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The yields of 2,8-dihalo analogues of Tröger's base in the condensation between 4-haloanilines and paraformaldehyde was found to be highly sensitive to the crucial reaction parameters of scale, stoichiometry and temperature. The reaction conditions were optimized allowing for the semi-large scale synthesis of the 2,8-diiodo- (**2**) and 2,8-dibromo- (**3**) analogues, respectively.

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Tröger's base (**1**) [1] is a chiral and rigid C_2 -symmetric molecule with a concave shape (Figure). Analogues of Tröger's base have found usage for a variety of purposes in supramolecular chemistry [2], and less frequently as ligands for asymmetric catalysis [3,4]. Tröger's base itself is synthesized by the condensation of *p*-toluidine and formaldehyde. However, the synthesis of analogues of Tröger's base has hitherto been hampered, because the Tröger's base condensation works best with anilines substituted with electron-donating substituents [5], with important exceptions [6]. In addition, it is a prerequisite that the aniline carries a substituent in the 4-position. Therefore, in order to fully exploit the potential for applications of Tröger's base analogues, there is a profound need for new synthetic strategies for their synthesis.

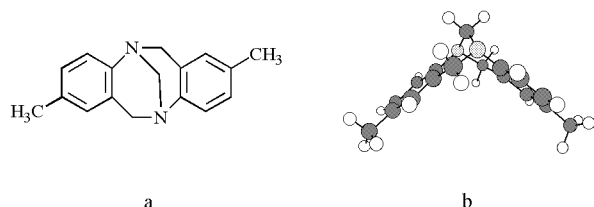
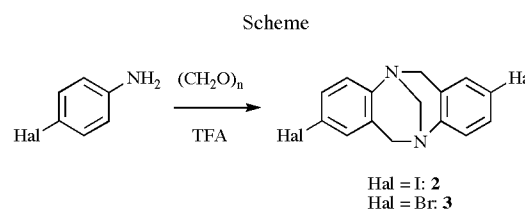


Figure. a) ChemDraw representation of Tröger's base (**1**). b) Chem 3D representation of the energy-minimized (Merck Molecular Force Field) Tröger's base.

Recently, we reported the synthesis of 2,8-dihalo substituted analogues of Tröger's bases from 4-halo substituted anilines in good to excellent yields in 1.0 mmol scale [6]. In addition, we demonstrated the utility of the 2,8-dibromo analogue of Tröger's base for the facile synthesis of symmetric and asymmetric analogues of Tröger's base [7]. Furthermore, 2,8-diiodo-4,10-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine was found to be a highly useful synthetic intermediate for the preparation of 2,8-diethynyl substituted analogues [8].

When applying the 2,8-dihalo analogues of Tröger's base, especially 2,8-diiodo-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine (**2**) and 2,8-dibromo-6*H*,12*H*-

5,11-methanodibenzo[*b,f*][1,5]diazocine (**3**), in research projects as the above mentioned, larger quantities of these compounds were needed. We then experienced that we were unable to reproduce the synthesis of these compounds, when using larger amounts of the corresponding anilines, paraformaldehyde and trifluoroacetic acid (Scheme). In fact, no analogues of Tröger's base were formed at all when attempts were made to synthesize **2** and **3** in scales larger than 20 mmol. Previously, similar difficulties of reproducing results in the Tröger's base condensation under standardized conditions were reported [9].



The Tröger's base condensation to afford **2** and **3**.

We were already aware of the fact that the reaction was sensitive to elevated temperatures [6]. Therefore, heat formation from the acid-base reaction upon addition of trifluoroacetic acid was considered to be one of the reasons why the reaction failed, when working in larger scales. Since following our previous procedure, now in 40 mmol scale, by adding trifluoroacetic acid at 0 °C afforded **2** in 6% yield only, it was realized that a thorough optimization of the synthesis of these two important molecules was necessary. 4-Iodoaniline was chosen as the model substrate as it reacts most reluctantly in the Tröger's base condensation, and because the analogue of Tröger's base **2** is the most reactive in the important transition-metal catalyzed coupling reactions [10]. In addition, a thoroughly optimized procedure for the synthesis of **2** was also expected to lead to better yields in synthesis of the 2,8-dibromo (**3**), 2,8-dichloro (**4**) and 2,8-difluoro (**5**) analogues of Tröger's base.

Since the Tröger's base condensation reaction is sluggish in general, we decided to start to investigate the influence of the crucial reaction conditions on the yield in the original 1.0 mmol scale. All results were obtained by isolating **2** after the reaction was completed according to lc (Table 1).

Table 1
Optimization of the synthesis of **2** in 1.0 mmol scale.

Entry	Temperature of addition of TFA	Equivalents of (CH ₂ O) _n	Temperature of reaction	Yield [a] (%)
1	rt	2.0	rt	41
2	0 °C	2.0	rt	43
3	-15 °C	2.0	rt	59
4	-15 °C	0.67	rt	49
5	-15 °C	1.5	rt	57
6	-15 °C	3.0	rt	54
7	-15 °C	1.5	0 °C	64
8	-15 °C	2.0	0 °C	58
9	-15 °C	1.5	-15 °C	49
10	-15 °C	2.0	-15 °C	55

[a] Isolated yields of chromatographically pure compound

First, the influence of the temperature of addition of trifluoroacetic acid was investigated (Table 1, entry 1-3). The best result, 59% yield, was obtained by addition of trifluoroacetic acid at -15 °C, which is the melting point of trifluoroacetic acid. Adding the trifluoroacetic acid at lower temperatures was not considered because it would result in a heterogeneous mixture.

Next, the optimal equivalents of paraformaldehyde was determined (Table 1, entries 3-6). It was found that there was not a considerable difference in the yields of using 1.5 and 2.0 equivalents, whereas both the use of deficient (Table 1, entry 4) and excessive amounts of paraformaldehyde (Table 1, entry 6) caused a decrease in the yield of **2**.

Furthermore, the optimal reaction temperature was established (Table 1, entries 3, 5, 7-10), in all cases both 1.5 and 2.0 equivalents of paraformaldehyde were used. The reaction temperature resulting in the highest yield of **2** was 0 °C, again there was not a considerable difference in the yield of **2**, resulting from the different equivalents of paraformaldehyde used. Based on the optimization experiments, it was concluded that the optimal reaction conditions for the Tröger's base condensation of 4-iodoaniline to **2** were adding trifluoroacetic acid at -15 °C, using 1.5 or 2.0 equivalents of paraformaldehyde and continuing the reaction at 0 °C.

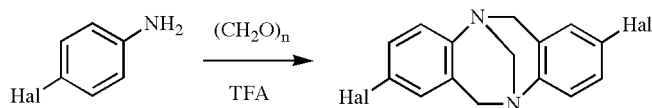
Moreover, the influence of the scale of the reaction was investigated using the optimized reaction conditions above. The larger scale was decided to be 40 mmol scale. For the diiodo analogue **2** both 1.5 and 2.0 equivalents of paraformaldehyde were used, which gave 23% and 37%

yield (Table 2, entry 1) respectively. This was a dramatic change from the 6% yield using the non-optimized conditions and a significant sensitivity was displayed towards the equivalents of paraformaldehyde, compared to working in the 1.0 mmol scale. The use of 2.0 equivalents of paraformaldehyde was after this considered optimal for the condensation on the larger scale. When working in 40 mmol scale, the effect of the reaction temperature was quite pronounced, as **2** was not produced at all if the reaction was run at room temperature, even if the other optimal conditions were used. The synthesis of the dibromo analogue **3** in 65% yield (Table 2, entry 2) in 40 mmol scale was the best result obtained in our laboratory when trying to synthesize this compound in larger scales.

Finally, we wanted to compare the effects on the yields of the 2,8-dihalo substituted analogues **2-5** (Table 2, entry 3-6) in the smaller 1.0 mmol scale when the optimized large scale conditions above were employed compared to our previously reported method. This gave the ambiguous result that for the 2,8-diiodo (**2**) and the 2,8-dichloro (**4**) analogues, the yields were increased, whereas the yields of the 2,8-dibromo (**3**) and the 2,8-difluoro (**5**) analogues were decreased, **5** significantly so (Table 2, entry 6).

Table 2

Synthesis of the Tröger's base analogues **2** and **3** in 40 mmol scale and of analogues **2-5** in 1.0 mmol scale using the novel reaction conditions [a].



Entry	Hal	Analogue of Tröger's base	Scale (mmol)	Yield [b] (%) previously reported [c]	Yield [a] (%)
1	I	2	40	-	37
2	Br	3	40	-	65
3	I	2	1	41	64
4	Br	3	1	63	55
5	Cl	4	1	63	67
6	F	5	1	61	29

[a] Adding trifluoroacetic acid at -15 °C, reaction temperature 0 °C and using 2.0 equivalents of paraformaldehyde. [b] Isolated yields of chromatographically pure compounds. [c] Reference [6].

In conclusion, the yields in the conversion of 4-iodoaniline into **2** by the Tröger's base condensation were sensitive to the scale of the reaction, the temperature of addition of trifluoroacetic acid, the equivalents of paraformaldehyde and the reaction temperature. The yields of the 2,8-diiodo (**2**) and 2,8-dibromo analogues (**3**) in the Tröger's base condensation reaction in the larger 40 mmol scale were found to be highest when 2.0 equivalents of

paraformaldehyde was used, the temperature of TFA addition was $-15\text{ }^{\circ}\text{C}$ and the reaction temperature was $0\text{ }^{\circ}\text{C}$ (37 and 65%, respectively). Contrarily, in the smaller 1.0 mmol scale, the same reaction condition resulted in significant improvement of the yield of the 2,8-iodo (**2**) analogue (from 41 to 64%), whereas the yield of the 2,8-dibromo analogue (**3**) was decreased (from 63 to 55%).

EXPERIMENTAL

All chemicals were used as received from commercial sources without further purification. Samples for TLC-analyses (Merck 60 F₂₅₄ sheets) were prepared by treating an aliquot of the reaction mixture with a saturated aqueous solution of ammonia and dissolving it in acetone. All sheets were visualized under UV light (254 nm). Column chromatography (CC) was performed on silica gel (Matrex 0.063-0.200 mm). The products were pure according to ¹H NMR, all of which were verified according to those previously reported [6].

Representative Example of the Synthesis of the 2,8-Diiodo and 2,8-Dibromo Analogues of Tröger's Base in 40 mmol Scale.

2,8-Diiodo-6*H*,12*H*-5,11-methanodibenzo[*b,f*][1,5]diazocine (**2**).

To a stirred mixture of 4-iodoaniline (8.82 g, 40.0 mmol) and paraformaldehyde (2.39 g, 80.0 mmol) at $-15\text{ }^{\circ}\text{C}$ was added dropwise TFA (80.0 mL; 1.04 mol) over 50 min. *via* a dropping funnel and stirring was continued for 143 h at $0\text{ }^{\circ}\text{C}$. TFA was removed *in vacuo*, water (50 mL) was added followed by addition of a saturated aqueous solution of ammonia (50 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried (MgSO₄), filtered,

concentrated *in vacuo* and purified by column chromatography (H: 15 cm, D: 6 cm) using EtOAc (10-20%) in heptane as the eluent. Forerun 1.5 L, fraction sizes, 200 mL, collecting fractions 1-7 and concentration *in vacuo* to give 3.50 g (37%) of **2** as a pale yellow solid.

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