DOTTADs – readily made novel metal ligands with multivariant functionality – trans-DOTTADs and semi-DOTTADs

Andrea Arany,a Otto Meth-Cohn,a István Berhésb and Miklós Nyergesabc

a Institute of Pharmacy, Chemistry and Biomedical Sciences, University of Sunderland, Wharcliffe Street, Sunderland, UK SR1 3SD
b Research Group of the Hungarian Academy of Sciences, Department of Organic Chemical Technology, Technical University of Budapest, H-1521 Budapest P.O.B. 91, Hungary

Introduction

Recently we described a new double cyclisation whereby 2,6-dimethylpyridine-3,5-dicarboxylic acid 1 (‘Hantzsch acid’) in which the methyl groups are ‘activated’, reacted with a Vilsmeier reagent in a multi-step but one-pot process to form a DOTTAD 2 (1,8-dioxo-1,2,7,8-tetrahydro-2,7,10-triazaanthracene-4,5-dicarbaldelydes). The reaction involved di- formylation by each of the two methyl groups followed by bis-intramolecular acylation at the introduced nitrogens and subsequent demethylation and hydrolysis to generate a new tricyclic dialdehyde, the DOTTAD 2. We have shown this reaction is quite general and is a highly efficient and versatile route to useful ligands for group I and II metal ions and some transition metals (Scheme 1).1

Results and discussion

The reaction of 2,5-dimethylpyrazine-3,6-dicarboxylic acid 3 and its diethyl ester (5) with Vilsmeier reagents – synthesis of trans-DOTTADs

The reaction of 2,5-dimethyl-3,6-dicarboxylic acid 2 (with different Vilsmeier reagents was conducted with preformed reagents, derived from the corresponding dialkylformamides using POCl3 as a solvent. After 12 hours at 80 °C, the usual aqueous work-up caused no precipitation, in contrast to the formation of the very insoluble DOTTADs (2). However, continuous extraction of the aqueous solution with chloroform yielded the expected trans-DOTTAD products (4a–e) in low yields (Scheme 2).

Better results were achieved using diethyl 2,5-dimethylpyrazine-3,6-dicarboxylate (5). The diester 5 was added to a dimethylformamide–POCl3 mixture and heated, the progress of the reaction being monitored by 1H-NMR spectroscopy. After 12 hours at 80 °C, when no more starting material was observed and indications of iminium salt formation seen in the NMR spectrum (see previous papers), the reaction mixture was worked up as usual. On addition of ammonium hydroxide to the resulting stable aqueous solution of the iminium salt intermediate (cf. Scheme 1), the parent dialdehyde (4d) was isolated in poor yield by continuous extraction, probably due to its high water-solubility. However when this iminium salt solution was stirred with a large excess of a primary amine, a tan coloured precipitate appeared, which after recrystallization...
proved to be the dimines 6a–e of the dialdehydes 4, some in good yield (Scheme 3). One of these imines 6a was quantitatively converted into the corresponding trans-DOTTAD aldehyde 4a by brief stirring with cold aqueous hydrochloric acid and THF.

![Scheme 3](image)

Scheme 3 Reagents and conditions: i. (a) POCl₃, DMF, 80 °C; (b) H₂O; (c) RNH₂. ii. (a) POCl₃, DMF, 80 °C; (b) H₂O; (c) NH₂OH.

A curious feature of the rather insoluble trans-DOTTADs 4a,b compared to the more soluble 4c was the 2.7 ppm upfield shift of the CHO protons of the former (~8.1 ppm) compared to the latter (normal aldehydes). We attribute this to the partial, and reversible hydration of these aldehydes in warm DMSO-d₆. A similar but smaller effect is noted with the imine 6a compared to 6b.

**Reaction of 2,6-dimethylpyridine-3,5-dicarboxylic acid ester (1) with benzaldehydes – synthesis of semi-DOTTADs**

In the next series of experiment we intended to examine the reaction of the bis-pyranopyridine 7 which was intended by Plieninger et al. in 1958 and which seemed a promising candidate for the effective synthesis of new DOTTAD-type ligands, such as 8 (Scheme 4). It should be noted that the ligand action of DOTTAD aldehydes is probably due to involvement of the hydrated aldehyde, as evidenced by our preliminary examination of isolated sodium complexes. Plieninger claimed to have generated these derivatives by treatment of the ester 1 with benzaldehyde.

![Scheme 4](image)

Scheme 4

The authors were uncertain about the structure of the condensation product of diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (1) and benzaldehyde: the compound did not dissolve in cold sodium carbonate solution which suggested the dilaconic structure (7). However, they were able to prepare its monohydrate which suggested at least one free carboxylic acid function. The only available spectral information, the UV-spectrum, was uninformative. Repeating the reaction gave a nicely crystalline product as described in their paper which proved to be the monocarboxylic acid (9) on the basis of its NMR, IR and mass spectra. Other aromatic aldehydes behaved differently in this reaction: the 2-bromo- and 4-chlorobenzaldehyde gave the dicarboxylic acids 10a and 10b while in the other cases (p-methoxybenzaldehyde, piperonal, 4-nitrobenzaldehyde) we observed the formation of a complex mixture of products.

The reaction of 7-phenyl-2-(2-phenylethenyl)-7,8-dihydropyran-4,3-b)pyridin-5-one-3-carboxylic acid (9) with different Vilsmeier reagents (preformed from the corresponding dialkylliformamides using POCl₃ as a solvent) after the usual work-up gave the expected ‘semi-DOTTADs’ 11 in acceptable yields (Scheme 5).

**Experimental**

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240C or Carlo Erba 1106 Elemental Analyser. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR or Unicam research series FTIR spectrophotometer using sodium chloride plates. ¹H NMR spectra were acquired on a Jeol JG 270 FT NMR at 270 MHz. Coupling constants are given in Hz and all chemical shifts are relative to an internal standard of tetramethylsilane. ¹³C NMR spectra were obtained on a Jeol GFX 270 FT NMR (68 MHz) spectrometer. The poor solubility of several of the compounds required elevated temperatures and use of DMSO-d₆ as solvent. Low resolution electron impact mass spectra were obtained on a Trio 2000 VG. High resolution spectra were obtained on a VG ZAB-E spectrometer (EPSRC Mass Spectrometry Service Centre, Swansea). Thin layer chromatography was performed on Merck silica gel 60F₂₅₄. All solvents were purified according to standard procedures. The 2,5-dimethylpyrazine-3,6-dicarboxylic acid and its ester 3 were prepared by the method of Albertson et al.; and the Hantzsch pyridine 1 was prepared by the method of Böcker and Guengerich.

**Synthesis of trans-DOTTADs from 2,5-dimethylpyrazine-3,6-dicarboxylic acid**

**General procedure.** POCl₃ (9.3 mL) was added dropwise to N-formylalaldialkylamine (40 mmol) with efficient stirring and external ice cooling. To this solution was added the 2,5-dimethylpyrazine-3,6-dicarboxylic acid (10 mmol) and after one minute stirring the mixture was heated at 80–85 °C for 12 h during which it became red. Most of the POCl₃ was removed in vacuo and ice–water added, followed by concentrated NH₄OH or the required amine until basic. The deep brown solution was continuously extracted with chloroform. The organic phase was dried with magnesium sulfate and evaporated to yield the products below.

**2,6-Dimethyl-1,5-dioxo-1,2,5,6-tetrahydro-2,5,7,10-tetraazaanthracene-4,9-dicarbaldehyde (4a).** Yield, 25%; pale brown powder, mp 263 °C; νₓ max, KBr cm⁻¹ 3409, 3249, 1697, 1664, 1614, 1434, 1409, 1326, 1166; δᵧ (270 MHz, DMSO-d₆, 50 °C); 8.10 (s, 2H, CHO), 7.75 (s, 2H, CH=), 2.69 (s, 6H, NCH₂); δᵦ (68 MHz, DMSO-d₆, 50 °C); 167.0, 155.7, 145.1, 128.7, 111.6, 21.8 (Found: 298.0714, C₄H₆N₂O₄ requires 298.0702).

**2,6-Diethyl-1,5-dioxo-1,2,5,6-tetrahydro-2,5,7,10-tetraazaanthracene-4,9-dicarbaldehyde (4b).** Yield, 35%; pale brown powder, mp > 250 °C; νₓ max, KBr cm⁻¹ 3411, 1696, 1662, 1614, 1437, 1411, 1322, 1106; δᵧ (270 MHz, DMSO-d₆, 50 °C); 8.12 (s, 2H, CHO), 7.72 (s, 2H, CH=), 4.13 (q, 4H, J = 7.3 Hz, CH₂), 1.35 (t, 6H, CH₃); δᵦ (68 MHz, DMSO-d₆, 50 °C); 167.2, 155.3, 148.8, 145.2, 128.7, 111.3, 44.4, 14.0 (Found: 326.1019, C₁₂H₁₆N₂O₄ requires 326.1015).

**2,6-Diethyl-1,5-dioxo-1,2,5,6-tetrahydro-2,5,7,10-tetraazaanthracene-4,9-dicarbaldehyde (4c).** Yield, 32% brown powder, mp > 250 °C; νₓ max, KBr cm⁻¹ 1682, 1669, 1594, 1508, 1348, 1321, 1283, 1238, 1166; δᵧ (270 MHz, DMSO-d₆, 50 °C); 10.85 (s, 2H,
CH=O), 8.27 (s, 2H, CH=), 5.93 (m, 1H, allyl), 5.38 (m, 2H, allyl), 4.72 (m, 2H, allyl); δC (68 MHz, DMSO-d6, 100°C): 186.4, 159.3, 145.6, 142.7, 137.5, 132.1, 118.5, 115.2, 51.0; m/z (EI): 350 (M+25), 232 (base peak), 281 (6), 91 (10), 69 (22) (Found: 350.1006, C14H14N2O4 requires 350.1015).

Synthesis of trans-DOTTADs from diethyl 2,5-dimethylpyrazine-3,6-dicarboxylate

General procedure. POCl3 (9.3 mL) was added dropwise to dimethylformamide (40 mmol) with efficient stirring and external ice cooling. To this solution was added diethyl 2,5-di(pyrazine-3,6-dicarboxylate) (10), 366 (7), 351 (17), 334 (22), 324 (13), 287 (13), 242 (base peak), 231 (31), 220 (72), 214 (15), 171 (16), 112 (32), 70 (27) (Found: 230.0396, C9H14N2O4 requires 230.0389).

2,6-Dibenzyl-4,9-bis(benzyliminomethylene)-1,5-dioxo-2,5,7,10-tetraazaanthracene (6d). Yield, 72%; yellow crystals (from ethyl acetate), mp 255°C (decomp.); v_(max) KBr/cm^-1: 3548, 3473, 3413, 2996, 2940, 2892, 2586, 1670, 1639, 1608, 1513, 1297, 1174, 1029, 827; δH (270 MHz, DMSO-d6, 100°C): 9.19 (s, 2H, N=CH), 8.49 (s, 2H), 7.39 (d, 4H, J = 8.0 Hz, Ar), 7.30 (d, 4H, J = 8.0 Hz, Ar), 6.93 (d, 8H, J = 8.0 Hz, Ar), 5.32 (s, 4H, CH2), 4.79 (s, 4H, CH2), 3.78 (s, 6H, OCH3), 3.77 (s, 6H, OCH3), 1.78 (s, 6H, CH2O), 1.34 (s, 12H, CH2). δC (270 MHz, DMSO-d6, 100°C): 159.3, 154.5, 152.7, 145.4, 139.3, 136.2, 136.2, 127.9, 127.5, 126.4, 111.9, 111.8, 63.2, 54.8, 51.0; m/z (EI): 748 (M+1), 572 (27), 429 (29), 279 (27), 224 (8), 209 (100) (Found: 748.3001, C41H30N2O8 requires 748.3009).

Synthesis of semi-DOTTADs

7-Phenyl-1-(2-phenylethenyl)-7,8-dihydroprano[4,3-b]pyridin-5-one-3-carboxylic acid (9). Diethyl 2,6-dimethylpyridine-3,5-dicarboxylate (1) (2.37 g, 10 mmol) and benzaldehyde (6.0 ml, 54.7 g, 44 mmol) was heated without solvent at 160–80°C for 2 h. After cooling the precipitated crystals were washed with ethanol and recrystallised from acetic acid. The title product (2.89 g, 78%) was obtained as a white powder, mp 268–269°C (lit. mp 269°C; v_(max) KBr/cm^-1: 3554, 3473, 3413, 269°C).
2.6-Bis[2-(bromophenylethenyl)pyridine-3,5-dicarboxylic acid (10a). Prepared from 2-bromobenzaldehyde and I as above. Yield, 80%; yellow powder, mp 288 °C (Found: C, 52.1; H, 2.7; N, 2.7; C₂H₅NO₂Br reacts C, 52.20; H, 2.86; N, 2.65%; νmax KBr/cm⁻¹: 2857, 2625, 1680, 1619, 1568, 1516, 1465, 1431, 1276, 1262, 1211, 1104, 1021; δH (250 MHz, DMSO-d₆): 11.25 (br s, 2H, CO₂H), 8.68 (s, 1H, H-4), 8.45 (d, 2H, J 15.5 Hz, CH=), 7.79 (d, 2H, J 7.6 Hz, Ar-H), 7.64 (d, 2H, J 7.6 Hz, Ar-H), 7.40 (t, 2H, J 7.6 Hz, Ar-H), 7.25 (t, 2H, J 7.6 Hz, Ar-H), 6.37 (s, 1H), 3.63 (s, 3H, J 2.7 Hz), 2.40 (s, 3H, J 2.7 Hz). 

6-Alkyl-2-(2-phenylethenyl)-8-(phenylhydroxymethyl)-6H-1.6-naphthryl-5-one-3-carboxylic acids (11)

General procedure. POCl₃ (9.3 mL) was added dropwise to an N-formyl dialkylamine (40 mmol) with stirring and external ice cooling. To this solution was added in one lot the 7-phenyl-2-(2-phenylethenyl)-7,8-dihydropyrimido[4,5-d]pyrimidine-5-one-3-carboxylic acid (10 mmol) and after one minute stirring the mixture was heated at 80–85 °C for 12 h during which it became red. Most of the POCl₃ was removed in vacuo and ice-water added, followed by required amine until basic. After 30 min stirring the tan coloured precipitate was filtered, washed well with water, dried and recrystallised.

6-Methyl-2-(2-phenylethenyl)-8-(phenylhydroxymethyl)-6H-1.6-naphthryl-5-one-3-carboxylic acid (11a). Yield, 57%; brown powder (from acetonitrile), mp 230 °C; νmax KBr/cm⁻¹: 3423, 1637, 1602, 1569, 1220; δH (270 MHz, DMSO-d₆): 8.90 (s, 1H, CO₂H), 8.20 (s, 1H, OH), 7.77 (m, 3H), 7.65 (m, 3H), 7.55–7.39 (m, 5H), 7.29 (t, 1H, J 7.4 Hz), 6.37 (s, 1H, J 6.3 Hz, 3.63 (s, 3H, Me); δC (68 MHz, DMSO-d₆): 167.0, 160.9, 157.0, 155.6, 151.9, 145.1, 133.7, 135.6, 129.6 (2×CH), 129.1, 128.1 (2×CH), 127.6, 127.5 (2×CH), 127.0, 125.2, 120.1, 118.2, 68.4, 39.1; m/z (EI): 412 (M⁺, 22), 410 (98), 396 (48), 381 (base peak).