Preparation of Complexing Compounds Containing Two 2,6-Bis[*N,N*-bis(carboxymethyl)aminomethyl]-4-ethynylpyridine Subunits

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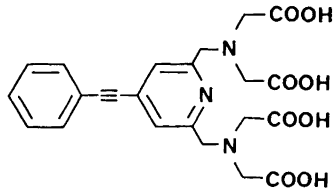
Compounds containing two 2,6-bis[*N,N*-bis(carboxymethyl)aminomethyl]-4-ethynylpyridine subunits have been prepared by coupling reactions between diiodoarenes and acetylenes in the presence of a small amount of a palladium catalyst and copper(I) iodide.

In our recent reports we described the synthesis of 2,6-bis[*N,N*-bis(carboxymethyl)aminomethyl]-4-(phenylethynyl)pyridine (**1**) and its analogues.[1,2] In these reactions the organometallic coupling with arylacetylenes and halides in the presence of amines plays an important role.[1–8] Rossi *et al.*[8] have reported a synthesis of diacetylenic compounds using dihaloarenes and acetylenes generated *in situ* from the corresponding halides and 2-methyl-3-butyn-2-ol.

We were interested in diacetylenic compounds, particularly those containing two complexing parts instead of one, as in **1**, and thus investigated the preparation of **7a–d** in Scheme 1. Since compounds **7a–d** can bind two metal ions they may have interesting spectral properties and these will be reported in a separate publication.



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The diiodo compounds **4a,b** used in this work were made from 4,4′-diiodobenzophenone oxime (**3**) which reacts with t-butyl bromoacetate to yield **4a**, and the reduction of **3** with titanium tetrachloride–sodium borohydride[9] gives **4b**. The amides **4c,d** were prepared from iodobenzoyl chlorides and 4-iodoaniline.

Compounds **4a–d** react with **5**[2] in the presence of a small amount of bis(triphenylphosphine)palladium(II) chloride and copper(I) iodide in a mixture of triethylamine and tetrahydrofuran to give the diacetylenic intermediates **6a–d**.[1–7] Also in these cases we found that the use of tetrahydrofuran increased the rate of reaction.[7] The reaction of **5** with **4a** and **4b** was complete in two hours while **4c** and **4d** required longer reaction times. The hydrolysis of **6a–d** was performed with trifluoroacetic acid and gave good results.

Experimental

The ^{1}H NMR spectra were recorded at 400 MHz.

4,4′-Diiodobenzophenone (**2**). Sodium nitrite (2.76 g, 40 mmol) in cold water (7 ml) was added to a cold (0 °C) suspension of 4,4′-diaminobenzophenone[10] (4.25 g, 20 mmol) in 2 M sulfuric acid (36 ml) over 30 min. After an hour of stirring at 0 °C, potassium iodide (9.96 g, 60 mmol) in 2 M sulfuric acid (18 ml) was added over 30 min. After a further 30 min of stirring at

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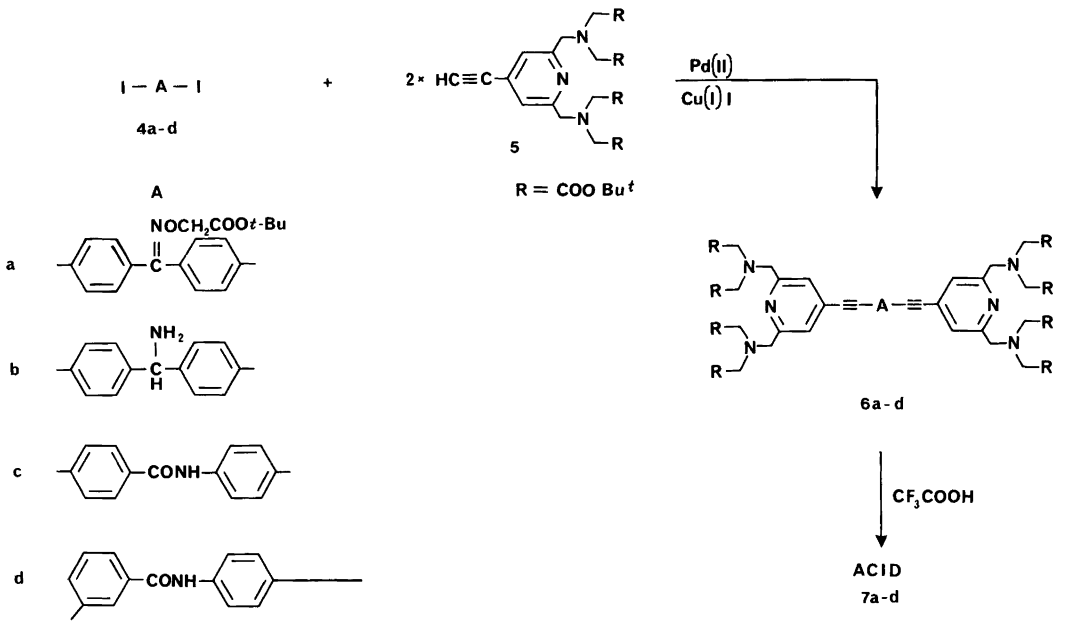

Scheme 1.

0 °C the ice bath was removed and stirring was continued for 1 h. The product was filtered, washed with water and crystallized from toluene after decantation from insoluble material. The yield was 5.36 g (62 %), m.p. 227 °C (lit.,[11] 233–234 °C).

4,4'-Diiodobenzophenone oxime (**3**). A mixture of **2** (4.34 g, 10 mmol)), hydroxylamine hydrochloride (2.08 g, 30 mmol) and potassium hydroxide (5.05 g, 90 mmol) in ethanol (200 ml) was refluxed for 5 h. Water (400 ml) was added to the cooled solution. The resulting yellowish solid was filtered, washed with water and recrystallized from acetonitrile–methanol. The yield was 3.58 g (80 %), m.p. 170–172 °C (lit.,[11] 171–173 °C).

4,4'-Diiodobenzophenone O-*t-butyloxycarbonylmethyloxime* (**4a**). Compound **3** (0.90 g, 2.0 mmol) was added to a solution of sodium ethoxide (20 mmol) in absolute ethanol (10 ml) and the mixture was stirred for 10 min. Following the addition of t-butyl bromoacetate (0.39 g, 2.0 mmol), the reaction mixture was stirred for 6 h at room temperature after which time it was evaporated *in vacuo*. The residue, in chloroform (25 ml), washed with 0.5 M sodium hydroxide (5 ml) and dried with sodium sulfate. After recrystallization from ethanol the yield of the product was 0.63 g (56 %), m.p. 94–97 °C. ^{1}H NMR ($CDCl_3$): 1.48 (9 H, s), 4.59 (2 H, s), 7.18 (2 H, d), 7.20 (2 H, d), 7.66 (2 H, d), 7.78 (2 H, d). IR (KBr): 1750, 1155 cm^{-1} (C=O and C–O). Anal. $C_{19}H_{19}I_2NO_3$: C, H, I, N.

Bis(4-iodophenyl)methylamine (**4b**). Titanium tetrachloride (1.00 g, 5.25 mmol) was added to a cold solution of sodium borohydride (0.40 g, 10.50 mmol) in 1,2-dimethoxyethane (10 ml) over 10 min. Thereafter **3** (1.12 g, 2.50 mmol) in 1,2-dimethoxyethane (6 ml) was added over 45 min. The mixture was stirred for 10 min at 0 °C whereupon the ice bath was removed and stirring was continued for 20 h at room temperature. Ice-cold water (25 ml) was carefully added to the cooled mixture, which was then made basic with concentrated ammonium hydroxide and extracted continuously for 24 h with diethyl ether. The product was recrystallized from acetonitrile–methanol. The yield was 0.44 g (40 %), m.p. 117–119 °C. ^{1}H NMR ([$^2H_6$]DMSO): 2.51 (2 H, s), 5.00 (1 H, s), 7.19 (4 H, d), 7.63 (2 H, d). IR (KBr): 3385, 3315 cm^{-1} (N–H). Anal. $C_{13}H_{11}I_2N$: C, H, I, N.

*4-Iodo-*N*-(4-iodophenyl)benzamide* (**4c**). A mixture of 4-iodobenzoyl chloride (0.33 g, 1.24 mmol) and 4-iodoaniline (2.27 g, 1.24 mmol) in dry pyridine (10 ml) was refluxed for 1 h. The cold solution was poured into water (50 ml) and the resulting solid was filtered and washed with water. After recrystallization from ethanol–tetrahydrofuran the yield of the product was 0.48 g (86 %), m.p. 286–288 °C (lit.,[12] 287 °C).

*3-Iodo-*N*-(4-iodophenyl)benzamide* (**4d**). Compound **4d** was made from 3-iodobenzoyl chloride and 4-iodoaniline analogously to **4c** and recrystallized from ethanol. The yield was 0.31 g (55 %), m.p. 188–190 °C. ^{1}H NMR ([$^2H_6$] acetone): 7.35 (1 H, t), 7.69 (2 H, d), 7.72 (2 H, d), 7.97 (1 H, d), 8.01 (1 H, d), 8.32 (1 H, s), 10.40 (1 H, s). IR (KBr): 1655, 1525 cm^{-1} (C=O and C–N). Anal. $C_{13}H_9I_2NO$: C, H, I, N.

*4,4'- Bis [4 - (2,6 - bis [*N, N - *bis (carboxymethyl)-aminomethyl]pyridyl)ethynyl]benzophenone* O-*(carboxymethyl)oxime* (**7a**). A mixture of **5**[2] (0.34 g, 0.56 mmol) and **4a** (0.14 g, 0.25 mmol) in dry triethylamine (2 ml) and tetrahydrofuran (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 and the reaction mixture was heated to 40 °C for 1.5 h. The mixture was filtered and the filtrate was evaporated *in vacuo*. The residue, in chloroform (15 ml), was washed with water (2×5ml) 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 5:1 and then 5:3. The resulting oil was dissolved in trifluoroacetic acid (10 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 (25 ml), filtered and recrystallized from ethanol. The yield was 0.18 g (70 %), m.p. decomp. >150 °C. ^{1}H NMR ([$^2H_6$]DMSO): 3.49 (8 H, s), 3.50 (8 H, s), 3.95 (4 H, s), 3.97 (4 H, s), 4.73 (2 H, s), 7.46 (2 H, d), 7.52 (2 H, d), 7.58 (2 H, s), 7.60 (2 H, s), 7.68 (2 H, d), 7.77 (2 H, d). IR (KBr): 2210 (C≡C), 1730, 1630, 1395, 1195 cm^{-1} (C=O and C–O). Anal. $C_{51}H_{48}F_3N_7O_{21}$: C, H, N.

*Bis(4,4'-bis[4-(2,6-bis[*N,N-*bis(carboxymethyl)-aminomethyl]pyridyl)ethynyl]phenyl)methylamine* (**7b**). Compound **7b** was made from **4b** and **5** analogously to **7a** using a coupling reaction time of 2 h at room temperature. The intermediate ester **6b** was purified by chromatography on silica using dichloromethane–methanol (10:1) as the eluent. After recrystallization from ethanol–water the yield was 0.20 g (83 %), m.p. decomp. >150 °C. ^{1}H NMR ([$^2H_6$]DMSO): 3.50 (16 H, s), 3.89 (1 H, s), 3.96 (8 H, s), 7.56 (4 H, d), 7.57 (4 H, s), 7.74 (4 H, d). IR (KBr): 2210 (C≡C), 1725, 1630, 1390, 1195 cm^{-1} (C=O and C–O). Anal. $C_{49}H_{48}F_3N_7O_{18}$: C, H, N.

*4-[4-(2,6-Bis[*N,N-*bis(carboxymethyl)aminomethyl]pyridyl)ethynyl]-*N*-4-[4-(2,6-bis[*N,N-*bis(carboxymethyl)aminomethyl]pyridyl)ethynyl]phenyl)benzamide* (**7c**). Compound **7c** was made from **4c** and **5** analogously to **7a** using a coupling reaction time of 24 h at room temperature. The ester **6c** was purified by chromatography on silica using light petroleum (b.p. 50–70 °C)–ethyl acetate (10:3) as the eluent. After recrystallization from ethanol the yield was 0.17 g (73 %), m.p. decomp. >140 °C. ^{1}H NMR ([$^2H_6$]DMSO): 3.58 (8 H, s), 3.62 (8 H, s), 4.06 (4 H, s), 4.10 (4 H, s), 7.64 (2 H, d), 7.69–7.72 (6 H, m), 7.80 (2 H, d), 8.04 (2 H, d), 10.50 (1 H, s). IR (KBr): 2210 (C≡C), 1730, 1630, 1525, 1390, 1200 cm^{-1} (C=O, C–O and C–N). Anal. $C_{49}H_{46}F_3N_7O_{19}$: C, H, N.

*3-[4-(2,6-Bis[*N,N-*bis(carboxymethyl)aminomethyl]pyridyl)ethynyl]-*N*-(4-[4-(2,6-bis[*N,N-*bis(carboxymethyl)aminomethyl]pyridyl)ethynyl]phenyl)benzamide* (**7d**). Compound **7d** was made from **4d** and **5** analogously to **7a** using a coupling reaction time of 20 h at room temperature. The ester **6d** was purified by chromatography on silica using light petroleum (b.p. 50–70 °C)–ethyl acetate as the eluent: first 5:1.5 then 5:3. After recrystallization from ethanol, the yield was 0.10 g (44 %), m.p. decomp. >144 °C. ^{1}H NMR ([$^2G_6$]DMSO): 3.56 (8 H, s). 3.57 (8 H, s), 4.04 (4 H, s), 4.05 (4 H, s), 7.64–8.23 (12 H, m), 10.62 (1 H, s). IR (KBr): 2210 (C≡C), 1735, 1630, 1515, 1405, 1200 cm^{-1} (C=O, C–O and C–N). Anal. $C_{49}H_{46}F_3N_7O_{19}$: C, H, N.

References

1. Takalo, H., Pasanen, P. and Kankare, J. *Acta Chem. Scand., Ser. B 42* (1988) 373.
2. Hänninen, E., Takalo, H. and Kankare, J. *Acta Chem. Scand., Ser. B 42* (1988) 614.
3. Sonogashire, K., Tohda, Y. and Hagihara, N. *Tetrahedron Lett.* (1975) 4467.
4. Dieck, H. A. and Heck, F. R. *J. Organomet. Chem. 93* (1975) 259.
5. Cassar, L. *J. Organomet. Chem. 93* (1975) 253.
6. Takalo, H. and Kankare, J. *Acta Chem. Scand., Ser. B 41* (1987) 219.
7. Takalo, H., Kankare, J. and Hänninen, E. *Acta Chem. Scand., Ser. B 42* (1988) 448.
8. Carpita, A., Lessi, A. and Rossi, R. *Synthesis* (1984) 571.
9. Kano, S., Tanaka, Y., Sugino, E. and Hibino, S. *Synthesis* (1980) 695.
10. Fierz, J. E. and Koechlin, H. *Helv. Chim. Acta 1* (1918) 218.
11. Hoffmann, E. *Justus Liebigs Ann. Chem. 264* (1891) 160.
12. Montagne, P. J. *Ber. Dtsch. Chem. Ges. 51* (1918) 1479.

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