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Overcoming Regioselectivity Issues Inherent in Bis-Tröger's Base Preparation

Martin Havlík, Vladimír Král, and Bohumil Dolenský*

Department of Analytical Chemistry, Institute of Chemical Technology, Prague, Technická 5, 166 28 Praha 6, Czech Republic

dolenskb@vscht.cz

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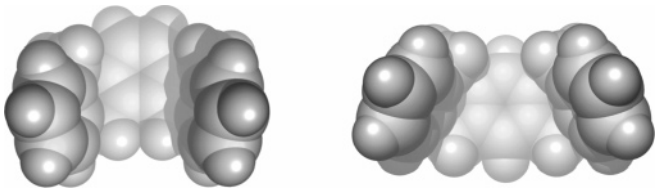
ABSTRACT



Bis-Tröger's base derivatives are a new family of molecular tweezers. A major drawback to their study is a lack of commercially available precursors, *ortho*-nitrocarboxylic acids. A reverse synthetic strategy starting from known dinitrodicarboxylic acids, which circumvents this problem, is presented. Via this methodology regioisomeric bis-TB derivatives can be prepared selectively, using only common aromatic amines that are typically commercially available.

Tröger's base derivatives are important building blocks in molecular engineering due to their V-shape and chirality.[1] In general, Tröger's bases are compounds containing two aromatic systems (sidewalls) annelated to a methano-1,5-diazocine (TB unit). The bis-TB derivatives could be described as compounds in which two TB units connect three aromatic systems, i.e., sidewall−TB−core−TB−sidewall. Probably the most important property of bis-TB derivatives is their ability to change their geometry under acidic conditions (diastereoisomerization).[2−5] The sidewalls can be situated on the same side of the core, as in the syn isomer (cavity shaped, meso form), or on opposite sides, as in the diastereoisomeric anti isomer (open cavity shaped, VA and AV enantiomers). Thus, one diastereoisomer would be active (e.g., able to bind a drug) and the second one would be inactive (no binding). Many useful applications, such as drug delivery or selective binding triggered by pH, can be realized.

The shape of the cavity of *syn*-bis-TB derivatives depends on the position of attachment of the sidewall−TB units to the core. In the case of benzene as the core unit, five possible bis-TB regioisomers are possible (Figure 1). The *syn*-bis-TB regioisomers with parallel sidewalls are represented by the regioisomer 1,2:4,3-bis-TB (the numbering of the parent core diamine is kept). The 1,6:3,4-bis-TB regioisomer represents a tweezer with divergent sidewalls, whereas the 1,6:2,3-bis-TB isomer is more like a molecular dish than a tweezer.

Known preparations of bis-TB derivatives to date include electrophilic attack at the core unit (benzene) to form a methylene bridge between a carbon of the core and nitrogen, which is connected to the sidewall. This attack was observed to take place with total regioselectivity (see Supporting Information). Thus, 1,4-diaminobenzene derivatives lead to 1,2:4,3-bis-TB regioisomers[2−9] and 1,3-diaminobenzene derivatives lead to 1,2:3,4-bis-TB regioisomers.[5] The difficulty

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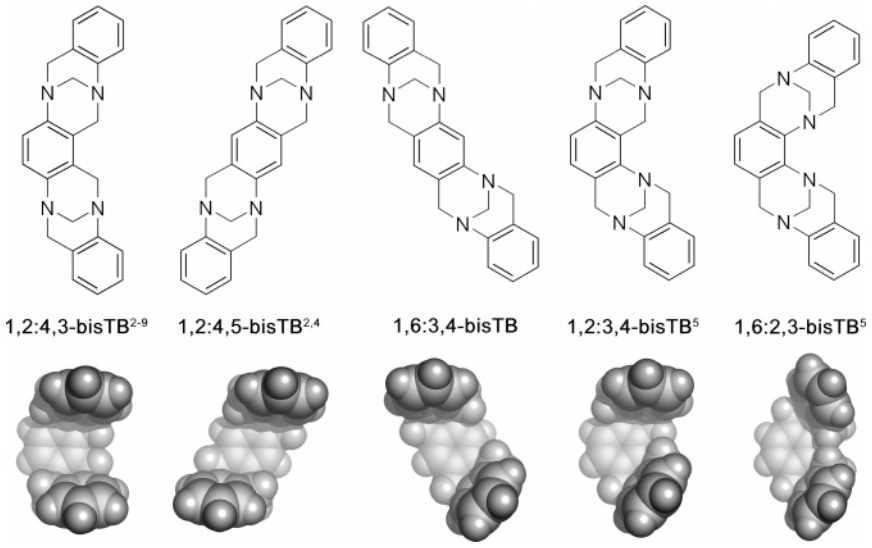

Figure 1. Regioisomers of bis-TB derived from benzene as the central unit. The space-filling computer models of syn isomers are shown, wherein the central benzene rings have the same orientations as those in the structure formulas.

in preparing the other isomers can be bypassed by blocking the reactive positions. Thus, protecting the positions with two methyl groups[4] or methyl and chlorine[2] enabled preparations of 1,2:4,5-bis-TB regioisomers. However, the blocking strategy is not acceptable in all cases. Another complication is the lack of commercially available starting compounds for bis-TB sidewall construction, i.e., the lack of aromatic *ortho*-nitrocarboxylic acids or their synthetic equivalents.

This situation necessitates an alternative synthetic strategy. The first step should be the preparation of the requisite (with respect to the targeted bis-TB regioisomer) dinitrodicarboxylic acid or its synthetic equivalent. This, in turn, would be used for the preparation of the diamide by treatment with the desired aromatic amine (hundreds are commercially available), followed by reduction to tetramine and "trogeration".

Herein, we present the first examples of this reverse synthetic approach, as well as the first synthesis of 1,6:3,4-bis-TB regioisomers.

First, we prepared known diastereoisomers of bis-TB **1a** as an example of 1,2:4,3-bis-TB regioisomers. The preparation starts from dinitrophthalic acid **2**, which can be easily prepared by the known[10] nitration−oxidation of dinitronaphthalene by fuming HNO_3.

The preparation of diamide **3** was found to be a nontrivial procedure. Although direct conversions of phthalic acids to diarylamides via generation of dichlorides are known,[11] all attempts (different ratios, temperatures, addition sequences) to convert diacid **2** directly to diamide **3** failed. Treatment of diacid **2** with $SOCl_2$ or $(COCl)_2$ followed by *p*-anisidine always afforded monoamide **4** with no traces of diamide **3** or imide **5a** (Scheme 1). This can be explained by the formation of anhydride **6**.[12] Fortunately, the treatment of monoamide **4** with $COCl_2$ at room temperature for 10 min (DMF is necessary), followed by quenching with *p*-anisidine, gave targeted diamide **3** in 67% preparative yield and only traces of imide **5a**. Longer reaction times (1−2 h) led to formation of imide **5a** quantitatively. Although direct conversions of phthalic acids[13] or phthalimides[14] to diamides via treatment with amines are known, in the case of diacid **2** and imide **5a**, we did not obtain satisfactory results. Treatment of diacid **2** or monoamide **4** with DCC and *p*-anisidine afforded a complex mixture with no traces of diamide **3**.

In the next step, the nitro groups were reduced to amines (**3** to **7**) by catalytic hydrogenation in near quantitative yield. It should be noted that the reaction temperature as well as the temperature during the workup procedures had to be kept at at least less than 40 °C, or aminoimide **5b** was formed spontaneously. Following reduction of the amide groups with LAH, tetraamine **8** was obtained in 62% yield. Direct reduction of **3** to **8** proceeded in 50% yield.

Treatment of tetraamine **8** with paraformaldehyde in TFA at 60 °C for 2 h furnished the targeted bis-TB **1** in 8%

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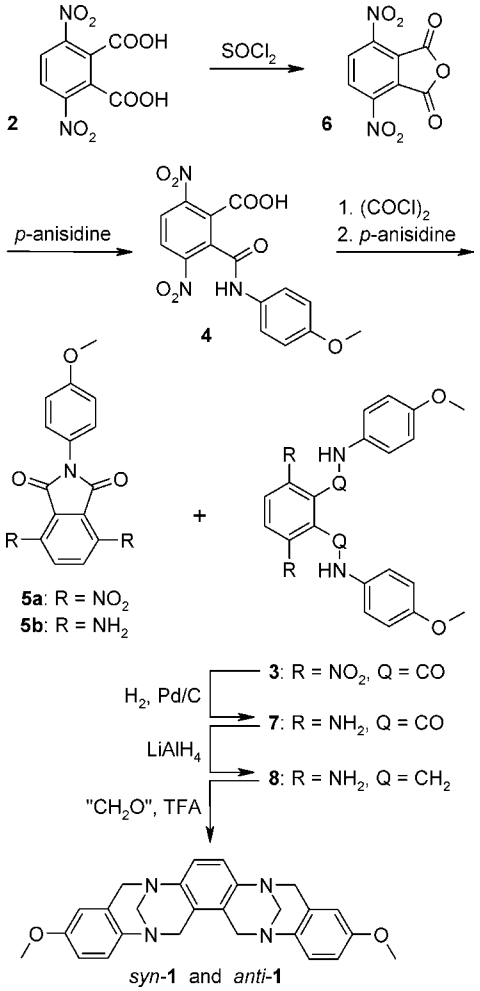
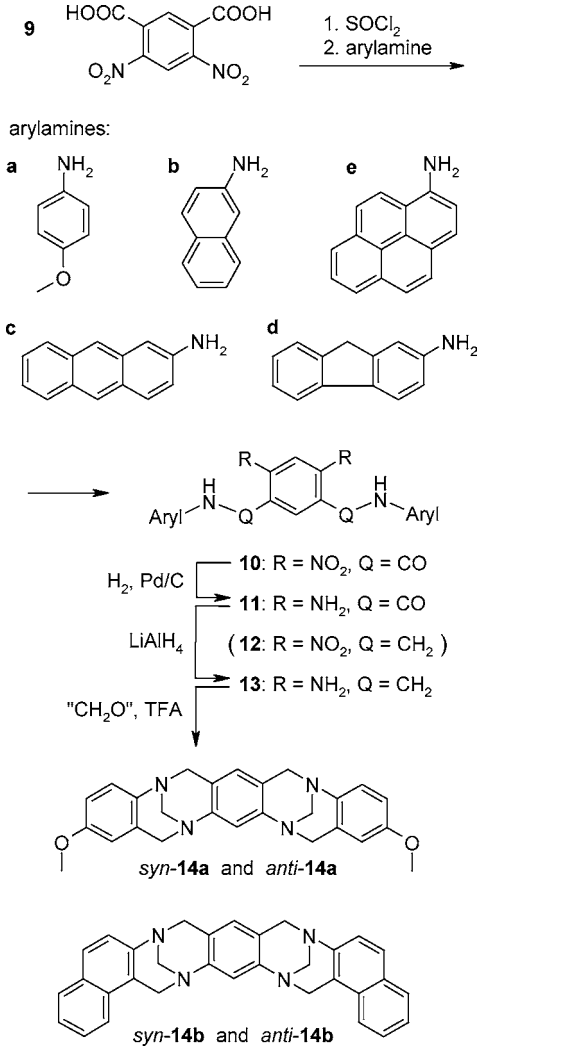
Scheme 1. Synthetic Pathway to 1,2:4,3-Bis-TB Derivatives



Scheme 2. Synthetic Pathway to 1,6:3,4-Bis-TB Derivatives



preparative yield as a mixture of the diastereoisomers *syn*-**1** and *anti*-**1** in a ratio of 1:1. This is a significantly lower yield compared to a previous method (40%, syn to anti 1:2);[3] however, no optimization has been performed to date.

Second, we addressed the preparation of 1,6:3,4-bis-TB regioisomers (Scheme 2). Nitration of 4-nitro-*m*-xylene, followed by oxidation of the methyl groups, afforded dinitroisophthalic acid **9**.[15] Because the carboxyl groups are not ortho (any imide or anhydride cannot be formed as in the case of **2**), treatment with $SOCl_2$ followed by treatment with amines **a**−**e** gave the corresponding diamides **10a**−**e** in approximately 80% yield. Catalytic reduction of the nitro groups furnished the corresponding aminoamides **11a**−**e** in quantitative yield (**11b**−**e** needed approximately 4 times longer reaction time than **11a**). The course of the reduction of the amide groups by LAH depended on the nature of the amine. In the case of *p*-anisidine, the corresponding tetraamine **13a** is obtained in 61% yield, without traces of *p*-anisidine. Naphthalene derivative **11b** gave expected tetraamine **13b** in 78% yield along with traces of 2-aminonaphthalene. In the case of anthracene, fluorene, and pyrene derivatives **11c**−**e**, only decomposition was observed (arylamines **c**−**e** were observed in complex mixtures by NMR) with no or only traces of the expected tetramines **13c**−**e**. Reductions of **11d**,**e** to **13d**,**e** or of **10d**,**e** to **12d**,**e** by BH_3·THF also led to decomposition, wherein the corresponding arylamines **d**,**e** were detected. This is obviously due to cleavage of the C−N bond instead of the C−O bond.[16]

Final trogeration (paraformaldehyde in TFA, 60 °C, 2 h) of tetraamine **13a** gave both diastereoisomers of bis-TB **14a** in 20% yield (**14a-1**:**14a-2** 1:1). Recently published[9] milder conditions (hexamethylentetramine, rt, 70 h) gave a lower product yield. Similarly, tetraamine **13b** was converted to diastereoisomers of bis-TB **14b** (7%, **14b-1**:**14b-2** 2:3).[17] Also, in this case, the milder trogeration conditions gave a lower yield.

In conclusion, we have presented the first synthetic protocol enabling the preparation of targeted regioisomeric

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bis-TBs. The basic idea of this protocol is bypassing the inherent regioselectivity of trogeration. Thus, we were able to describe the first preparation of 1,6:3,4-bis-TB derivatives. In addition, we synthesized the first deeper sidewall derivatives of bis-TBs, i.e., naphthalene derivatives. Although in working through the synthetic methodology we encountered some problematic reductions with specific aryl derivatives, these preliminary studies serve as the proof-of-concept of an alternative, potentially very general new protocol for attaining a wide variety of novel bis-TB derivatives.

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Supporting Information Available: A detailed Experimental Section, spectral properties of prepared compounds, and the NMR spectra of **14a** and **14b** are included. This material is available free of charge via the Internet at http://pubs.acs.org.

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