Acta Chemica Scandinavica, 1995: 49: 230–232
Printed in Belgium – all rights reserved

ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

An Alternative Synthesis of the NMDA Antagonist CGS 19755 via Free Radical Carbamoylation of Ethyl Isonicotinate

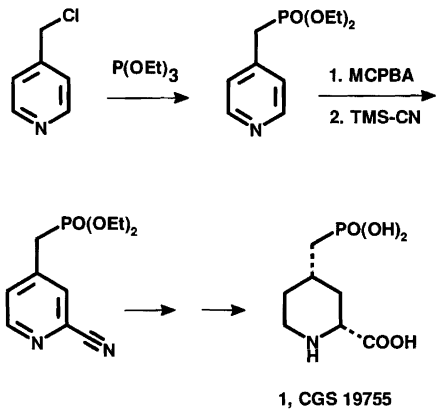
Ivar Martin,[a] Jaan Anvelt,[a] Lauri Vares,[a] Ingrid Kühn[a] and Alf Claesson[†,b]

[a]Department of Bioorganic Chemistry, Institute of Chemistry, Akadeemia tee 15, EE0026, Tallinn, Estonia and [b]Preclinical Research, Astra Pain Control, 151 85 Södertälje, Sweden

Martin, I., Anvelt, J., Vares, L., Kühn, I. and Claesson, A., 1995. An Alternative Synthesis of the NMDA Antagonist CGS 19755 via Free Radical Carbamoylation of Ethyl Isonicotinate. – Acta Chem. Scand. 49: 230–232 © Acta Chemica Scandinavica 1995.

The NMDA antagonist CGS 19755 (*cis*-4-phosphonomethyl-2-piperidinecarboxylic acid) has been prepared by applying Minisci reaction conditions [formamide, hydrogen peroxide, iron(II) sulfate] to ethyl isonicotinate, reduction of the ester with sodium borohydride, alcoholysis of the 2-carboxamide, formation of 4-(diethylphosphonomethyl)-2-pyridinecarboxylate, hydrogenation of the pyridine nucleus, and acid hydrolysis. The overall, unoptimized yield was around 11%. The procedure employs cheap starting materials, is practical and avoids the use of toxic and hazardous cyanotrimethylsilane which is used in the published procedure.

Over the last decade a number of phosphonate-containing amino acids have been synthesized as antagonists at the NMDA subtype of glutamate receptors.[1] Owing to our interest in the field we wanted to obtain useful quantities of the compound **1** (CGS 19755), which serves as a reference and which is available in radioactively labeled form. The literature synthesis of **1** (Scheme 1) employs cyanotrimethylsilane for the introduction of cyanide, as a carboxylate equivalent, onto 4-(diethylphosphonomethyl)pyridine *N*-oxide.[2] This reagent is somewhat expensive and transport and handling are regulated owing to the compound's hazardous nature. We therefore sought an alternative synthetic route and have carried out some experiments which have resulted in a practical synthesis of **1** by use of a Minisci-type reaction for the introduction of carboxamide as a carboxylate precursor.

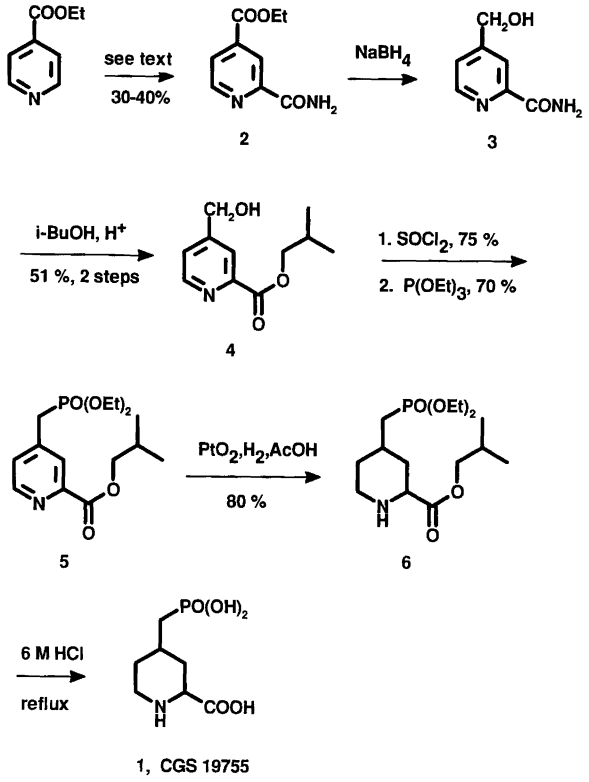


Scheme 1.

Certain nitrogen heterocycles, in particular pyridines and quinolines in protonated forms, are excellent substrates for a variety of carbon-centered radicals which allow introduction of many functional groups.[3] One variation of this reaction is carbamoylation with the acyl radical generated from formamide in the presence of a peroxide and an iron(II) salt. We employed ethyl 4-pyridinecarboxylate as the substrate and hydrogen peroxide and iron(II) sulfate as reagents (Scheme 2) which gave 30–40% of the amide **2**. Initially we tried to use *tert*-butyl hydroperoxide, but later found the work-up procedure to be simpler when hydrogen peroxide was used. In order to obtain a better yield the crude product was subjected to a second round of carbamoylation; the yield after this treatment was typically 60% of nicely crystalline material (traces of diamide product were removed by recrystallization from ethanol in which it is not soluble). An increase in the excess of redox reagents and/or sulfuric acid did not ameliorate the situation as shown in three additional experiments. In the original paper by Minisci and Gardini a yield of 82% of 2-quinoxalinecarboxamide was reported,[4] which indicates that there might be room for an increased yield in the present reaction. However, since ethyl isonicotinoate is a very cheap chemical and non-converted material is easy to wash away, we had little motivation to try to optimize the yield further.

† To whom correspondence should be addressed.

The amide **2** was selectively reduced at the ester group using sodium borohydride in ethanol, followed by alcoholysis of the amide **3** in acidic isobutyl alcohol to give the ester **4**. Conversion into the phosphonate **5** went via the chloride plus an Arbuzov reaction which after silica gel chromatography gave **5** in 53% yield from **4**. Hydrogenation over PtO_2 in acetic acid then gave **6** in 80% yield. Hydrolysis of the ester groups was carried out as described[2] to give pure **1** in 85% yield from **6**.



Scheme 2.

The overall yield of CGS 19755 (**1**) from cheap ethyl isonicotinoate was 11% in seven non-optimized steps using very simple reagents and procedures which should make the present route an attractive alternative to the published[2] synthesis.

Experimental

General. Melting points were determined with an electrothermal capillary melting point apparatus. IR spectra were recorded on a Specord 71 IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-500 spectrometer, with $CDCl_3$ as the solvent and Me_4Si as an internal standard. All organic solvents were of reagent grade and were distilled prior to use with the following exceptions: CH_2Cl_2 was distilled over CaH_2, pyridine was distilled over BaO, formamide was distilled *in vacuo*. All silica gel chromatographic separations were carried out on KSK 0.04–0.1 mm from Lääne Kalur, Estonia.

*4-Ethoxycarbonyl-2-pyridinecarboxamide (**2**).* To a solution of ethyl isonicotinate (25 g, 0.165 mol) and concentrated sulfuric acid (8.8 ml, 0.165 mol) in 200 ml of formamide, 30% hydrogen peroxide (25.6 ml, 0.248 mol) and finely powdered ferrous sulfate ($FeSO_4 \cdot 7H_2O$, 69 g, 0.248 mol) were separately and simultaneously added over 15 min with efficient stirring and cooling at 10°C. After stirring for 2 h at r.t., trisodium citrate solution (350 ml, 0.33 mol) was added, and the mixture was brought to pH 8 by addition of saturated $NaHCO_3$. The resultant mixture was extracted with $CHCl_3$ (3 × 200 ml), the combined organic extracts were washed with cold water (2 × 100 ml) and dried (Na_2SO_4). The solid residue (22 g) after concentration contained a 1:1 mixture of ethyl isonicotinate and **2**; it was subjected to the same procedure described above to afford 19.3 g (60%) of **2** as white crystals after recrystallization from EtOH, m.p. 136–137°C. ^1H NMR (500 MHz): δ 1.43 (t, 3 H, Me), 4.45 (q, 2 H, $-CH_2-$), 8.04 (dd, $^3J = 4.9$ Hz, $^5J = 1.5$ Hz, 1 H, –HC = N–), 8.71 (dd, $^4J = 0.7$ Hz, $^5J = 1.5$ Hz, 1 H, –HC =), 8.74 (dd, $^3J = 4.9$ Hz, $^4J = 0.7$ Hz, 1 H, –HC =). ^{13}C NMR (125 MHz): δ 14.0 (Me), 62.1 ($-CH_2-$), 121.6 (CH =), 125.6 (CH =), 139.3 (C-4), 149.1 (CH =), 150.4 (C-2), 164.4 (COOEt), 166.3 ($CONH_2$). MS (70 eV): $m/z = 194$ (M^+, 100), 177 (22), 165 (40), 121 (21), 78 (25), 44 (46).

*Isobutyl 4-(hydroxymethyl)-2-pyridinecarboxylate (**4**).* A solution of **2** (19.3 g, 99.4 mmol) and $NaBH_4$ (3.76 g, 99.4 mmol) in EtOH (500 ml) was stirred for 24 h at r.t. followed by quenching with aq. NH_4Cl. The solvents were removed under reduced pressure. To the solid residue, isobutyl alcohol (200 ml) and aq. 36% HCl (30 ml) were added and the mixture was refluxed for 6 h with concurrent separation of water. After cooling to r.t., the mixture was poured into sat. $NaHCO_3$. The organic layer was separated, the aqueous solution was extracted with EtOAc (2 × 100 ml) and the combined organic layers were washed with brine (2 × 100 ml) and dried (Na_2SO_4). After removal of solvents the residue was purified by column chromatography (silica gel, 300 g, 2-propanol–$CHCl_3$, 1:20) to give 10.6 g (51%) of **3** as a pale yellow oil. IR (film): 3400, 1785, 1768, 1630, 1060, 1030, 970. ^1H NMR (500 MHz): δ 0.89 (d, 6 H, Me), 1.92 (m, 1 H, CH–), 4.05 (d, 2 H, CH_2-), 4.70 (s, 2 H, CH_2-), 5.13 (br s, 1 H, OH), 7.38 (dd, $^3J = 4.9$ Hz, $^4J = 0.7$ Hz, 1 H, CH =), 7.965 (dd, $^4J = 0.7$ Hz, $^5J = 0.5$ Hz, 1 H, CH =), 8.425 (dd, $^3J = 4.9$ Hz, $^5J = 0.5$ Hz, 1 H, CH = N–). ^{13}C NMR (125 MHz): δ 18.8 (Me), 27.4 (CH–), 62.3 (CH_2–OH), 70.2 (CH_2–O–), 122.3 (C-3), 124.0 (C-5), 147.4 (C-2), 149.1 (C-6), 152.6 (C-4), 164.8 (COO–).

Isobutyl cis*-4-[(diethylphosphono)methyl]-2-piperidinecarboxylate (**6**).* To a stirred solution of **4** (10.6 g, 50.7 mmol) and pyridine (6.15 ml, 76 mmol) in dry CH_2Cl_2 (170 ml) under Ar, $SOCl_2$ (5.54 ml, 76 mmol) was added drop-

wise. After 12 h at r.t., the mixture was poured into sat. $NaHCO_3$. The organic layer was separated and the aqueous solution was extracted with CH_2Cl_2 (2 × 100 ml). The combined organic layers were washed with brine (2 × 100 ml) and dried (Na_2SO_4). The solvents were removed *in vacuo* to afford 9.5 g of chloride. This material was refluxed in 40 ml of $(EtO)_3P$ for 8 h. After removal of the solvent under reduced pressure and chromatography (silica gel, 250 g, 2-propanol–$CHCl_3$, 3:100), 9.6 g of phosphonate **5** were obtained. A mixture of the phosphonate (9.6 g, 29.2 mmol), acetic acid (60 ml), and PtO_2 (0.66 g, 2.34 mmol) was hydrogenated at r.t. for 72 h. The reaction mixture was filtered, and the solvent was removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (200 ml), washed with 5% $NaHCO_3$ (3 × 50 ml), and dried (Na_2SO_4). The solvents were removed *in vacuo*. The residue was purified by column chromatography (silica gel, 200 g, 2-propanol–$CHCl_3$–Et_3N, 7.5:91.5:1) to give 7.24 g (42% overall yield) of **6** as a colorless oil. ^{1}H NMR (500 MHz): δ 0.871 (d, 6 H, Me), 1.132 [ddd, ^2J = 12 Hz, ^3J = 11.7 Hz, ^3J = 12 Hz, 1 H C(3)H(ax)], 1.14 [d, ^3J = 12.3 Hz, 1 H, C(5)H(ax)], 1.27 (t, 6 H, Me), 1.658 (dd, $^2J_{HP}$ = 18.3 Hz, 2 H, CH_2–PO), 1.813 [m, 1 H, C(5)H(eq)], 1.88 [m, ^3J = 12 Hz, 1 H, C(4)H(ax)], 1.886 [m, 1 H, $CH(CH_3)_2$], 2.200 [dd, ^2J = 12 Hz, ^3J = 2.6 Hz, 1 H, C(3)H(eq)], 2.618 [dd, ^2J = 12.3 Hz, ^3J = 12.3 Hz, 1 H, C(6)H(ax)], 3.117 [d, ^2J = 12.3 Hz, 1 H, C(6)H(eq)], 3.309 [dd, ^3J = 2.6 Hz, ^3J = 11.7 Hz, 1 H, C(2)H(ax)], 3.89 (d, 2 H, CH_2CH), 4.04 (q, 4 H, CH_2CH_3). ^{13}C NMR (125 MHz): δ 16.3 (J_{CP} = 6.2 Hz, Me), 18.9 (Me), 27.6 [$CH(CH_3)_2$], 31.2 [J_{CP} = 4.1 Hz, C(4)], 32.9 (J_{CP} = 139.5 Hz, CH_2–PO), 33.6 (C-5), 36.8 (C-3), 45.5 (C-6), 58.6 (C-2), 61.3 (J_{CP} = 2.5 Hz, CH_2Me), 70.3 (CH_2CHMe_2), 172.7 (COO).

cis-*4-(Phosphonomethyl)-2-piperidinecarboxylic acid* (**1**). A mixture of **6** (7.24 g, 21.6 mmol) and 6 M HCl (100 ml) was refluxed with stirring for 16 h. The solvent was removed *in vacuo*, and the residue was dissolved in 70% EtOH (35 ml) and treated with propylene oxide (10 ml, 140 mmol). The resulting precipitate was filtered off and dried *in vacuo* to afford 4.1 g (18.4 mmol, 85%) of **1**: m.p. 285°C. ^{1}H NMR (400 MHz, D_2O): δ 3.55 (d, 1 H), 3.28 (d, 1 H), 2.85 (t, 1 H), 2.26 (d, 1 H), 1.97 (d, 1 H), 1.85 (m, 1 H), 1.55–1.4 (m, 4 H), 1.25 (m, 4 H). ^{13}C NMR (100 MHz, D_2O): δ 174.0, 59.0, 43.4, 34.3 (d, J = 132 Hz), 34.0 (d, J = 13 Hz), 30.2 (d, J = 3 Hz), 28.9 (d, J = 9 Hz).

References

1. Bigge, C. F. *Biochem. Pharmacol. 45* (1993) 1547; Ornstein, P. L., Monn, J. A. and Schoepp, D. D. *Drug News Perspec. 7* (1994) 5.
2. Hutchison, A. J., Williams, M., Angst, C., de Jesus, R., Blanchard, L., Jackson, R. H., Wilusz, E. J., Murphy, D. E., Bernard, P. S., Schneider, J., Campbell, T., Guida, W. and Sills, M. A. *J. Med. Chem. 32* (1989) 2171.
3. Minisci, F. *Synthesis* (1973) 1.
4. Minisci, F. and Gardini, G. P. *Tetrahedron Lett.* (1970) 15.

Received September 5, 1994.