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Isolation of a Highly Functionalized Tröger's Base Derivative via a Novel Reaction

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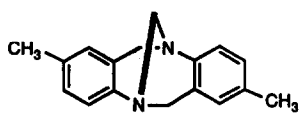
Abstract: Heating a solution of methyl 5-chloro-4-[(ethoxyoxoacetyl)amino]-2-methoxybenz-oate **3** in DMSO gave rise to the formation of the highly substituted Tröger's base derivative dimethyl 4,10-dichloro-1,7-dimethoxy-6H,12H-5,11-methano-dibenzo[b,f][1,5]diazocine-2,8-dicarboxylate **4** as well as methyl 8-chloro-5-methoxy-6-quinolinecarboxylate **5**.

The synthesis of 2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f][1,5]-diazocine **1** from *p*-toluidine and formaldehyde was originally reported by Tröger[1] in 1887 and the structure was later elucidated by Spielman.[2] It is of further historical interest that Prelog recognized that **1** is asymmetric at pyramidal nitrogens and he succeeded in resolving **1** into its enantiomers via resolution.[3] There are numerous reports of chromatographic resolutions of **1**.[3,4] however, due to problems encountered with acid-catalyzed racemization, this molecule has only recently yielded to classical resolution via diastereomeric salt formation.[5]



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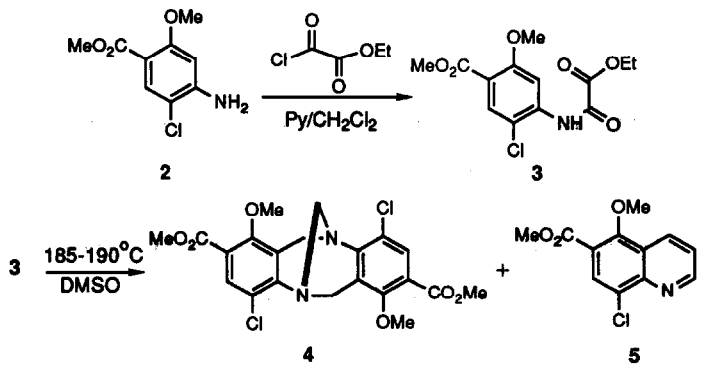
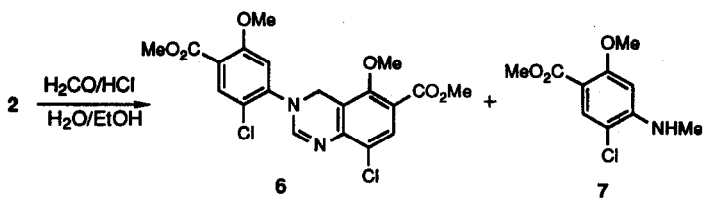
The rigid 6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine skeleton has recently gained additional prominence by serving as the framework of molecular armatures.[6] One limitation to its usefulness in this regard has been the inability to prepare the ring system with a wide variety of functional groups on the aromatic rings.[7] We have observed the unexpected formation of a highly functionalized Tröger's base derivative by a convenient and novel route which is described below.

Treatment of methyl 4-amino-5-chloro-2-methoxybenzoate **2**[8] with ethyl oxalyl chloride gave the ethyl oxalate **3** in 95% yield (Scheme I). When a solution of **3** in DMSO was heated to 185-190°C for 9 hours, the starting material was slowly consumed. No reaction occurred at lower temperatures. Chromatographic separation of the product mixture gave the Tröger's base derivative **4** in 16% yield, as well as a small amount (6%) of the quinoline derivative **5**. No isatin formation was observed.



Scheme I

An attempt was made to convert **2** directly to the Tröger's base derivative **4** under the standard conditions[7] for preparing the 5,11-methanodibenzo[b,f][1,5]diazocine ring system from substituted anilines. Thus, treatment of **2** (Scheme II) with 37% formalin and hydrochloric acid in ethanol gave the condensation derivative **6** as the major product in 30% isolated yield along with the known[9] N-methylated product **7** (12%). In addition, 12% of the starting material was recovered. Only a trace (<1%) of the expected 5,11-methanodibenzo[b,f][1,5]diazocine **4** could be detected by ^{1}H NMR.



Scheme II

An interesting feature of the conversion of **3** to **4** is the unusual role of DMSO as a formaldehyde equivalent under the severe reaction conditions. Presumably the mechanism involves nucleophilic removal of the ethyl oxalyl moiety by DMSO with concomitant activation of the sulfoxide as an O-acylated species reminiscent of the Pummerer[10] reaction. Accordingly an N-methylthiomethyl aniline could be an intermediate in the formation of both **4** and the unexpected quinoline derivative **5**, as is well known that activated DMSO can act as an electrophilic source of a CH_2SCH_3 group.[11] Thus, the reaction provides a functional equivalent of formaldehyde under conditions which are quite different from the direct reaction of Scheme II. It is also interesting to note that the C2 symmetry is maintained in the highly substituted derivative **4**.

Although the yield of **4** is low, this compound constitutes the most highly substituted monomeric 6H,12H-5,11-methanodibenzo-[b,f][1,5]diazocine yet synthesized to the best of our knowledge. Although it is

not yet clear how general this reaction sequence may be for the production of different substitution patterns, the synthesis of **4** is extremely short and suggests interesting possibilities for the synthesis of other useful 6H,12H-5,11-methanodibenzo- [b,f][1,5]-diazocine derivatives. This may in turn have an impact on the utilization of this unique ring system in such applications as molecular armatures.

Experimental Section

General. All reactions were performed under an atmosphere of argon. Merck silica gel 60 (230-400 mesh) was used for flash chromatography. Merck Kieselgel 60 F254 DC-Fertigplatten (0.25 mm, Art. 5719) were used for TLC. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz. Noise-decoupled and APT ^{13}C NMR spectra were recorded at 75 MHz on a General Electric QE-300 spectrometer. IR spectra were recorded on a Perkin Elmer 685 spectrophotometer. High-resolution mass spectra were recorded on a Finnigan MAT8430 instrument. Elemental analyses were conducted on a Control Equipment CEC240-XA instrument.

Methyl 5-chloro-4-[(ethoxyoxoacetyl)amino]-2-methoxybenz-oate 3. A solution of methyl 4-amino-5-chloro-2-methoxybenzoate[9] (1.00 g, 4.63 mmol) in CH_2Cl_2 (14 mL) containing pyridine (0.44 g, 5.56 mmol) was cooled to -78°C and ethyl oxalyl chloride (0.66 g, 4.9 mmol) was added dropwise. After the addition was complete, the reaction was allowed to warm to r.t. over 1 h. The reaction was then quenched with H_2O (50 mL) and extracted with CH_2Cl_2 (3X). The combined extracts were washed successively with H_2O and brine and dried over Na_2SO_4. Concentration gave **3** (1.39 g, 95%) as an off-white powder: mp 138-140°C: IR (KBr) u 3420 (br), 3345, 1725, 1711, 1599, 1579, 1300, 1228, 1212 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) d 9.59 (1 H, s), 8.31 (1 H, s), 7.91 (1 H, s), 4.46 (2 H, q, J = 7.1 Hz), 3.94 (3 H, s), 3.89 (3 H, s) 1.46 (3 H, t, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) d 164.6, 159.9, 159.0, 154.1, 137.3, 132.1, 116.4, 113.5, 104.2, 64.0, 56.3, 52.1, 13.9 ppm; Anal. calcd for $C_{13}H_{14}ClNO_6$: C, 49.46; H, 4.47; N, 4.44; Cl, 11.23. Found: C, 49.35; H, 4.41; N, 4.41; Cl, 11.17.

Dimethyl 4,10-dichloro-1,7-dimethoxy-6H,12H-5,11-methano-dibenzo[b,f][1,5]diazocine-2,8-dicarboxylate 4 and Methyl 8-chloro-5-methoxy-6-quinolinecarboxylate 5. A solution of ethyl oxalate **3** (100 mg, 0.317 mmol) in DMSO (5 mL) was heated in a sealed tube at 185-190°C for 9 h. After the volatiles were removed under high vacuum, H_2O (2 mL) was added and the suspension was extracted with EtOAc (3X). Removal of insoluble material by filtration and concentration gave a residue (64 mg) which was chromatographed on silica gel eluting with EtOAc/hexane (20/80) to give **4** (12 mg, 16%) as a colorless solid: IR (MIR) u 1727, 1587, 1461, 1434, 1390, 1290, 1259, 1198 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) d 7.80 (2H, s), 4.58 (2H, d, J = 19 Hz), 4.49 (2H, d, J = 19 Hz), 4.28 (2 H, s) 3.88 (6 H, s), 3.79 (6 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d 164.8, 157.0, 148.2, 131.0, 124.8, 123.9, 119.7, 66.5, 61.9, 52.3, 51.3 ppm; HRMS *m/z* calcd for $C_{21}H_{20}N_2O_6{}^{35}Cl^{37}Cl$: 468.0669. Found: 468.0670.
Continued elution gave quinoline derivative **5** (5 mg, 6%) as a yellow solid: IR (MIR) u 1733, 1605, 1437, 1357, 1309, 1267, 1215 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) d 9.13 (1H, dd, J = 4.3 1.5 Hz), 8.65 (1H, dd, J = 8.6, 1.5 Hz), 8.26 (1H, s), 7.58 (1H, dd, J = 8.6, 4.3 Hz), 4.07 (3H, s), 4.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d 164.9, 157.0, 152.8, 146.8, 132.9, 129.9, 128.6, 125.2, 122.2, 119.8, 64.0, 52.6 ppm; HRMS *m/z* calcd for $C_{12}H_{10}{}^{35}ClNO_3$: 251.0349. Found: 251.0353.

Methyl 8-chloro-3-[2-chloro-5-methoxy-4-(methoxycarbon-yl)phenyl]-3,4-dihydro-5-methoxy-6-quinazolinecarboxylate 6 and Methyl 5-chloro-4-methylamino-2-methoxybenzoate 7. To a suspension of aniline **2** (500 mg, 2.32 mmol) at 0°C in EtOH (2 mL) was added hydrochloric acid (0.94 mL of a 12 M solution, 11.6 mmol) followed by the addition of formalin (1.13 mL of a 37% aqueous solution, 13.9 mmol). The homogeneous solution was then warmed to r.t. and stirred for 2.5 h. Concentrated ammonium hydroxide (3 mL) was then added and the resulting mixture was extracted with CH_2Cl_2 (3X). The combined extracts were washed successively with aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Concentration gave a colorless foam (435 mg) which was chromatographed on silica gel eluting with an EtOAc/hexane gradient (5/95-65/45) to give the N-methyl aniline derivative **7** (61 mg, 12%): mp 126-127°C (Hoover, uncorrected; lit.[12] 129-130°C); IR (KBr) u 3370, 1708, 1607, 1570, 1430, 1348, 1236, 1099 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) d 7.82 (1 H, s), 6.09 (1 H, s), 4.84 (1 H, br m), 3.90 (3 H, s), 3.82 (3 H, s),

2.93 (3 H, d, J = 5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 165.1, 160.7, 149.0, 132.3, 109.6, 106.9, 93.4, 55.9, 51.3, 29.8 ppm; Anal. calcd for $C_{10}H_{12}ClNO_3$: C, 52.30; H, 5.27; N, 6.10; C., 15.44. Found: C, 52.27; H, 5.28; N, 6.08; Cl, 15.47. Continued elution gave a small amount of recovered starting material **2** (61 mg, 12%). Further elution gave the adduct **6** (158 mg, 30%) as a colorless foam: IR (KBr) u 1729, 1604, 1570, 1558, 1284, 1241, 1157 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) d 7.94 (1 H, s), 7.84 (1 H, s), 7.33 (1 H, s), 7.04 (1 H, s), 4.94 (2 H, s), 3.96 (3 H, s), 3.92 (3 H, s), 3.91 (3 H, s), 3.81 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d 164.2, 158.7, 155.0, 150.2, 143.6, 143.2, 133.7, 131.8, 124.0, 121.2, 120.7, 120.4, 116.7, 111.2, 61.7, 56.5, 52.2, 52.0, 44.5 ppm; HRMS *m/z* calcd for $C_{20}H_{18}{}^{35}Cl^{37}ClN_2O_6$: 454.0513. Found: 454.0518.

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