Preparative Route to 2-Ethoxycarbonylimidazole-4-phosphonate and Diethyl imidazole-2,4-dicarboxylate

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Practical synthesis of 2-ethoxycarbonylimidazole-4-phosphonate (**1a**) and diethyl imidazole-2,4-dicarboxylate (**1b**) are described.

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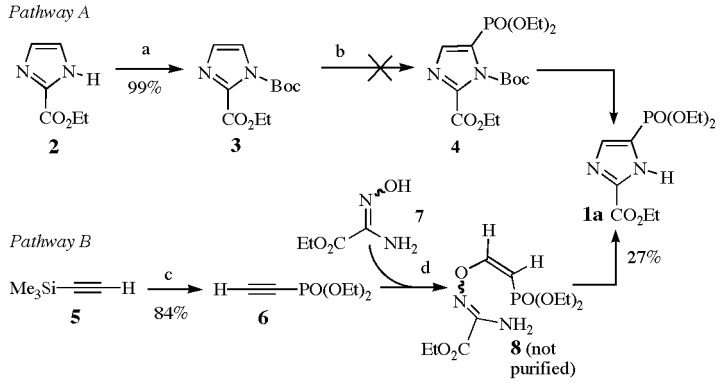
Over the last twenty years, it has been well established that L-glutamate was the major excitatory neurotransmitter in the mammalian central nervous system (CNS) [1]. Glutamate plays an essential role in many physiological CNS functions through the activation of three major types of postsynaptic ionotropic receptors designated according to the non-natural substances that selectively activates them: NMDA (*N*-Methyl-D-Aspartate), AMPA 2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid) and Kainate receptors. In addition, glutamate activates several types of metabotropic receptors signalling through a G-protein coupled [2]. In connection with our program aimed at the development of potent and selective AMPA antagonists as source of potential drugs for cerebral ischemia or epilepsy [3], we needed to develop easy and efficient methods leading to 2-ethoxycarbonylimidazole-4-phosphonate (**1a**, Scheme 1) and diethyl imidazole-2,4-dicarboxylate (**1b**, Scheme 2) [4].

To our knowledge, few phosphorylated imidazoles were already described. Thus, the imidazol-2-ylphosphonic acids were prepared by direct action of the corresponding *N*-protected imidazoles with various phosphorus (V) acid chlorides following hydrolysis [5a], whereas the imidazole-4(5)-phosphonates were obtained through either a heterocyclization of functionalised enamines [5b], base-induced cycloaddition of diethyl isocyanomethylphosphonate [5c], Pd-catalyzed phosphonylation of 4(5)-bromo-imidazoles [5d], lithiation of corresponding halogeno-imidazoles followed by the addition of diethylchlorophosphate [5e] or by the condensation of secondary amines with diethyl [(2,2-dichloro-1-isocyano)-ethenyl]phosphonate [5f]. Likewise, relatively few 1*H*-Imidazole-2,4-dicarboxylates have been synthesized to date. Thus, **1b** was only prepared *via* the hydrogenation of diethyl 1-(*p*-methoxybenzyl)imidazole-2,4-dicarboxylate which was obtained in a two steps synthesis from 2-amino-2-cyano acetate and 1-ethoxycarbonylformimidate in a 25 % overall yield [6]. The corresponding dimethyl imidazole-2,4-dicarboxylate was synthesized by photolysis of methyl (*E*)-3-(5-methoxycarbonyltetrazol-1-yl) propenoate [7]. 2-Carboxy-4-carbomethoxyimidazole has been obtained by the condensation of ethyl amino-oximinoacetate with methylpropiolate followed by an *in situ* thermolysis reaction [8]. Finally, diethyl 4-amino-1-(*H*)imidazole-2,5-dicarboxylate has been prepared from carboxyethoxyformimidate [9].

Scheme 1

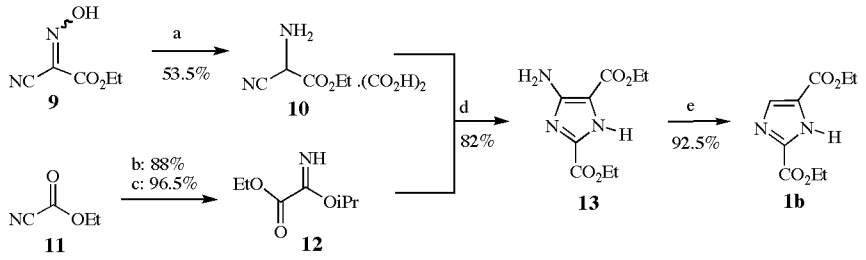


Reaction conditions: a) *1.* **2**, Boc_2O, DMAP, MeCN, 2 h, rt *2.* $MgSO_4$, silica gel and the mixture was filtered through a small Celite column (eluent: CH_2Cl_2); b) *1.* **3**, 1.3 *M sec*-BuLi, THF, -60 °C, *2.* $ClP(O)(OEt)_2$, -60 °C, 3 h and then rt, 12 h; c) *1.* **5**, THF, rt then 3 *M* EtMgBr in ether, 2 h *2.* $ClP(O)(OEt)_2$, 0 °C, 1 h and then rt, 1 h; d) *1.* **7**, TEA, $CHCl_3$, 10 °C then **6**, $CHCl_3$, 45 min. then rt, 21 h *2.* xylene, reflux, 24 h.

Preparation of 2-Ethoxycarbonylimidazole-4-phosphonate (**1a**).

As outlined in Scheme 1 (Pathway A), our fist attempt was based on the simple 5-lithiation reaction [10] of the

Scheme 2



Reaction conditions: a) **9**, EtOH (1.1 L), 50% Pt/C (30g), H_2, 40 °C, 72 h; b) **11**, 2-propanol, 10 °C then $HCl_{(g)}$ during 20 minutes then the reaction was stirred at rt for 12 h; c) **12** (HCl), *tert*-BuOMe, K_2CO_3, H_2O , -5 °C, 10 minutes; d) **10** (oxalate), 12, rt, 3 h; e) *1)* **13**, 50% H_3PO_2, $NaNO_2$, rt, 2 h *2)* 3% NaOH.

N-Boc-2-ethoxycarbonylimidazole derivative **3** using *sec*-butyllithium (1.1 equivalents) at –60 °C in tetrahydrofuran [11]. After one hour, freshly distilled diethyl chlorophosphate was added and the resulting mixture was stirred for an additional 3 h period of time at the same temperature and finally allowed to reach room temperature. A TLC analysis (ethyl acetate:cyclohexane 8:2) showed the presence of a complex mixture of compounds. Surprisingly this synthetic pathway was unsuccessful to afford **4**, which was the expected starting material for the preparation of our target compound **1a**. Investigating alternative routes to **1a**, we found interestingly that the thermal Claisen-type rearrangement of the intermediate **8** could lead directly to the targeted pure compound **1a** as outlined in Scheme 1 (Pathway B). To our knowledge, relatively few thermal rearrangements of *O*-vinyloxime derivatives have been described to date. Thus, only the preparation of pyrroles and indoles [12a], 2-butyl(phenyl, ethoxycarbonyl)imidazoles [12b], pyrrolylindoles [12c], oxazoles [12d], and isoxazolines [12e] have been reported. In addition, starting from their corresponding *O*-vinyloximes, pyrroles were obtained using super-basic media [13], whereas oxadiazoles were prepared under mild reaction conditions (dichloromethane, room temperature) [8]. The preparation of **1a** started from the commercially available trimethylsilylacetylene **5** which was readily converted into diethyl ethynylphosphate **6** [14] in 84% yield by the condensation of freshly distilled diethyl chlorophosphate to a solution of trimethylsilylethynyl magnesium bromide in tetrahydrofuran. Then, conjugate addition of the amino-oxime **7** [15] to **6** in the presence of triethylamine in chlororoform at room temperature led to the *O*-vinyloxime derivative [16] **8** as a single isomer which was directly transformed *via* a thermal rearrangement (xylene, reflux, 24 h) onto pure **1a** in 27% yield in large scale (~20 g).

Preparation of Diethyl Imidazole-2,4-dicarboxylate (**1b**).

As outlined in Scheme 2, our synthetic approach started from ethyl 2-amino-2-cyano-acetate **10** [17] (oxalate) which was easily obtained by the hydrogenation of hydroxyimino-cyano-acetate **9** in a mixture of ethanol-water in presence of Pt/C in 53.5% yield. Then, the key step was the condensation of **10** (oxalate) with ethyl 2-imino-2-isopropyloxy-acetate **12** [18] in ethanol at room temperature leading to the amino-imidazole derivative **13** in 82% yield. Treatment of ethyl cyanoformate **11** in 2-propanol in presence of hydrogen chloride (gas) followed by the action of potassium carbonate in *tert*-butyl methyl ether afforded the 2-imino-2-isopropyloxy acetate derivative **12** in a 85% overall yield. Finally, a Sandmeyer diazotisation in presence of hypophosphorous acid and sodium nitrite at room temperature gave the expected imidazole derivative **1b** in 92.5% yield. Note that according to this straightforward synthetic pathway, pure **1b** was obtained in an overall yield of 75% from **10** without any chromatographic operation or any protection of the nitrogen atoms of the imidazole-2,5-dicarboxylate ring. According to the same experimental reaction conditions, **1b** was prepared in large-scale (100 g) in 43% overall yield.

Conclusion.

We have developed rapid and useful synthetic routes towards the preparation of 2-ethoxycarbonylimidazole-4-phosphonate (**1a**, 3-step synthesis) and diethyl imidazole-2,4-dicarboxylate (**1b**, 5-step synthesis). These conditions made the preparation of **1a** and **1b** of valuable interest for preparative scales.

EXPERIMENTAL

Commercially available reagents were used as received from suppliers, while solvents were dried using classical methods. Reaction progress was monitored using TLC on silica gel plates (Merck Kieselgel $60F_{254}$). Melting points were determined on a Reicher-Kofler instrument and are uncorrected. ^1H NMR spectra were recorded using AC 200, AC 300 or Avance 500 Bruker spectrometers. Chemical shifts are given in ppm (δ DMSO-d_6 = 2.5 or $CDCl_3$ = 7.24) while coupling constants J are expressed in Hz. IR spectra were recorded on a FT-IR 60SX-R Nicolet spectrophotometer, samples being dispersed as a KBr pellet. MS spectra were obtained on a Finnigan 4000 (EI, 70eV) or a VG Autospec (FAB) mass spectrometers.

Diethyl Ethynylphosphate (**6**).

To a stirred solution of **5** (9.15 g, 91 mmol) in dry THF (300 ml), kept under nitrogen atmosphere, 3 *M* EtMgBr (40 mL, 120 mmol) in ether was added dropwise at rt. The reaction mixture was stirred for 2 h at rt, and then cooled to 0 °C. At this temperature, $ClP(O)(OEt)_2$ (13.7 mL, 91 mmol) was added, the reaction mixture stirred for an additional 1 h and allowed to reach rt (1 h). Then, saturated aq. NH_4Cl (30 mL) was added and the resulting pale yellow precipitate filtered and washed with ether (2 x 50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* (35 °C) to a brown oil which was immediately solubilized in $CHCl_3$ (450 mL). Then, 10% aq. Na_2CO_3 (300 mL) was added at rt and the reaction mixture stirred for 0.5 h. The aq. phase was extracted with $CHCl_3$ (2x50 mL) and the combined organic phases dried over $MgSO_4$ and concentrated *in vacuo* to give 12.4 g (84%) of **6** as a yellow oil. The product was sufficiently pure (TLC R_f = 0.25, silica gel, cyclohexane-ethyl acetate 1:1) for direct use in the next step without further purification.

2-Ethoxycarbonylimidazole-4-phosphonate (**1a**).

To a stirred solution of **7** (30.5 g, 231 mmol), TEA (38.6 ml, 277 mmol) in $CHCl_3$ (500 mL) at 10 °C was added dropwise **6** (57.6 g, 231 mmol) in $CHCl_3$ (100 mL) during 45 min. The reaction mixture was stirred for 21 h at rt. The mixture was washed successively with sat. NaCl (3x100 mL) and H_2O (30 mL) and the organic phase dried over $MgSO_4$. Then silica gel (50 g) was added and finally the mixture filtered through a small Celite column. The filtrate was concentrated *in vacuo* to afford 82 g of crude **8** as a pale yellow oil (TLC R_f = 0.8, silica gel, ethyl acetate-methanol 9:1) which was used in the next step without further purification. ^{1}H NMR (400MHz, DMSO): δ 1.26 (m, 9H, CH_3), 3.98 (m, 6H, CH_2), 5.16 (dd, 1H, $^3J_{HH}$= 12Hz - *cis*; $^2J_{PH}$=12Hz, C*H*=), 7.02 (bs, 2H, NH_2), 7.32 (dd, 1H, $^3J_{HH}$= 12Hz – *cis*; $^3J_{PH}$= 11Hz, C*H*=). MS(FAB,Gly-SGly): m/z 295 (MH^+). Determination of the *syn-anti* stereochemistry was out of the scope of this study.

Compound **8** was dissolved in xylene (400 ml) and the solution was heated at reflux for 24 h and cooled to rt and the solid was filtered, washed with CH_2Cl_2 (3x50 mL) and the combined organic phases concentrated *in vacuo* to give a red oil which was purified by silica gel chromatography using a ethyl acetate-methanol mixture (9-1) as eluent to give **1a** (21 g, 27%) as a pale yellow oil (TLC R_f = 0.53, silica gel, ethyl acetate-methanol 9:1). ^{1}H NMR (500 MHz, DMSO): δ 1.24 (t, 6H, J= 7Hz, 2x CH_3), 1.34 (t, 3H, J= 7Hz, CH_3), 4.02 (q, 4H, J=7Hz, CH_2O), 4.45 (q, 2H, J= 7Hz, CH_2O), 7.82 (bs, 1H, CH=), 13.85 (bs, 1H, NH). MS (EI): m/z 276 ($M^{+\cdot}$). IR (CCl_4) 2984, 1723, 1482, 1382, 1248, 1031 cm^{-1}.

Anal. Calcd for $C_{10}H_{17}N_2O_5P$: C, 43.48; H, 6.20; N, 10.14 %. Found: C, 43.72; H, 6.34; N, 10.18 %.

2-Amino-2-cyano-acetate (**10•oxalate**).

To a stirred solution of **9** (120 g, 0.85 mol) in ethanol (1.1 L), 50% Pt/C (30g) in water (30 mL) were added at rt. The reaction mixture was hydrogenated under a pressure of 59 psi during 72 h. The resulting solid was filtered off, washed with ethanol (2 x 100 mL), and finally the filtrate treated with oxalic acid (73.7 g) in ethanol (440 mL) at 5 °C to give a white solid which was washed with ethanol (4 x 100 mL) and dried to afford 92.2 g of **10•oxalate** (53.5%), m.p. 106-108 °C (not recrystallized).

Ethyl 2-Imino-2-isopropyloxy-acetate (**12**).

To a solution of **11** (25 g, 0.25 mol) in 2-propanol (60 mL) and under a nitrogen atmosphere, $HCl_{(g)}$ was added during 20 minutes at 10 °C. Stirring was continued for 12 h at the same temperature. After cooling (0 °C), the reaction mixture was filtered and the solid thus obtained washed with 2-propanol (10 mL), and dried to give **12•HCl** (43.4 g, 88%) as a white solid (m.p. 113 °C, not recrystallized). Then, to a stirred solution of K_2CO_3 (46.6 g, 0.33 mol) in water (185 mL) and *tert*-BuOMe (176 mL) at 5 °C was added **12•HCl** (110g, 0.56 mol). The water phase was extracted with *tert*-BuOMe (88 mL), and the resulting organic layers concentrated under reduced pressure to give 43.4 g of **12** (96.5%) as an colorless oil, b.p. 62 °C (0.2 psi).

4-Amino-imidazole-2,5-dicarboxylate (**13**).

To a stirred solution of **10•oxalate** (2.3 g, 10 mmol) in ethanol (23 mL), **12** (2 g, 12 mmol) in neat phase was slowly added for 30 minutes at rt. Then the reaction mixture was stirred for 3 h, and the resulting precipitate was collected by filtration, washed with ethanol (2 mL) and dried to afford 2.21 g of **13** (82%) as a white solid, m.p. 192-194 °C (not recrystallized). ^{1}H NMR (300 MHz, DMSO): δ 1.3 (m, 6H, CH_3), 4.25 (m, 4H, CH_2), 5.92 (bs, 2H, NH_2), 12.42 (bs, NH). MS (EI): m/z 227 (100%). IR (KBr) 3480, 3220, 3055, 1677, 1628, 1273, 1152 cm^{-1}.

Diethyl Imidazole-2,4-dicarboxylate (**1b**).

To a solution of **13** (1 g, 4.4 mmol) in a 50% aq. solution of H_3PO_2 (2.5 mL), $NaNO_2$ (0.46 g, 6.7 mmol) in water (3.4 mL) was added dropwise at rt. The reaction mixture was stirred for 2 h, and 3% NaOH (5 mL) was added until pH = 7-8. Then, the precipitate was collected by filtration, washed with water (3 x 5 mL) and dried to give 0.82 g of **1b** (92.5%) as a white solid, m.p. 174-176 °C (not recrystallized). ^{1}H NMR (250 MHz DMSO): δ 1.32 (m, 6H, CH_3), 4.34 (m, 4H, CH_2), 8.04 (s, CH), 14 (very bs, NH). MS (EI): m/z 212 (16%), 140 (100%). IR (KBr) 3125, 1730, 1700, 1282, 1177, 1030 cm^{-1}.

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.95; H, 5.70; N, 13.20 %. Found: C, 50.70; H, 5.53; N, 13.24 %.

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[15] See ref. 8. **7**: ^{1}H NMR (400MHz, $CDCl_3$): δ 1.4 (3H, t, J= 7Hz, CH_3), 4.38 (2H, q, J=7Hz, CH_2), 5.08 (2H, bs, NH_2), 7.12 (1H, bs, OH). MS (EI): m/z 132 ($M^{+\cdot}$). Determination of the *syn-anti* arrangement was out of the scope of this study.

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