Synthesis of 4-(Phenylethynyl)-2,6-bis[*N,N*-bis-(carboxymethyl)aminomethyl]pyridine

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The synthesis of 4-(phenylethynyl)-2,6-bis[*N,N*-bis(carboxymethyl)aminomethyl]pyridine is described. Two separate routes were investigated to reach the key intermediate 4-bromo-2,6-bis(bromomethyl)pyridine.

It is well known that 1,2-ethanediamine-*N,N,N',N'*-tetraacetic acid (EDTA) and its analogues form quite strong complexes with metal ions.[1,2] The synthesis of compounds which also contain a pyridine subunit as a part of the ligand has been reported.[3–6] We have recently described the synthesis of substituted dialkyl 4-(phenylethynyl)-2,6-pyridinedicarboxylates.[7,8] Since the corresponding acids have only three coordination sites, the stabilities of the metal complexes of these acids would be expected to be lower than those of EDTA analogues. Because of our interest in the properties of metal complexes, and especially in the good aqueous stability of conjugated pyridine structures, we investigated the preparation of 4-(phenylethynyl)-2,6-bis-[*N,N*-bis-(carboxymethyl)aminomethyl]pyridine (**10** in Scheme 1). We believed that the long and rigid conjugated system of this molecule would confer interesting spectral properties on its metal complexes.

Results and discussion

Two potential approaches starting from **1** or **5** were considered in order to reach the key intermediate **4**. Firstly, dehydracetic acid (**1**),[9] when reacted with concentrated aqueous ammonia, is a convenient source of 4-hydroxy-2,6-dimethylpyridine (**2**).[9–11] In our experiments better results (85 vs. 75 %) were obtained using recrystallization (water and methanol) as the purification method instead of the laborious high temperature distillation.[11]

4-Halogenopyridines could be prepared from pyridine *N*-oxides through their 4-nitro,[12–14] 4-amino[15] or 4-nitramino[16] derivatives, but the total yields have been notably low (10–20 %) in reported cases of 4-brominated products.[12–16] A modification of two old procedures[17,18] utilizing treatment of **2** with phosphorus pentabromide in a suitable solvent system ($CHCl_3/POX_3$) was found to be a superior approach to the target molecule **3**, giving yields of 55–60 %. This circumvents the lengthy procedures usually employed to obtain the above 4-functionalized intermediates.[12–16]

The most critical step in this route is the halogenation of the aralkyl side chain. Treatment of **3** with *N*-bromosuccinimide under free radical conditions[19–20] was not successful. After a 20 h reaction time, ^{1}H NMR and TLC analyses (silica; cyclohexane/ethyl acetate, 5:1) indicated a complex mixture of **3**, **4a** and several other bromination products, none of which was predominant. Several attempts to fractionate the oily material by crystallization or column chromatography with varying solvent combinations were unsuccessful. Nevertheless, the corresponding transformation using *N*-chlorosuccinimide in a traditional solvent (CCl_4)[22–24] gave cleanly the desired bis(chloromethyl) derivative **4b** (isolated yield 33 %). Both benzoyl peroxide and AIBN proved to be effective initiators, whereas UV

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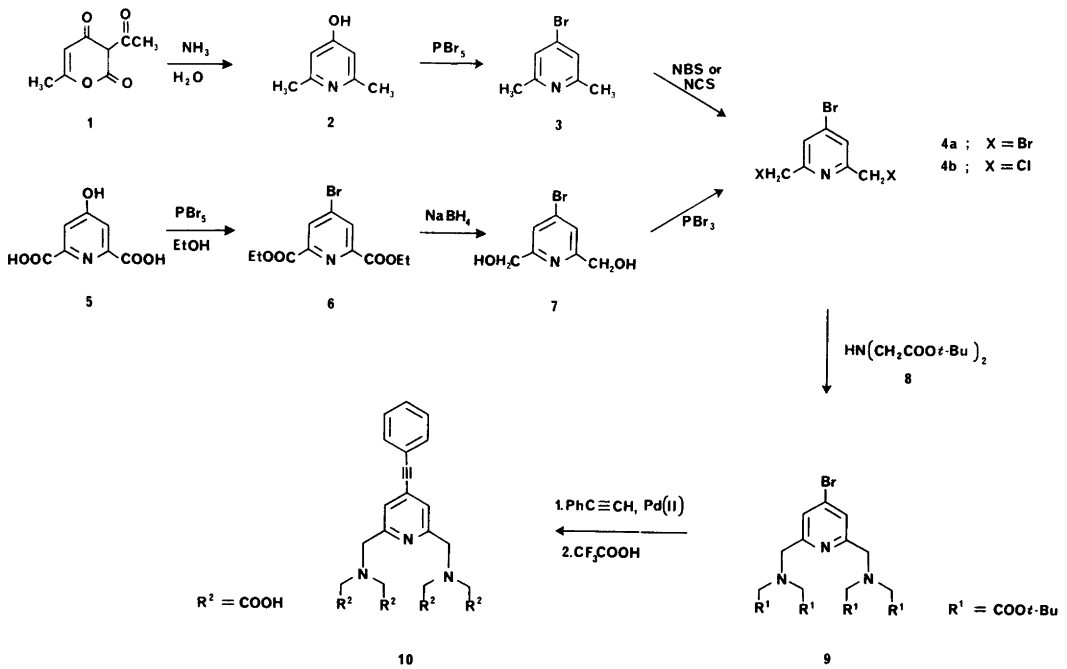
irradiation was not essential in the formation of the desired product. Dichloromethane, chloroform or benzene[19–21] offered no advantage over tetrachloromethane as solvent, but further studies in this area are needed to formulate the optimal conditions for the formation of the desired product.

Synthesis via the alternative route starts from 4-hydroxy-2,6-pyridinedicarboxylic acid (**5**), which reacts with phosphorus pentabromide to yield 4-bromo-2,6-pyridinedicarboxylic bromide. After this, treatment with absolute ethanol generates the corresponding ester **6**.[7] The ester groups of **6** are reduced by sodium borohydride.[4] Bromination of **7** with phosphorus tribromide produces an almost quantitative yield of **4a** (96 % in the best case). According to our experiments, better results are obtained when the bromination reagent is added directly in one portion instead of by gradual addition. This latter route produces a markedly higher total yield (65 %, X = Br) than the former (18 %, X = Cl).

In addition, **4a** is more reactive towards di-*t*-butyl iminodiacetate (**8**), and **4b** requires vigorous reaction conditions. We also found that the 4-bromo group may react with amino compounds if harsh conditions are used. In order to avoid side reactions this step was therefore carried out at room temperature. The reaction time was quite long but the yield was nearly quantitative.

Phenylacetylene reacts with **9** in the presence of a small amount of a palladium catalyst and copper(I) iodide.[7,8,25–27] The 4-bromo group of **9** is less reactive than that reported for **6**,[7] but, nevertheless, the yields of this step are good. The ester which is formed is hydrolyzed to the corresponding acid **10** with trifluoroacetic acid. We used the *t*-butyl ester instead of the methyl or ethyl ester because of its faster rate of acid hydrolysis. The reaction took place at room temperature during a short period (1–2 h). Moreover, if base hydrolysis is used, during acidification of the hydrolysed base material, a small amount of inorganic salt which was difficult to remove precipitated along with the product, except for barium hydroxide.[4] We found that during prolonged hydrolysis, trifluoroacetic acid adds to the triple bond. To minimize this, optimum reaction times were estimated by ^{1}H NMR monitoring.

4-Iodo-2,6-pyridinedicarboxylate (**11**)[28] can be used instead of **6**. It gives almost the same results (89 % in reduction and 64 % in bromination) as



1 2 3 5 6 7 10 9

Scheme 1.

the corresponding bromo compound, but the synthesis of **11** involves two more steps. In the coupling reaction with phenylacetylene the iodo derivative **14** is more reactive than **9**. 4-Chloro-2,6-pyridinedicarboxylate[29] was also considered but unfortunately the 4-chloro group failed to undergo the substitution reaction. The reactivity order, I > Br > Cl, is in agreement with earlier experiments.[7,26,30,31]

Vögtle *et al.*[4] have reported stabilities of complexes of metal ions with 2,6-bis[*N*,*N*-bis(carboxymethyl)aminomethyl]pyridines. The complexing properties of 4-(phenylethynyl)-2,6-bis[*N*, *N*-bis(carboxymethyl)aminomethyl]pyridine (**10**) will be reported in a separate publication.

Experimental

4-Hydroxy-2,6-dimethylpyridine (**2**). Dehydracetic acid[9] (16.8 g, 0.1 mol) was heated with a large excess of concentrated aqueous ammonia (60 ml, 0.8 mol) at 120–130 °C in a closed container for 8–10 h. The mixture was concentrated *in vacuo* and suspended in ice-cold water. The resulting greyish solid was filtered off and washed with cold water. The crude product was recrystallized successively from water and methanol, and dried in a vacuum oven at 100 °C. The yield was 10.5 g (85 %); m.p. 220–223 °C (lit. 225 °C).[11]

4-Bromo-2,6-dimethylpyridine (**3**). Dry **2** (12.3 g, 0.1 mol) was mixed with phosphorus pentabromide[18] in a vessel protected from moisture. After addition of chloroform (5 ml) and phosphorus oxybromide[18] (5 ml), the bulk mixture liquefied and was heated at 80–110 °C until the evolution of hydrogen bromide ceased (4–5 h). Most of the phosphorus oxybromide was distilled off *in vacuo* (30–50 °C/15 mmHg). The reaction mixture was then treated cautiously with ice and water (250 ml), neutralized with potassium hydroxide solution and extracted several times with ether. After drying with magnesium sulfate, the ether was removed on a rotary evaporator and the residue was purified by vacuum distillation. The yield was 12.1 g (65 %); b.p. 78–82 °C/9 mmHg; m.p. 32–33 °C (lit. 34 °C).[16]

4-Bromo-2,6-bis(chloromethyl)pyridine (**4b**). A stirred mixture of **3** (10.2 g, 55 mmol), *N*-chlorosuccinimide (14.5 g, 110 mmol) and benzoyl peroxide (250 mg, 1.0 mmol) in tetrachloromethane (150 ml) was heated under reflux and a nitrogen atmosphere for about 1.5–3.0 h. Small portions of NCS and the catalyst were added during the reaction (6.5 h), the total amounts being 33.0 g (250 mmol) and 800 mg (3.3 mmol), respectively. The cold mixture was filtered and the filtrate washed with sodium carbonate solution. After drying with magnesium sulfate the filtrate was evaporated *in vacuo*. The crude product was recrystallized twice from hexane. The yield was 4.7 g (33 %); m.p. 83–84 °C. ^{1}H NMR (60 MHz $CDCl_3$): δ 4.62 (4 H, s), 7.60 (2 H, s). Anal. $C_7H_6BrCl_2N$: C, H, Br, Cl, N.

4-Bromo-2,6-pyridinedimethanol (**7**). Sodium borohydride (3.40 g, 90 mmol) was added in small portions to a suspension of **6**[7] (6.04 g, 20 mmol) in absolute ethanol (250 ml) over a period of 0.5 h. After stirring for 2 h at room temperature the mixture was heated under reflux for 15 h and evaporated *in vacuo*. A saturated solution of sodium hydrogen carbonate (32 ml) was added to the residue, the solution was brought to boiling and water (45 ml) was added. The mixture was allowed to stand overnight in the cold. The precipitate was filtered, dried in air and extracted continuously for 24 h with acetone. The product crystallized from the acetone solution after concentration. A small amount of the product was obtained from the aqueous filtrate when extracted with chloroform (5×70 ml), dried with sodium sulfate and evaporated *in vacuo*. The total yield was 2.3–3.7 g (53–86 %); m.p. 162–164 °C. ^{1}H NMR (60 MHz, DMSO): δ 4.52 (4 H, d), 5.53 (2 H, t), 7.51 (2 H, s). Anal. $C_7H_8BrNO_2$: C, H, Br, N.

4-Iodo-2,6-pyridinedimethanol (**12**). Compound **12** was prepared from **11**[29] in analogy with **7**, and crystallized from chloroform. The yield was 3.7–4.7 g (70–89 %); m.p. 153 °C. ^{1}H NMR (60 MHz, CD_3COCD_3): δ 4.54 (2 H, t), 4.64 (4 H, d), 7.78 (2 H, s). Anal. $C_7H_8INO_2$: C, H, I, N.

4-Bromo-2,6-bis(bromomethyl)pyridine (**4a**). A solution of phosphorus tribromide (4.68 g, 17.3 mmol) in chloroform (40 ml) was added in one portion to a suspension of **7** (2.51 g, 11.5 mmol) in chloroform (70 ml). The reaction mixture was heated under reflux for 8 h. The cooled mixture was neutralized with 5 % sodium hydrogen car-

bonate and the chloroform layer was separated. The aqueous layer was extracted with chloroform (6×100 ml). The combined organic phase was dried with sodium sulfate and evaporated *in vacuo*. The residue was recrystallized from a mixture of dichloromethane and hexane. The yield was 2.5–4.1 g (64–96 %); m.p. 128–129 °C. ^{1}H NMR (60 MHz, DMSO): δ 4.66 (4 H, s), 7.81 (2 H, s). Found: C 25.16; H 1.90; Br 68.44; N 4.21. Cal. for $C_7H_6Br_3N$: C 24.45; H 1.76; Br 69.72; N 4.07.

4-Iodo-2,6-bis(bromomethyl)pyridine (**13**). This compound was prepared from **12** in a manner similar to **4a**, and crystallized from acetone. The yield was 1.8–2.9 g (41–64 %); m.p. 147–149 °C. ^{1}H NMR (60 MHz, CD_3COCD_3): δ 4.60 (4 H, s), 7.95 (2 H, s). Anal. $C_7H_6Br_2IN$: C, H, N.

Di-t-butyl iminodiacetate (**8**). Cold liquid isobutene (50 ml) was added to a cold mixture of iminodiacetic acid (13.3 g, 0.1 mol), *t*-butyl acetate (200 ml), 70 % $HClO_4$ (10 ml) and *t*-butanol (25 ml). After stirring for 3 days in an autoclave at room temperature the solution was poured into a cold stirred mixture of dichloromethane (150 ml) and water (150 ml), and neutralized with solid potassium carbonate. After filtration the organic layer was separated, and the aqueous layer was extracted with dichloromethane (4×100 ml). The combined organic phase was washed with water (100 ml) and dried with sodium sulfate. Evaporation *in vacuo* gave a liquid product which crystallized on standing. The yield was 12.4 g (51 %); m.p. 40–41 °C. ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.45 (18 H, s), 2.15 (1 H, broad s), 3.35 (4 H, s). IR (KBr): 3370 cm^{-1} (N–H), 1735, 1161 cm^{-1} (C=O and C–O). Anal. $C_{12}H_{23}NO_4$: C, H, N.

*4-Bromo-2,6-bis[*N,N-*bis(*t-*butoxycarbonylmethyl)aminomethyl]pyridine* (**9**). A solution of **4a** (3.43 g, 10 mmol), **8** (4.91 g, 20 mmol) and sodium carbonate (10.60 g, 100 mmol) in dry acetonitrile (80 ml) was stirred under a nitrogen atmosphere for 24 h at room temperature. The mixture was filtered and the filtrate was evaporated *in vacuo*. The oily residue was taken up in chloroform (100 ml), and the chloroform solution was washed with water (2×20 ml) and dried with sodium sulfate. Evaporation *in vacuo* left a yellow oil. The yield was 6.60–6.72 g (98–100 %). ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.47 (36 H, s), 3.48 (8 H, s), 4.15 (4 H, s), 7.75 (2 H, s). IR (KBr): 1730, 1145 cm^{-1} (C=O and C–O). Anal. $C_{31}H_{50}BrN_3O_8$: C, H, Br, N.

*4-Iodo-2,6-bis[*N,N-*bis(*t-*butoxycarbonylmethyl)aminomethyl]pyridine* (**14**). Compound **14** was prepared from **13** in the same way as **9**, giving a quantitative yield (7.2 g) of an oily product. ^{1}H NMR (60 MHz, $CDCl_3$): δ 1.55 (36 H, s), 3.55 (8 H, s), 4.06 (4 H, s), 8.00 (2 H, s). IR (KBr): 1740, 1140 cm^{-1} (C=O and C–O). Anal. $C_{31}H_{50}IN_3O_8$: C, H, I, N.

*4-(Phenylethynyl)-2,6-bis[*N,N-*bis(carboxymethyl)aminomethyl]pyridine* (**10**). A mixture of **9** or **14** (2.0 mmol), bis(triphenylphosphine)palladium(II) chloride (28 mg, 0.04 mmol), and copper(I) iodide (15 mg, 0.08 mmol) in dry triethylamine (10 ml) and tetrahydrofuran (10 ml) was deaerated with nitrogen. Phenylacetylene (0.25 g, 2.4 mmol) was added and the reaction mixture was heated to the desired temperature. When the reaction was complete (50 °C and 20 h for **9**; 40 °C and 5 h for **14**) the mixture was evaporated *in vacuo*. The residue was taken up in chloroform (30 ml), and the chloroform solution was washed with water (3×10 ml) and dried with sodium sulfate. Evaporation *in vacuo* left a yellowish oil which was purified by chromatography on silica using petroleum ether (b.p. 50–70 °C)/ethyl acetate as eluent: first 10:1 then 5:3. The resulting oil was dissolved in trifluoroacetic acid (60 ml) and the solution kept at room temperature for 1.5 h. The trifluoroacetic acid was evaporated *in vacuo* without heating. The residue was triturated with diethyl ether (50 ml), filtered and finally recrystallized from ethanol. The yield in both cases was 0.52 g (59–61 %); m.p. 180–181 °C. ^{1}H NMR (60 MHz, DMSO): δ 3.35 (2 H, broad s), 3.50 (8 H, s), 3.95 (4 H, s), 7.45–7.70 (7 H, m), 12.40 (4 H, broad s). IR (KBr): 2210 cm^{-1} (C≡C), 1730, 1630, 1385, 1205 cm^{-1} (C=O and C–O). Found: C 57.52; H 4.61; N 8.64. Calc. for $C_{23}H_{23}N_3O_8$: C 58.85; H 4.94; N 8.95.

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