

# Preparation of New Complexing Agents Containing a Highly Conjugated Ethynylated Pyridine Subunit

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Highly conjugated 4-ethynyl derivatives of 2,6-pyridinedicarboxylic acid and 2,6-bis[*N,N*-bis(carboxymethyl)aminomethyl]pyridine have been prepared using coupling reactions between 4-bromo- and 4-ethynyl-pyridines and acetylenes in the presence of a small amount of a palladium catalyst and copper(I) iodide.

We have recently reported the synthesis of dialkyl 4-(phenylethynyl)-2,6-pyridinedicarboxylate<sup>1</sup> and 4-(phenylethynyl)-2,6-bis[*N,N*-bis(carboxymethyl)aminomethyl]pyridine<sup>2</sup> (**5** and **8**, R<sup>1</sup>=H in Scheme 1). Because we were interested in the properties of the metal complexes of conjugated pyridine structures we investigated the preparation of highly conjugated ethynylated pyridine derivatives (**6**, **8**, **12** and **14** in Schemes 1 and 2). The long and rigid conjugation system of these molecules was expected to provide interesting spectral properties for its metal complexes. The complexing properties of **6**, **8**, **12** and **14** will be reported in a separate publication.

## Results and discussion

1-Ethynyl-4-(phenylethynyl)benzene (**3**) – the key intermediate in Scheme 1 – has already been prepared from 3-[4-(phenylethynyl)phenyl]propenoic acid in four steps and in good yield,<sup>3</sup> but unfortunately the starting material is not commercially available. Synthesis via the alternative three-step route starts with 4-iodoaniline which reacts with 2-methyl-3-butyn-2-ol to yield **1**.<sup>4</sup> Replacement of the diazonium salt of **1** with iodide generates **2** which undergoes facile coupling<sup>5–7</sup> with phenylacetylene in the presence of bis(tri-

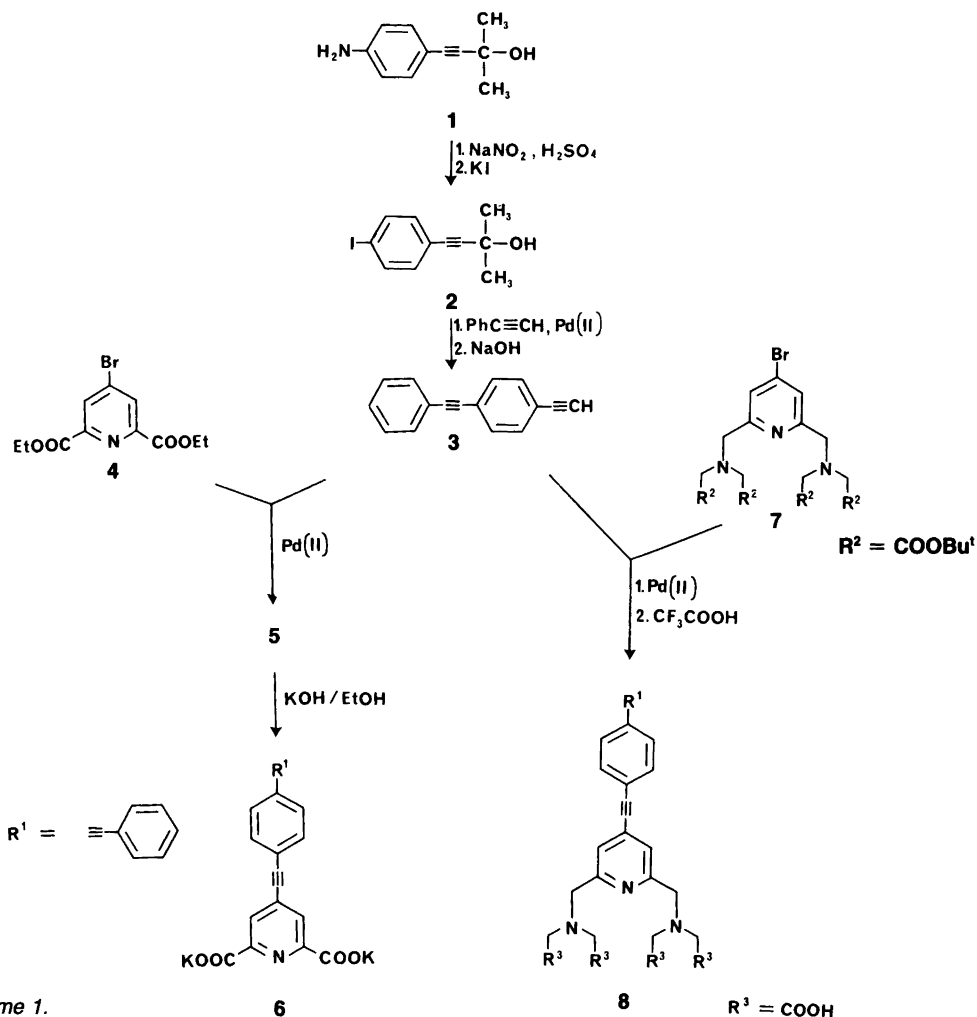
phenylphosphine)palladium(II) chloride and copper(I) iodide. The crude product was deprotected using sodium hydroxide<sup>8,9</sup> to produce **3** in good yield (64 %).

In the reaction between **3** and **4**<sup>1</sup> or **7**,<sup>2</sup> a highly conjugated pyridine subunit was formed by using organopalladium catalysis.<sup>1,2,4–7</sup> Hydrolysis of the esters formed gave the final products **6** and **8**. Compound **3** was less reactive towards **4** than phenylacetylene.<sup>1</sup> The reaction with **3** was complete after 24 h at 50 °C whereas phenylacetylene required only 2 h at the same temperature. In addition, also the yield was lower (50 vs. 75 %). However, **3** gave a higher yield with **7** than that reported for phenylacetylene<sup>2</sup> under similar reaction conditions, but this difference may be due to the loss during recrystallization of the final products.

Cadiot–Chodkiewicz coupling of a terminal alkyne with bromoacetylene in the presence of cuprous ions and a simple amine constitutes a method for preparing unsymmetrical polyacetylenes in which the triple bonds are coupled directly to each other.<sup>10–12</sup> 1-Bromo-2-phenylethyne (**9**), which was used in these reactions, was made by treating phenylacetylene with sodium hypobromite.<sup>13</sup> The long reaction time (60 h) of this procedure can be reduced (to 2–4 h) with a somewhat better yield (89 vs. 83 %) by using a phase-transfer catalyst (10 mol %) in the reaction mixture. The synthesis of phenylbutadiyne (**10**) has been described in many papers,<sup>14–17</sup> but either the

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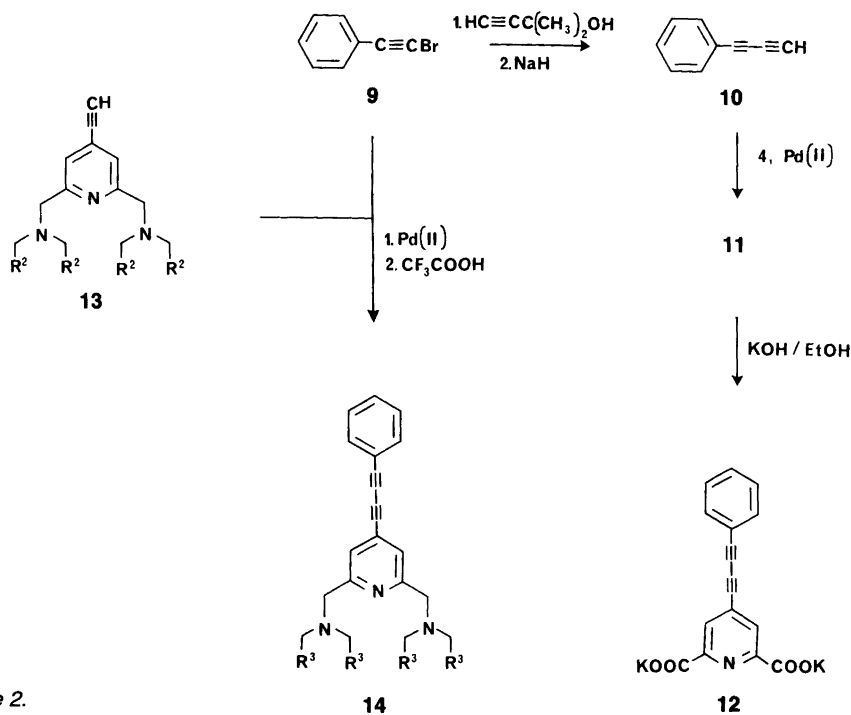
Scheme 1.

methods comprise numerous steps, or the starting materials are expensive. The method outlined in Scheme 2 offers a simple synthesis of **10** of reasonable yield. The protecting group of the triple bond in 5-methyl-1-phenyl-1,3-hexadiyn-5-ol formed in the Cadiot–Chodkiewicz coupling of **9** and 2-methyl-3-butyn-2-ol<sup>12</sup> can be cleaved using sodium hydride.<sup>18</sup> Light petroleum (b.p. 50–70 °C) was used as the solvent instead of toluene to prevent the decomposition of **10**.<sup>13,16</sup>

Phenylbutadiyne (**10**) reacted with **4** in the presence of a small amount of the palladium catalyst and copper(I) iodide, and saponification of the resulting ester (**11**) produced **12**. Unfortu-

nately, **10** failed to react analogously with **7**. Obviously, the diyne is unstable under the more vigorous reaction conditions needed in the coupling reaction with **7**.

However, the desired compound (**14**) can be made via an alternative route. The reaction of **9** with **13** under palladium catalysis took place at room temperature without difficulty, and finally, acid hydrolysis of the ester groups generated product **14**. The ethynyl compound (**13**) was made from **7** by using (trimethylsilyl)acetylene.<sup>19,20</sup> 2-Methyl-3-butyn-2-ol was also tried in this coupling reaction<sup>8,9,21</sup> but unfortunately the



Scheme 2.

deprotection of the triple bond by sodium hydride<sup>18</sup> failed.

The reaction between **9** and 4-ethynyl-2,6-pyridinedicarboxylate was also attempted using Cadot–Chodkiewicz and organopalladium coupling conditions. However, in contrast with compound **13**, in both cases dimers of the starting materials were the major products and only small amounts of the desired product were obtained. The undesired reactions must arise from the cupric ion formed during the self-coupling of the bromoalkyne.<sup>12</sup> The cupric ion may then effect Claser coupling of the ethynyl compound. For some reason, when 4-ethynyl-2,6-pyridinedicarboxylate was used instead of **13**, dimerisation was rapid.

## Experimental

**4-(4-Iodophenyl)-2-methyl-3-butyn-2-ol (2).** Sodium nitrite (1.84 g, 26.6 mmol) in water (10 ml) was added to a cold (below 5 °C) mixture of **1**<sup>4</sup> (4.67 g, 26.6 mmol) and 2 M H<sub>2</sub>SO<sub>4</sub> (50 ml) during 30 min. When the mixture had been stirred for 1 h below 5 °C, potassium iodide (1.42 g, 8.55 mmol) in 2 M H<sub>2</sub>SO<sub>4</sub> (25 ml) was added

during 30 min. After a further 30 min of stirring below 5 °C the ice-bath was removed and stirring was continued for 1 h. Water was removed by decantation and the dark residue was dissolved in chloroform (100 ml), the solution was washed successively with 5% sodium hydrogen sulfite (2×50 ml), 5% sodium hydrogen carbonate (50 ml) and dried with sodium sulfate. Evaporation *in vacuo* gave a product which was recrystallized from hexane by decantation of the insoluble material. The yield was 3.62 g (48%), m.p. 87–88 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.62 (6 H, s), 1.84 (1 H, br s), 7.15 (2 H, d), 7.65 (2 H, d). Anal. Calc. for C<sub>11</sub>H<sub>11</sub>IO: C, 46.18; H, 3.88; I, 44.35. Found: C, 47.01; H, 3.28; I, 45.10.

**1-Ethynyl-4-(phenylethynyl)benzene (3).** A mixture of **2** (0.72 g, 2.5 mmol), bis(triphenylphosphine)palladium(II) chloride (35 mg, 0.05 mmol) and copper(I) iodide (19 mg, 0.10 mmol) in dry triethylamine (10 ml) was deaerated with nitrogen, whereafter phenylacetylene (0.26 g, 2.5 mmol) was added. After having been stirred for 2 h at room temperature the reaction mixture was filtered and the filtrate was evaporated *in*

*vacuo*. The residue was dissolved in dichloromethane (20 ml), and the solution was washed with water (3×5 ml) and dried with sodium sulfate. Evaporation *in vacuo* gave a yellow solid which was heated under reflux in the presence of one pellet of sodium hydroxide in toluene (30 ml). When the reaction was complete (2–4 h), the cold mixture was filtered and the filtrate was evaporated *in vacuo*. The product was recrystallized from ethanol or light-petroleum (b.p. 50–70°C). The yield was 0.32 g (64%), m.p. 76°C (lit.,<sup>3</sup> 90.5–91°C). Although the melting point was incorrect, the product was of greater than 95% purity according to NMR spectroscopy, and was used as such.

*Diethyl 4-[4-(phenylethynyl)phenylethynyl]-2,6-pyridinedicarboxylate (5)*. A mixture of **4**<sup>1</sup> (0.30 g, 1.0 mmol), bis(triphenylphosphine)palladium (II) chloride (14 mg, 0.02 mmol) and copper(I) iodide (8 mg, 0.04 mmol) in dry triethylamine (4 ml) and tetrahydrofuran (3 ml) was deaerated with nitrogen, and **3** (0.20 g, 1.0 mmol) was added to the reaction mixture. After having been stirred for 3 h at 35°C the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in chloroform (15 ml), and the solution was washed with water (3×5 ml) and dried with sodium sulfate. Evaporation *in vacuo* gave a crude material which was recrystallized from ethanol. The yield was 0.21 g (50%), m.p. 119–120°C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.47 (6 H, t), 4.50 (4 H, q), 7.26–7.51 (9 H, m), 8.34 (2 H, s). IR (KBr): 2210 (C≡C), 1721, 1260 cm<sup>-1</sup> (C=O and C–O). Anal. Calc. for C<sub>27</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>: C, 76.58; H, 5.00; N, 3.31. Found: C, 76.91; H, 5.30; N, 3.14.

*Dipotassium salt of 4-[4-(phenylethynyl)phenylethynyl]-2,6-pyridinedicarboxylic acid (6)*. A mixture of **5** (106 mg, 0.25 mmol) in 0.5 M potassium hydroxide in ethanol (5 ml) was stirred for 2 h at room temperature. The resulting solid was filtered, washed with ethanol and finally recrystallized from water. The yield was 104 mg (94%). IR (KBr): 2210 (C≡C), 1635, 1410, 1342 cm<sup>-1</sup> (C=O and C–O). Anal. Calc. for C<sub>23</sub>H<sub>11</sub>K<sub>2</sub>N<sub>3</sub>O<sub>4</sub>: C, 62.28; H, 2.50; K, 17.63; N, 3.16. Found: C, 62.57; H, 2.75; K, 17.94; N, 3.00.

*4-[4-(Phenylethynyl)phenylethynyl]-2,6-bis[N,N-bis(carboxymethyl)aminomethyl]pyridine (8)*. A

mixture of **7**<sup>2</sup> (0.67 g, 1.0 mmol), bis(triphenylphosphine)palladium(II) chloride (14 mg, 0.02 mmol) and copper(I) iodide (8 mg, 0.04 mmol) in dry triethylamine (5 ml) and tetrahydrofuran (3 ml) was deaerated with nitrogen, and **3** (0.20 g, 1.0 mmol) was added to the reaction mixture. After having been stirred for 24 h at 50°C, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in dichloromethane (15 ml), and the solution was washed with water (3×5 ml) and dried with sodium sulfate. The resulting oil was dissolved in trifluoroacetic acid (20 ml) and kept at room temperature for 1.5 h. The trifluoroacetic acid was evaporated *in vacuo* without heating, and the residue was triturated with diethyl ether (40 ml), filtered and finally recrystallized from 1-propanol. The yield was 0.51 g (88%), m.p. 144–145°C. <sup>1</sup>H NMR ([<sup>2</sup>H<sub>6</sub>]DMSO): δ 3.62 (8 H, s), 4.02 (4 H, s), 7.20–7.78 (11 H, m). IR (KBr): 2210 (C≡C), 1734, 1630, 1400, 1194 cm<sup>-1</sup> (C=O and C–O). Anal. Calc. for C<sub>31</sub>H<sub>27</sub>N<sub>3</sub>O<sub>8</sub>: C, 65.37; H, 4.78; N, 7.38. Found: C, 65.09; H, 4.46; N, 7.70.

*1-Bromo-2-phenylethyne (9)*. Phenylacetylene (1.02 g, 10 mmol) was added dropwise to a cold mixture of bromine (1.76 g, 11 mmol) and tetrabutylammonium bromide (0.32 g, 1 mmol) in 10 M sodium hydroxide (2.5 ml). The ice-bath was removed and the reaction flask was protected from light. After 2–4 h at room temperature, 10% ammonium chloride solution was added to the cold reaction mixture to destroy excess hypobromite, and the mixture was extracted with diethyl ether (3×25 ml). The combined organic phases were washed with water (15 ml) and dried with sodium sulfate. Evaporation *in vacuo* gave a yellow oil. The yield was 1.61 g (89%),  $n_D^{22} = 1.6085$  (lit.,<sup>11</sup>  $n_D^{20} = 1.6080$ ).

*Phenylbutadiyne (10)*. The product, 5-methyl-1-phenyl-1,3-hexadiyn-5-ol (1.50 g, 8.14 mmol), which was made from **9** and 2-methyl-3-butyn-2-ol as described previously<sup>12</sup> was added to a mixture of sodium hydride (0.1 g) in light petroleum (b.p. 50–70°C). The mixture was heated under reflux until the reaction was complete (ca. 14 h) and filtered. Evaporation *in vacuo* left a yellow oil which was used without further purification. The yield was 0.55 g (54%),  $n_D^{20} = 1.6160$  (lit.,<sup>12</sup>  $n_D^{19.5} = 1.6230$ ).

*Diethyl 4-(phenylbutadiynyl)-2,6-pyridinedicarboxylate (11)*. A mixture of **4** (0.60 g, 2.0 mmol), bis(triphenylphosphine)palladium(II) chloride (28 mg, 0.04 mmol) and copper(I) iodide (16 mg, 0.08 mmol) in dry triethylamine (3 ml) and tetrahydrofuran (3 ml) was deaerated with nitrogen, and **10** (0.31 g, 2.4 mmol) was added. After having been stirred for 48 h at 30 °C, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in chloroform (15 ml), washed with water (3×5 ml) and dried with sodium sulfate. Evaporation *in vacuo* left a dark material which was purified by chromatography on silica using light petroleum (b.p. 50–70 °C)–ethyl acetate as the eluent: first 10:0.5 then 10:2. The product was recrystallized from ethanol. The yield was 0.35 g (50%), m.p. 114–115 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.43 (6 H, t), 4.47 (4 H, q), 7.40–7.65 (5 H, m), 8.43 (2 H, s). IR (KBr): 2225 (C≡C), 1720, 1240 cm<sup>-1</sup> (C=O and C–O). Anal. Calc. for C<sub>21</sub>H<sub>17</sub>NO<sub>4</sub>: C, 72.61; H, 4.93; N, 4.03. Found: C, 71.95; H, 4.60; N, 3.79.

*Dipotassium salt of 4-(phenylbutadiynyl)-2,6-pyridinedicarboxylic acid (12)*. A mixture of **11** (174 mg, 0.50 mmol) in 0.5 M potassium hydroxide in ethanol (10 ml) was stirred for 2 h at room temperature. The resulting solid was filtered, washed with ethanol and crystallized from water–ethanol. The yield was 120 mg (65%). IR (KBr): 2220 (C≡C), 1640, 1410, 1341 cm<sup>-1</sup> (C=O and C–O). Further crystallization did not give an analytically pure sample.

*2,6-Bis[N,N-bis(t-butoxycarbonylmethyl)aminomethyl]-4-ethynylpyridine (13)*. A mixture of **7** (6.72 g, 10 mmol), bis(triphenylphosphine)palladium(II) chloride (140 mg, 0.2 mmol), copper(I) iodide (76 mg, 0.4 mmol) in dry triethylamine (11 ml) and tetrahydrofuran (11 ml) was deaerated with nitrogen, and (trimethylsilyl)acetylene (1.18 g, 12 mmol) was added. After having been stirred for 24 h at 50 °C, the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in chloroform (40 ml), washed with water (2×30 ml) and dried with sodium sulfate. Evaporation *in vacuo* left a dark oil which was dissolved in methanol (28 ml). The solution was deaerated with nitrogen, potassium carbonate (138 mg, 1.0 mmol) was added, and the mixture was stirred for 2 h at room temperature, after which time it was evaporated *in vacuo*. The resi-

due was dissolved in dichloromethane (60 ml), washed successively with 5% sodium hydrogen carbonate (12 ml) and water (12 ml), and dried with sodium sulfate. Evaporation *in vacuo* left a dark oil which was purified by chromatography on silica using light petroleum (b.p. 50–70 °C)–ethyl acetate (10:1) as the eluent. The product was a yellowish oil, yield 2.53–4.46 g (41–72%). <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.46 (36 H, s), 3.22 (1 H, s), 3.48 (8 H, s), 4.03 (4 H, s), 7.61 (2 H, s). IR (KBr): 3260 (C≡C–H), 2210 (C≡C), 1740, 1155 cm<sup>-1</sup> (C=O and C–O). Anal. Calc. for C<sub>33</sub>H<sub>51</sub>N<sub>3</sub>O<sub>8</sub>: C, 67.16; H, 8.32; N, 6.80. Found: C, 63.96; H, 8.23; N, 6.76.

*2,6-Bis[N,N-bis(carboxymethyl)aminomethyl]-4-(phenylbutadiynyl)pyridine (14)*. A mixture of **9** (52 mg, 0.5 mmol) and **13** (0.34 g, 0.56 mmol) in dry triethylamine (2.5 ml) was deaerated with nitrogen. Bis(triphenylphosphine)palladium(II) chloride (7 mg, 0.01 mmol) and copper(I) iodide (4 mg, 0.02 mmol) was added to the reaction vessel. After having been stirred for 6 h at room temperature the mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was dissolved in chloroform (25 ml), and the solution was washed with water (2×5 ml) and dried with sodium sulfate. Evaporation left an oil which was purified by chromatography on silica using light petroleum (b.p. 50–70 °C)–ethyl acetate as the eluent: first 10:1 then 5:3. The resulting oil was dissolved in trifluoroacetic acid (17 ml) and kept at room temperature for 1.5 h. The trifluoroacetic acid was evaporated *in vacuo*, and the residue was triturated with diethyl ether (20 ml), filtered and recrystallized from ethanol. The yield was 0.19 g (77%), m.p. 185–186 °C. <sup>1</sup>H NMR([<sup>2</sup>H<sub>6</sub>] DMSO): δ 3.48 (8 H, s), 3.95 (4 H, s), 7.45–7.67 (5 H, m), 7.59 (2 H, s). IR (KBr): 2220 (C≡C), 1731, 1635, 1395, 1200 cm<sup>-1</sup> (C=O and C–O). Anal. Calc. for C<sub>25</sub>H<sub>23</sub>N<sub>3</sub>O<sub>8</sub>: C, 60.85; H, 4.70; N, 8.52. Found: C, 61.53; H, 4.68; N, 8.48.

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