An Unusual Synthesis of Tröger's Bases Using DMSO/HCl as Formaldehyde Equivalent

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Abstract: The reactions between anilines and DMSO/HCl produce Tröger's bases in moderate yield. The Tröger's bases bearing an electron-withdrawing group can also be synthesized through this procedure. In this reaction, DMSO/HCl acts as formaldehyde equivalent.

Key words: Tröger's bases, DMSO/HCl, formaldehyde equivalent

2,8-Dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine Tröger's base (**1**) was first isolated by Tröger in 1887,[1] and was structurally characterized in 1935 as the product of the reaction between *p*-toluidine and formaldehyde in acidic aqueous solution.[2] In recent years, Tröger's base and its analogs have been describeded as 'fascinating molecules' due to their particular structures.[3,4] The rigid 6*H*,12*H*-5,11-methanodibenzo [*b*,*f*][1,5]diazocine skeleton has recently gained additional prominence by serving as a molecular framework.[5–7] The two aromatic rings, oriented at a right angles, delimit a V-structure which makes this substrate suitable for the recognition of specific shapes or conformation of substrates. This unique geometry has been exploited for the design of recognition of DNA sequences,[8] and dicarboxylic acids.[9] Furthermore, their applications were also reported in novel molecular replication system,[10] chiral solvating agents,[11] and chiral molecular tweezers.[12]

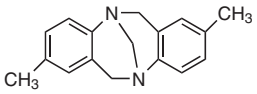

Figure 1 Tröger's base (**1**)

One limitation to its usefulness, in this regard, has been the inability to prepare the ring systems with a wide variety of functional groups on the aromatic rings.[13] Common synthetic procedures involve reaction with aqueous formaldehyde and a strong acid in a protic solvent. However, this method does not work well with many substrates, presumably due to solubility problems.[14] In addition, the accumulated evidence supported the conclusion that the deactivation of the aromatic ring by electron-withdrawing groups was preventing the formation of Tröger's base.[15,16] However, -CN, -NO_2, -COOR, and -CF_3, are very useful functional groups, which can be further elaborated to expand their application. Therefore, it is important to find and develop the synthesis of symmetrical Tröger's base analogs bearing a strong electron-withdrawing group directly from substituted anilines.

In order to explore the synthesis of Tröger's base analogs bearing an electron-withdrawing group, Wilcox had reported the synthesis of unsymmetrical Tröger's base analogues bearing -NO_2 on one aromatic ring, but the procedure has to start from substituted 2-amino-benzylamines.[5] Via double bromine–lithium exchange reaction of Tröger's base, Wärnmark reported a procedure to obtain some Tröger's base analogs bearing -COOH and -CHO substituents in moderate yield, but the same procedure only produced impure dicyano-substituted compound.[6] Kobayashi had reported the synthesis and functionalization of thiophene congeners of Tröger's base.[7] Goswami obtained the ethyl ester compound from ethyl *p*-aminobenzoate and hexamethylenetetramine in 23% yield,[9] and Mederski reported the efficient procedure to synthesize nitro functionalized Tröger's base directly from diglycolic acid in 56% yield.[17]

Herein, we report an unusual synthesis of Tröger's bases via the reaction of substituted anilines with DMSO and anhydrous HCl (g), in which DMSO acts as a formaldehyde equivalent under the conditions. Interestingly, this procedure could also yield 2,8-dicyano-6*H*,12*H*-5,11-methanodibenzo [*b*,*f*][1,5] diazocine directly from 4-cyano-aniline.

From our understanding, DMSO/HCl (g) was normally used for thiomethylation of phenols[18] and in some cases, DMSO/HCl (37% aqueous)[19] or DMSO/HBr (40% aqueous)[20] respectively acted as chlorination or bromination reagents. In a previous report on the synthesis of Tröger's base, DMSO was presumed to act as a formaldehyde equivalent, however, only under drastic conditions of 185-190 °C.[4]

In our research upon chlorination of substituted anilines with DMSO/HCl (g), we observed that, besides chlorinated products, analogs of Tröger's base (**1**) were obtained in very low yield. After optimization, this reaction can give moderate yields of Tröger's bases. For the substituted anilines containing electron-donating or weak electron-

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withdrawing groups, such as *p*-toluidine, *p*-anisidine, *p*-chloroaniline, *p*-fluoroaniline, 2,4-dimethylaniline, and so on, all the reactions were carried out at room temperature to give moderate yields (45–60%). For the anilines bearing electron-withdrawing groups (-NO_2, -CN, and -$COOC_2H_5$), the reaction needed to be performed at 80 °C, and the corresponding Tröger's bases were obtained in 23%, 21%, and 37% yield, respectively. It has been known for some time that the fluorine atom can lead to unexpected biological activity arising due to the special properties of the fluorine atom, such as the high electronegativity of fluorine and high carbon–fluorine bond energy.[21] We tried to synthesis Tröger's bases bearing -CF_3 and -2,4-F, the yields were 20% and 17%, respectively (Scheme 1, Table 1).

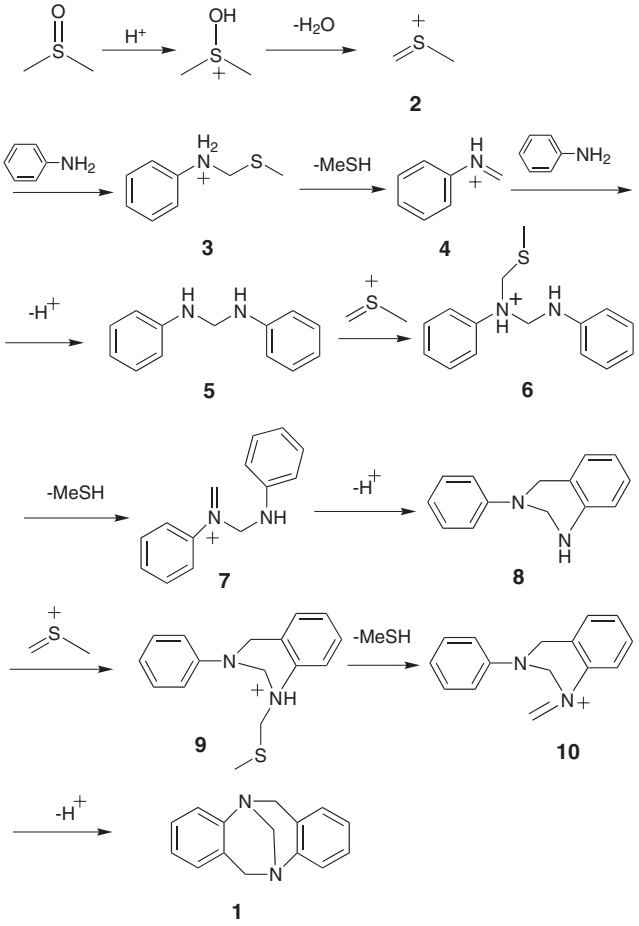
Scheme 1 Synthesis of Tröger's base from aniline and DMSO/HCl (g)

Table 1 Synthesis of Tröger's Base Analogs from Anilines and DMSO/HCl

Analog	R	Mp (°C)	Mp (°C, Lit.)	Yield (%)
1a	4-CH_3	128–129	127–128[15]	55
1b	4-OCH_3	173–174	172–173[2]	60
1c	4-Cl	143–144	140–141[22]	45
1d	H	130–131	127–128[23]	53
1e	4-OC_2H_5	134–136	131–132[24]	58
1f	4-F	116–117	112–113[22]	61
1g	2,4-Dimethyl	110–112	104–106[15]	57
1h	4-NO_2	258–259	258–260[17]	23
1i	4-$COOC_2H_5$	152–153	126–128[9]	37
1j	4-CN	248–249	–	21
1k	4-CF_3	130–131	–	20
1l	2,4-F	135–136	–	17

We believe the mechanism to be similar to that of the Pummerer rearrangement, a plausible mechanism for the reaction is proposed as shown in Scheme 2. First, DMSO/HCl forms sulfonium intermediate **2**, which reacts with aniline to form diaminomethane **5** via the iminium intermediate **4**. Then, the diaminomethane compound **5** reacts with sulfonium intermediate **2** again to generate iminium intermediate **7,** which undergoes intramolecular cyclization to form compound **8**. In the same way, compound **8** reacts with the sulfonium intermediate **2** to give Tröger's base **1** as the final product.

In summary, we introduce here an efficient and convenient method for the preparation of Tröger's base analogs from substituted anilines and DMSO/HCl(g). This procedure could also produce di-cyano, di-trifluoromethyl, and di-2,4-difluoro, three novel Tröger's base compounds. Under these reaction, conditions DMSO appears to be a formaldehyde equivalent.



Scheme 2 Plausible mechanism of the reaction between anilines and DMSO/HCl

All chemicals or reagents were purchased from standard commercial suppliers. Melting points were determined on XT4-100X melting point apparatus and were uncorrected. Infrared spectra were measured on a Nicolet FT-IR-20SX instrument using a pressed KBr pellet, scanning from 625–4000 cm^{-1}. High resolution mass spectra were obtained on MicroMass GCT CA 055 spectrometer. ^1H NMR spectra were obtained on a Bruker-AC 500 (500 MHz) spectrometer using $CDCl_3$ as the solvent and were reported in ppm (δ) downfield from TMS (internal reference). The analyses for elemental composition were undertaken with an Italy MOD-1106 analyzer.

Tröger's Base Derivatives; General Procedure

DMSO (5 mL) was added to the appropriate aniline (0.005 mol) solution in HOAc (5 mL) in a 50-mL three-neck flask. Then, anhyd HCl (g) was continuously passed through the mixture. An exothermic reaction ensued, which made the mixture very warm, and the color gradually turned to dark red. After the starting material was consumed as indicated by TLC, the mixture was quenched with ice water (20 mL), and neutralized with sat. aq Na_2CO_3. The mixture

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was extracted with CH_2Cl_2 (2 × 20 mL). The combined extracts were washed successively with water (10 mL) and brine (10 mL), and dried over Na_2SO_4. After concentration, the residue was chromatographed on silica gel (EtOAc–hexane) to give target compounds **1a–l**. The procedure for the synthesis of **1h**,**l** is similar to that mentioned above, except for the fact, that the mixtures had to be heated to 80 °C prior to passing anhyd HCl through them.

Compounds **1a–g** was confirmed by mp, GC-MS, and spectral data obtained were compared with those from the literature.[15]

1h
Yield: 180 mg (23%); yellow crystals; mp 258–259 °C.

IR (KBr): 2960, 2926, 1610, 1570, 1510, 1480, 1340, 1310, 1210, 1090, 950 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.32 (d, 2 H, H-6,12$_{endo}$, *J* = 15.7 Hz), 4.34 (s, 2 H, H-13), 4.83 (d, 2 H, H-6,12$_{exo}$, *J* = 17.1 Hz), 7.27 (d, 2 H, H-4, *J* = 8.5 Hz), 7.89 (d, 2 H, H-1, *J* = 1.9 Hz), 8.06 (dd, 2 H, H-3, *J* = 8.9, 2.3 Hz).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{12}N_4O_4$, 312.0859; found, 312.0869;

Anal. Calcd for $C_{15}H_{12}N_4O_4$: C, 57.69; H, 3.87; N, 17.94. Found: C, 57.55; H, 3.62; N, 18.22.

1i
Yield: 338 mg (37%); white crystals; mp 152–153 °C.

IR (KBr): 2983, 2952, 1710, 1607, 1566, 1489, 1283, 1186, 1104, 903, 841, 770 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.33 (t, 6 H, CH_3, *J* = 7.1 Hz), 4.25 (d, 2 H, H-6,12$_{endo}$, *J* = 16.9 Hz), 4.31 (q, 4 H, OCH_2, *J* = 7.2 Hz), 4.33 (s, 2 H, H-4), 4.75 (d, 2 H, H-6,12$_{exo}$, *J* = 16.6 Hz), 7.17 (d, 2 H, H-4, *J* = 8.4 Hz), 7.64 (s, 2 H, H-1), 7.84 (dd, 2 H, H-3, *J* = 8.5, 1.3 Hz).

HRMS (EI): *m*/*z* calcd for $C_{21}H_{22}N_2O_4$, 366.1580; found, 366.1540.

1j
Yield: 143 mg (21%); white crystals; mp 248–249 °C.

IR (KBr): 3065, 3029, 2958, 2223, 1607, 1489, 1442, 1211, 1098, 949, 893, 841, 772 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.21 (d, 2 H, H-6,12$_{endo}$, *J* = 16.8 Hz), 4.29 (s, 2 H, H-13), 4.73 (d, 2 H, H-6,12$_{exo}$, *J* = 16.7 Hz), 7.21 (d, 2 H, H-4, *J* = 8.4 Hz), 7.24 (s, 2 H, H-1), 7.46 (dd, 2 H, H-3, *J* = 8.5, 1.5 Hz).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{12}N_4$, 272.1062; found, 272.1054.

1k
Yield: 178 mg (20%), white crystals; mp 130–131 °C.

IR (KBr): 2962, 2917, 1628, 1586, 1503, 1332, 1306, 1152, 1123, 874, 835 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.24 (d, 2 H, H-6,12$_{endo}$, *J* = 16.8Hz), 4.32 (s, 2 H, H-13), 4.76 (d, 2 H, H-6,12$_{exo}$, *J* = 16.8 Hz), 7.20 (s, 2 H, H-1), 7.24 (d, 2 H, H-4, *J* = 8.4 Hz), 7.43 (d, 2 H, H-3, *J* = 8.4 Hz).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{12}N_2F_6$, 358.0905; found, 358.0881.

1l
Yield: 125 mg (17%); white crystals; mp 135–136 °C.

IR (KBr): 3058, 2905, 2859, 1633, 1597, 1482, 1316, 1118, 930, 852, 710 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 4.12 (d, 2 H, H-6,12$_{endo}$, *J* = 17.3 Hz), 4.29 (s, 2 H, H-4), 4.58 (d, 2 H, H-6,12$_{exo}$, *J* = 17.3 Hz), 6.52 (d, 2H, H-1, *J* = 8.2 Hz), 6.72 (m, 2 H, H-3).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{10}N_2F_4$, 294.0780; found, 294.0751.

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