent was evaporated. The oily residue was dissolved in dichloromethane (10 mL), washed with 5% $NaHCO_3$ solution to pH > 7, dried over Na_2SO_4. Then the solvent was evaporated again, and the residue was dried under reduced pressure to give compound **11** as colorless solid. Yield: 0.58 g (98%); mp 86–87°C. IR (KBr, cm^{-1}), ν_{max}: 542, 706, 753, 777, 799, 830, 902, 975, 1017, 1162, 1192, 1232, 1259, 1294, 1345, 1693, 2875, 2989, 3072, 3190. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.04$ (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 1.24 (t, $J = 7.0$ Hz, 3H, $CH_2\underline{CH_3}$), 3.90 (m, 2H, OCH_2), 4.09 (m, 2H, OCH_2), 5.26 (d, $J = 14.6$ Hz, 1H, NCHP), 7.56 (m, 1H, arom-H), 7.66 (m, 2H, arom-H), 7.73 (d, $J = 7.7$ Hz, 1H, arom-H), 9.24 (s, 1H, NH). ^{13}C NMR (100.6 MHz, DMSO-d_6): $\delta = 16.0$ (d, $J = 5.5$ Hz), 16.2 (d, $J = 5.5$ Hz), 53.4 (d, $J = 153$ Hz), 62.9 (d, $J = 7.0$ Hz), 62.6 (d, $J = 7.0$ Hz), 123.0 (d, $J = 1.4$ Hz), 124.0 (d, $J = 2.7$ Hz), 128.4 (d, $J = 2.1$ Hz), 131.4 (d, $J = 2.5$ Hz), 132.4 (d, $J = 4.6$ Hz), 140.6 (d, $J = 6.1$ Hz), 169.7 (d, $J = 3.2$ Hz). ^{31}P NMR (80 MHz, DMSO-d_6): $\delta = 19.6$. Anal. Calcd. for $C_{12}H_{16}NO_4P$ (269.24): C, 53.53; H, 5.99; P, 11.50. Found: C, 53.49; H, 5.95; P, 11.57%.

Investigation of Oxidative Cascade Conversion of Diethyl Isoindoline-1-one-3-yl-phosphonate (11)

A solution of **10** (0.25 g, 0.77 mmol) in trifluoroacetic acid (2.5 mL) was refluxed for 1.5 h, cooled, and the solvent was evaporated. The oily residue was additionally dried under

reduced pressure to give **11** in a quantitative yield (0.21 g) as viscous oil. Its analysis and spectral data were identical to **11** obtained by method described above using 5% $NaHCO_3$ solution washing procedure. Upon 3 weeks standing at ambient temperature, this oil crystallized. According to the NMR spectra and LCMS spectral data, it is a mixture that consists of **11**:**16**:**17**:**18** in ratio 5:50:40:5. Phthalimide (**16**): APCI MS: m/z (M+1) 148; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 7.84$ (s, 4H, arom-H), 11.37 (s, 1H, NH). Diethylphosphate (**17**): ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.22$ (t, $J = 7.0$ Hz, 6H, $CH_2\underline{CH_3}$), 3.92 (m, 4H, OCH_2); ^{31}P NMR (80 MHz, DMSO–d_6): $\delta = -0.4$. 3,3-Bis(diethylphosphonyl)-isoindoline-1-one (**18**): APCI MS: m/z (M+1) 406; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.08$ (t, $J = 7.0$ Hz, 6H, $CH_2\underline{CH_3}$), 1.17 (t, $J = 7.0$ Hz, 6H, $CH_2\underline{CH_3}$), 3.90 (m, 4H, OCH_2), 4.13 (m, 4H, OCH_2), 7.56 (m, 1H, arom-H), 7.67 (m, 2H, arom-H), 7.74 (d, $J = 4.7$ Hz, 1H, Ar), 9.37 (s, 1H, NH); ^{31}P NMR (80 MHz, DMSO–d_6): $\delta = 17.7$.

REFERENCES

1. E. Valencia, I. Weiss, S. Firdous, A. J. Freyer, and M. Shamma, *Tetrahedron*, **40,** 3957 (1984).
2. G. Nannin, P. N. Griraldi, G. Molgora, G. Biasoli, F. Spinelli, L. Logemann, E. Dradi, G. Zanni, A. Buttinoni, and R. Tommasini, *Arzneim. Forsch.*, **23,** 1090 (1973).
3. T. R. Belliotti, W. A. Brink, S. R. Kesten, J. R. Rubin, D. J. Wustrow, K. T. Zoski, S. Z. Whetzel, A. E. Corbin, T. A. Pugsley, T. G. Heffner, and L. D. Wise, *Bioorg. Med. Chem. Lett.*, **8,** 1499 (1998).
4. Z. P. Zhuang, M. P. Kung, M. Mu, and H. F. Kung, *J. Med. Chem.*, **41,** 157 (1998).
5. M. H. Norman, D. J. Minick, and G. C. Rigdon, *J. Med. Chem.*, **39,** 149 (1996).
6. J. A. Lowe and F. E. Ewing, *J. Heterocycl. Chem.*, **24,** 877 (1987).
7. H. Maeda, M. Suzuki, H. Sugano, M. Yamamura, and R. Ishida, *Chem. Pharm. Bull.*, **36,** 190 (1988).
8. A.I. Vovk, I.M. Mischenko, V.Yu. Tanchuk, G.A. Kachkovskii, S. Yu. Sheiko, O.I. Kolodyazhnyi, and V.P. Kukhar, *Bioorg. Med. Chem. Lett.*, **18,** 4620 (2008).
9. S. A. Beers, C. F. Schwender, D. A. Loughney, E. Malloy, K. Demarest, and J. Jordan, *Bioorg. Med. Chem.*, **4,** 1693 (1996).
10. R. F. Frechette, C. Ackerman, S. Beers, R. Look, and J. Moore, *Bioorg. Med. Chem. Lett.*, **7,** 2169 (1997).
11. G. O. Kachkovskyi and O. I. Kolodiazhnyi, *Tetrahedron*, **63,** 12576 (2007).
12. G. O. Kachkovskyi and O. I. Kolodiazhnyi, *Phosphorus, Sulfur, and Silicon*, **184,** 890 (2009).
13. V. V. Nesterov and O. I. Kolodiazhnyi, *Tetrahedron*, **63,** 6720 (2007).
14. V. V. Nesterov and O. I. Kolodiazhnyi, *Synlett*, 2400 (2007).
15. P. Savignac and B. Iorga, *Modern Phosphonate Chemistry* (CRC Press, Boca Raton, FL, 2003), Chap. 7, and references cited therein.
16. K. D. Berlin, R. T. Claunch, and E. T. Gaudy, *J. Org. Chem.*, **33,** 3090 (1968).
17. K. D. Berlin, N. K. Roy, and R. T. Claunch, *J. Am. Chem. Soc.*, **90,** 4494 (1968).
18. J. Kowalik, L. Kupczyk-Subotkowska, and P. Mastalerz, *Synthesis*, 57 (1981).
19. E. Breuer, R. Karaman, A. Goldblum, D. Gibson, H. Leader, B. V. L. Potter, and J. H. Cummins, *J. Chem. Soc., Perkin Trans. 1*, 3047 (1988).
20. D. L. Hughes, *Org. Prep. Proced. Int.*, **28,** 127 (1996).
21. T. Gajda and M. Matusaik, *Synthesis*, 367 (1992).
22. For phosphorylation of *N*-acyliminium salt, see:T. Goto, S. Utsunomiya, H. Aiba, H. Hayasaka, M. Endo, R. Watanabe, T. Ishizaki, R. Sato, and M. Saito, *Bull. Chem. Soc. Jpn.*, **64,** 1901 (1991).
23. The autooxidation of imine **12** proceeds similarly to the autooxidation of aldehydes to carboxylic acids. The mechanism of autooxidation is described in: M. B. Smith and J. March,

March's Advanced Organic Chemistry. Reactions, Mechanisms, and Structures, 6th ed. (Wiley, New York, 2007), p. 967.
24. *Organic Syntheses: An Annual Publication of Satisfactory Methods for the Preparation of Organic Chemicals* (Wiley, New York, 1949), vol. 29, p. 18.
25. M. H. B. Stowell, J. M. Ueland, and R. W. McClard, *Tetrahedron Lett.*, **31,** 3261 (1990).
26. T. Nishio and H. Yamamoto, *J. Heterocycl. Chem.*, **32,** 883 (1995).