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An efficient access to new Tröger's bases using superacidic chemistry

Emilie Vardelle [a], Agnès Martin-Mingot [a,*], Marie-Paule Jouannetaud [a], Jean-Claude Jacquesy [a], Jérôme Marrot [b]

[a] Université de Poitiers—UMR 6514-Laboratoire 'Synthèse et Réactivité des Substances Naturelles', 40, avenue du Recteur Pineau, F-86022 Poitiers Cedex, France
[b] Institut Lavoisier de Versailles, UMR 8180, Université de Versailles, 45 Avenue des Etats Unis, F-78035 Versailles Cedex, France

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ABSTRACT

In the superacidic media HF/SbF_5, hydroxylation of several Tröger's bases was performed using sodium persulfate as a hydroperoxonium $H_3O_2^+$ precursor. The obtained products are selectively hydroxylated in good yields on unusual positions of the aromatic rings.

Tröger's base **1** (Fig. 1) was first synthesized, then isolated in 1887,[1] but its methanodiazocine structure was elucidated only about 50 years later.[2] Tröger's bases were initially used in recognition phenomena.[3] This class of compounds has been the subject of increased interest due to their potential applications in many other fields such as drug development,[4] supramolecular chemistry,[5] or stereoselective catalysis.[6]

Tröger's base derivatives are usually synthesized by a reaction between aromatic amines and formaldehyde in various solvents in the presence of concentrated acid used as a catalyst.[1,3a] Over the past two decades, many Tröger's base derivatives have been synthesized by increasing the functionalities of starting anilines,[3a,7] by catalyzed coupling reactions with already prepared halogenated Tröger's bases,[8] or by modifications of the diazocine bridge.[9]

To the best of our knowledge, few direct functionalizations of the aromatic moiety have been reported. The most effective functionalization describes the synthesis of halogenated analogs obtained by a reaction between Tröger's bases and *N*-halosuccinimide.[10]

In this Letter, we would like to report a novel method for direct hydroxylation of Tröger's bases discovered in the course of our work on unusual functionalizations of aromatic compounds using superacidic chemistry.

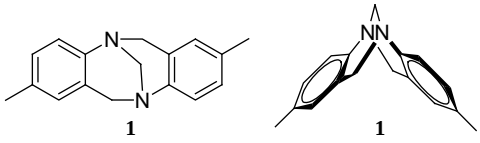
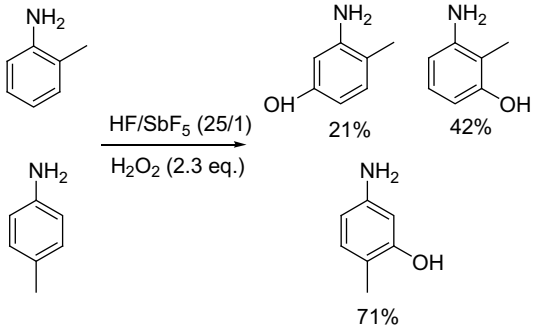


Figure 1. Structure of Tröger's base **1**.

The direct hydroxylation of substituted anilines in superacid has been previously reported.[11] This work showed that it was possible to synthesize regioselectively hydroxylated anilines in usually unreactive positions (Scheme 1).



Scheme 1. Hydroxylation of anilines in superacidic media.

* Corresponding author. Tel.: +33 5 49 45 38 93; fax: +33 5 49 45 35 01.
E-mail address: agnes.mingot@univ-poitiers.fr (A. Martin-Mingot).

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Continuing this work, we submitted a series of Tröger's base derivatives to hydroxylation in superacid, in the presence of H_2O_2.

The first attempt was performed in HF/SbF_5 (50/1) at −20 °C for 15 min, using **1** as a model substrate, but no reaction occurred. When the acidity was increased (HF/SbF_5 molar ratio 25/1), a small amount of hydroxylated products **1a** and **1b** was detected by NMR spectroscopy (<10%) in the crude mixture as well as a significant amount of starting material. More acidic conditions were used (HF/SbF_5 (17/1)) attempting to enhance the rate of the reaction but it was unsuccessful, as the reaction became not selective.

Various amounts of H_2O_2 were used. It appeared that the optimized conditions are a molar ratio HF/SbF_5 of 25/1, using 6 equiv of H_2O_2 at −20 °C for 15 min. Under these conditions, substrate **1** yielded 27% of **1a** and 32% of **1b**.

It should be pointed out that when hydrogen peroxide was used as a hydroxylating agent with levels above 1 mmol of Tröger's base derivatives, violent reactions occurred.

Sodium persulfate, a reagent already used to achieve hydroxylation of yohimbine in superacidic media,[12] was then used as a hydroperoxonium precursor under the same reaction conditions on **1** and gave similar results, with no violent reaction in larger scale.

Tröger's bases **1**–**4** were submitted to reactions under the novel optimized conditions (HF/SbF_5 molar ratio 25/1), sodium persulfate (2.3 equiv) at the required temperature (−20 °C or −40 °C) during the optimized time (10 or 15 min) to yield the expected hydroxylated derivatives (Table 1, Fig. 2).

All the products were characterized by the usual spectroscopic methods.[13] The crystal structure of 1,7-dihydroxy-derivatives **1a** was determined by X-ray analysis (Fig. 3). To the best of our knowledge, this is the first reported X-ray structure of dihydroxylated analogs of a Tröger's base.

The obtained results deserve several comments:

Tröger's bases are stable in the superacid with no added oxidizing agent due to a protection effect caused by the polyprotonation of the nitrogen atoms.

All the products result from a regioselective monohydroxylation on a *meta* position of the amino group on each aromatic moiety, and are obtained in good yields.

Based on these results, a mechanism could be proposed (Scheme 2).

Protonation of anilines was previously studied by Hartshorn and Ridd who showed that in concentrated sulfuric acid ($-12 < H_0 < -10$) an anilinium ion is formed, which only exchanges very slowly its proton with the media.[14] Several studies have highlighted that anilines are irreversibly protonated in HF/SbF_5 ($H_0 = -20$).[15,16] By analogy, we can postulate that Tröger's bases are biprotonated on both nitrogen atoms to yield ion **I** and, consequently, all the positions are deactivated for subsequent electrophilic attacks. The observed regioselectivity in the *meta* position of anilinium moiety could be explained by the activating effects of alkyl groups.

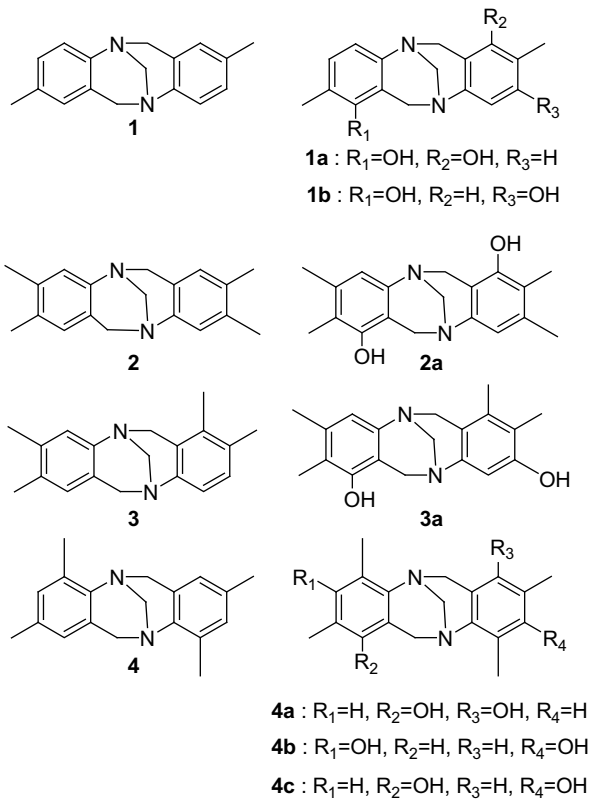


Figure 2. Structures of Tröger's Bases **1**–**4** and of their hydroxylated analogs.

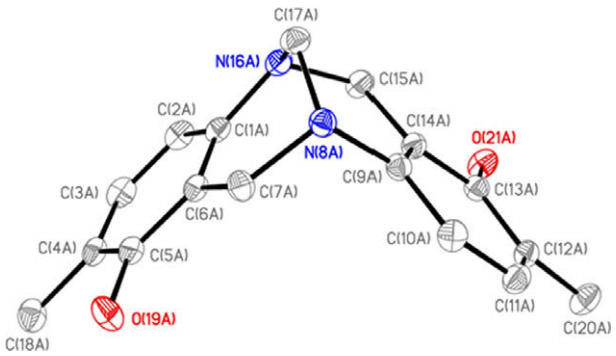


Figure 3. X-ray analysis of **1a**.

In superacid HF/SbF_5, hydrogen peroxide is protonated and leads to the hydroperoxoxium ion $H_3O_2^+$ from which some resulting salts have been isolated and characterized. The hydroperoxonium ion behaves as an 'OH^+' equivalent (Scheme 3).[17]

The obtained results showed that sodium persulfate in superacidic media leads to unidentified protonated species, which showed a similar behavior to hydroperoxonium ion.

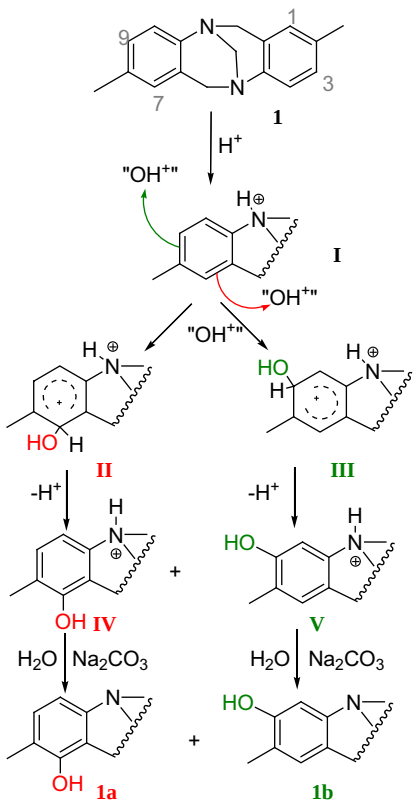
All the orientations of electrophilic substitutions with 'OH^+' were in accordance with the presence of a protonated amine and with the orientating effect of alkyl (methyl or cyclic moiety) substituents. The substitution occurred consequently in the *meta* position of the protonated amino group.

It should be noted that with Tröger's base **1** the two obtained products result from at least one substitution on the most encumbered position, as already observed in the aniline series.[11]

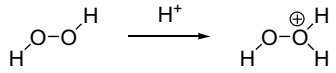
Table 1
Hydroxylation of Tröger's base **1** in HF/SbF_5

Substrates	Time (min)	*T* (°C)	Products (%)
1	15	−20	**1a** (40) + **1b** (43)
2	15	−20	**2a** (46)
2 (82)/**3** (18)[a]	10	−40	(55)[b] **2a** (46) + **3a** (93)[c]
4	10	−20	**4a**/**4b** (48)[d] + **4c** (45)

[a] Compounds **3** could not be isolated. The mixture is composed of 82% of **2** and 18% of **3** (molar ratio evaluated by NMR).
[b] Total yield in products **2a** and **3a** calculated compared to the **2**/**3** mixture.
[c] Yield in isolated product (**2a** or **3a**) calculated starting from the pure starting material corresponding (**2** or **3**).
[d] Molar ratio evaluated by NMR: 45/55 (**4a**/**4b**).



Scheme 2. Proposed mechanism for hydroxylation of Tröger's bases.



Scheme 3. Hydrogen peroxide protonation in superacid.

This result could be explained by the higher stability of intermediate **II** compared to intermediate **III** (less repulsion of charges).

In superacid, N-protonated intermediate aminophenols **IV** and V must also be protonated on the hydroxyl groups. This second protonation prevents the Tröger's base derivatives from a later electrophilic hydroxylation by deactivating the aromatic rings.

To summarize, we have reported the first direct synthesis of symmetrical or unsymmetrical hydroxylated Tröger's base derivatives. This original functionalization in superacid opens great opportunities in the synthesis of novel Tröger's base derivatives.

Acknowledgments

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13. *Experimental details*:
The authors draw the reader's attention to the dangerous features of superacidic chemistry. Handling of hydrogen fluoride and antimony pentafluoride must be done by experienced chemists with all the necessary safety arrangements in place.
Reactions performed in superacid were carried out in a sealed Teflon® flask with a magnetic stirrer. No further precautions have to be taken to prevent mixture from moisture (test reaction worked out under anhydrous conditions leads to the same results as expected).
Yields refer to isolated pure products.
^{1}H, ^{13}C, and ^{19}F NMR were recorded on a 300 MHz Bruker spectrometer using $CDCl_3$ as solvent.
Melting points were determined in a capillary tube and are uncorrected.
High-resolution mass spectra were performed on a Micromass ZABSpec TOF by the Centre Regional de Mesures Physiques de l'Ouest, Université Rennes (France).
All separations were done under flash-chromatography conditions on silica gel (15–40 μm).
*Optimized procedure for hydroxylation of compounds **1**, **4**, **5**, and **6** by $Na_2S_2O_8$ in HF/SbF_5*:
At a given volume of the mixture HF/SbF_5 (molar ratio 25/1) maintained at reaction temperature in a Teflon® flask are added successively the sodium persulfate (2.3 equiv) and then, after 3 min, substrate (reactions with sodium persulfate), or the substrate then successively hydrogen peroxide (6 equiv) (reactions with hydrogen peroxide).
The reaction mixture is kept under stirring at a temperature of reaction for a variable time depending on the type of substrate, and then hydrolyzed in water–ice-sodium carbonate and extracted with a suitable solvent. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Products were isolated by column chromatography over silica gel.
*Hydroxylation of compound **1***:
To a mixture of HF/SbF_5 (31 mL, molar ratio 25/1) maintained at the indicated temperature was added sodium persulfate (1.100 g, 2.3 equiv, 4.64 mmol). The mixture was kept at −20 °C for 3 min. The base **1** was then added (500 mg, 2 mmol). The mixture was magnetically stirred at −20 °C for 15 min. The reaction mixture was then neutralized with water–ice-Na_2CO_3, extracted with dichloromethane (×3). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Products were isolated by column chromatography over silica gel. Purification by flash column chromatography (95/5: dichloromethane /methanol) afforded 226 mg of compound **1a** as a colorless powder (40%) and 243 mg of compound **1b** as a colorless powder (43%).
*Compound **1a**:1,7-dihydroxy-2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f]-[1,5]-diazocine*:
^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 2.09 (s, 6H, $2CH_3$); 4.21 (d, 2H, J = 16.2 Hz, H-6 et H-12 *endo*); 4.21 (s, 2H, H-13); 4.40 (d, 2H, J = 17.3 Hz, H-6 et H-12 *exo*); 6.59 (d, 2H, J = 8.3 Hz, H-4 et H-10); 6.88 (d, 2H, J = 8.1 Hz, H-3 et H-9). ^{13}C NMR (75 MHz, $CDCl_3$, ppm: δ 16.1 ($2CH_3$); 56.2 ($2CH_2$, C-6 et C-12); 66.9 (CH_2, C-13); 116.7 (2C); 117.1 (2CH, C-4 et C-10); 120.8 (2C); 130.1 (2CH, C-3 et C-9); 147.2 (2C, C-2 et C-8); 153.0 (2C, C-1 et C-7). IR (ν, cm^{-1}): 3119 (ν_{O-H} phenol), 1652, 1613 et 1579 ($\nu_{C=C\ Ar}$). MS (EI, 70 eV): *m/z* (relative intensity %) 283 (14) $MH^{+\cdot}$; 268 (100); 266 (71). HRMS (ESI): Calcd for $C_{17}H_{18}N_2O_2$ 282.13683, found 282.1373. Melting point: 273–275 °C.
*Compound **1b**: 3,7-dihydroxy-2,8-dimethyl-6H,12H-5,11-methanodibenzo[b,f]-[1,5]-diazocine*:

^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.95 (s, 3H, H-2); 2.01 (s, 3H, H-8); 3.92 (d, 1H, J = 15.6 Hz, H-12 *endo*); 4.08 (d, 1H, J = 16.3 Hz, H-6 *endo*); 4.10 et 4.12 (2s, 2 × 1H, H-13); 4.28 (d, 1H, J = 16.8 Hz, H-6 *exo*); 4.40 (d, 1H, J = 16.1 Hz, H-12 *exo*); 6.41(s, 1H, H-4); 6.48 (d, 1H, J = 8.0 Hz, H-10); 6.49 (s, 1H, H-1); 6.79 (d, 1H, J = 8.0 Hz, H-9). ^{13}C NMR (75 MHz, $CDCl_3$, ppm: δ 15.8 et 16.0 (2 × 1CH_3, CH_3); 56.1 (CH_2, C-6); 59.0 (CH_2, C-12); 67.3 (CH_2, C-13); 111.1 (CH, C-4); 116.6 (C); 117.0 (CH, C-10); 119.1 (C); 120.7 (C); 123.0 (C); 129.5 (CH, C-1); 130.1 (CH, C-9); 146.6 (C, C-2); 147.0 (C, C-8); 153.0 (C, C-7); 155.7 (C, C-3). IR (ν, cm^{-1}): 3134 (ν_{O-H} phenol), 1620 et 1582 ($\nu_{C=C\ Ar}$). MS (EI, 70 eV): m/z (relative intensity %) 283 (14) $MH^{+\cdot}$; 268 (100); 266 (71). HRMS (ESI): Calcd for $C_{17}H_{18}N_2O_2$ 282.13683, found 282.1371. Melting point: 244–246 °C.

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