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New Synthetic Path to 2,2′-Bipyridine-5,5′-dicarbaldehyde and Its Use in the [3+3] Cyclocondensation with *trans*-1,2-Diaminocyclohexane

Jana Hodačová*,†,‡ and Miloš Buděšínský†

Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Flemingovo nám. 2, 16610 Prague 6, Czech Republic, and Department of Organic Chemistry, Institute of Chemical Technology, Technická 5, 16628 Prague 6, Czech Republic

hodacova@uochb.cas.cz

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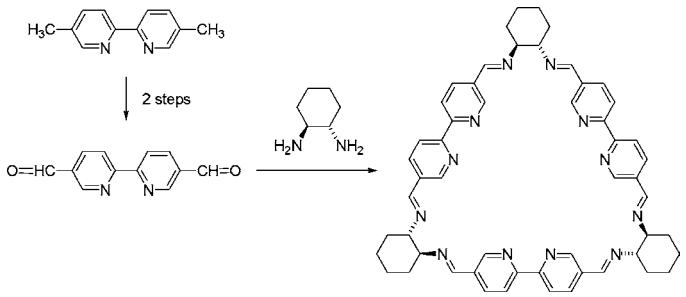
ABSTRACT



2,2′-Bipyridine-5,5′-dicarbaldehyde has been prepared in two steps by enamination of 5,5′-dimethyl-2,2′-bipyridine with Bredereck's reagent, and subsequent oxidative cleavage of the enamine groups with sodium periodate. On condensation of this dialdehyde with enantiomerically pure *trans*-1,2-diaminocyclohexane, the macrocyclic [3+3] hexa Schiff base has been obtained in excellent yield. Its reduction has given large macrocyclic hexaamine having three bipyridine units incorporated into the macrocycle structure.

Recent discovery of the highly efficient [3+3] cyclocondensation of (*1R,2R*)-*trans*-1,2-diaminocyclohexane with terephthaldehyde[1] has initiated research in the field of formation of novel chiral trianglimines.[2] Our interest in this area has focused on incorporation of suitable units into the macrocycle structure that can be further used in construction of more complex molecular and supramolecular systems. Highly efficient synthesis of trianglimine **1** possessing three bipyridyl units in the macrocycle has been one of our aims.

To synthesize the trianglimine **1**, we needed 2,2′-bipyridine-5,5′-dicarbaldehyde **2** as a starting material. Previously, two synthetic strategies have been published to synthesize **2**. In the first one, starting 5,5′-dimethyl-2,2′-bipyridine has been transformed by radical bromination to 5,5′-bis(bromomethyl)-2,2′-bipyridine, from which **2** has been synthesized by the Sommelet reaction.[3] In the second approach, 5,5′-bis(hydroxymethyl)-2,2′-bipyridine has been selectively

† Academy of Sciences of the Czech Republic.
‡ Institute of Chemical Technology.

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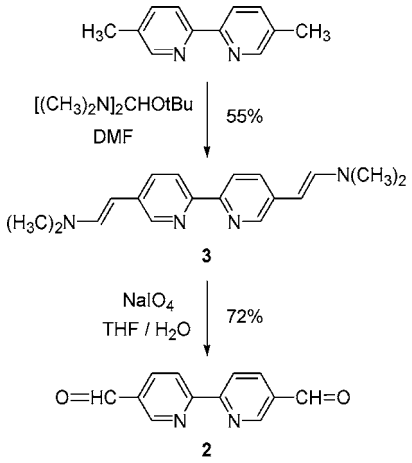
oxidized either by the Swern method[3] or by using lead(IV) acetate.[4] Starting 5,5′-bis(hydroxymethyl)-2,2′-bipyridine has been prepared by either hydrolysis of the bromomethyl derivative[3] or sodium borohydride reduction of 5,5′-bis-(carboxyethyl)-2,2′-bipyridine.[4] Both approaches suffer from low overall yield of dialdehyde **2**.

We have developed a convenient synthetic method in which commercially available 5,5′-dimethyl-2,2′-bipyridine is transformed to dialdehyde **2** in two steps through the bis-(enamine) intermediate **3** (Scheme 1).

Scheme 1. Synthesis of Dialdehyde **2**



The same synthetic approach already has been used to synthesize 2,2′-bipyridine-4,4′-dicarbaldehyde.[5] Formation of enamine on the reaction of 4-methylpyridine[6] or 4,4′-dimethyl-2,2′-bipyridine[5] with the Bredereck's reagent is facilitated by acidity of the methyl group located in the para position to the pyridine nitrogen. It is rather surprising that enamine has been obtained even from 5,5′-dimethyl-2,2′-bipyridine, in which the methyl group is located in the meta position and therefore its sufficient acidity should not be expected. Compared with the 4,4′-dimethyl analogue, 5,5′-dimethyl-2,2′-bipyridine reacts with the Bredereck's reagent more slowly and the bis(enamine) product has been obtained in significantly lower yield. In spite of this, the reaction has its appeal as bis(enamine) **3** is a useful intermediate in the synthesis of dialdehyde **2**. From a practical point of view, the advantage of the synthetic procedure is simple isolation of bis(enamine) **3** that crystallizes from the crude reaction mixture upon cooling (for experimental details see the Supporting Information). Bis(enamine) **3** has been obtained repeatedly in 49−62% yield. Oxidative cleavage[7] of bis-(enamine) **3** by sodium periodate in aqueous THF at room temperature has given dialdehyde **2** in 70−75% yield.

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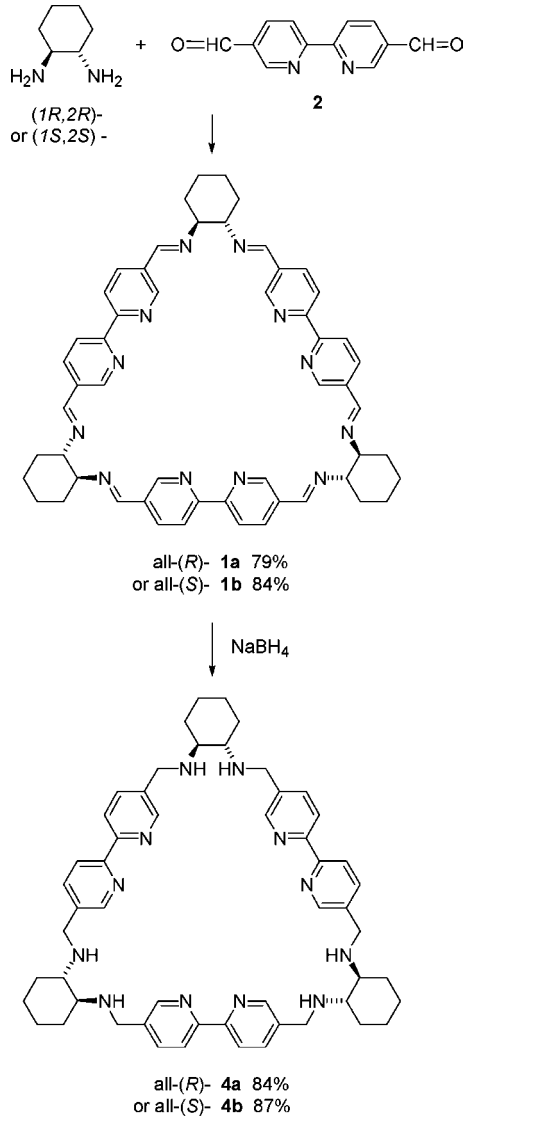
Condensation reaction of enantiomerically pure *trans*-1,2-diaminocyclohexane with dialdehyde **2** led to the expected product of the [3+3] cyclocondensation **1** (Scheme 2).

Scheme 2. Synthesis of Trianglimine **1** and Its Reduction



Macrocycle **1** has been obtained as the only product in excellent yield. Formation of a single condensation product has been confirmed by gel permeation chromatography of the crude reaction mixture as well as by FAB mass spectrometry of the isolated product. Likewise in the previous cases,[1,2] the large 42-membered macrocycle **1** has been formed in a single reaction step without need to use a template or the high-dilution method. The reaction has been carried out also in such a variant where *trans*-1,2-diaminocyclohexane has been generated directly in the reaction mixture from its tartrate salt in the presence of triethylamine. From a practical point of view, it is more convenient to work with crystalline 1,2-diaminocyclohexane tartrate than with slushy free diamine. Both variants have given comparable yield of **1**.

Schiff base **1** has been further reduced to the corresponding hexaamine **4**. Sodium borohydride reduction has given trianglamine **4** in very good yield. An attempt to combine both steps, i.e., cyclocondensation and reduction, into a one-pot procedure has not met with success. We failed to purify the crude product that contained more impurities. Even so, the two-step procedure to hexaamine **4** is a highly efficient synthetic approach. No protection/deprotection steps, which are typical of the macrocyclic polyamine syntheses, are needed to make this large chiral hexaamine.

In conclusion, we report on a convenient synthesis of dialdehyde **2**, and its subsequent use in cyclocondensation with enantiomerically pure *trans*-1,2-diaminocyclohexane leading to chiral [3+3] macrocyclic hexa Schiff base **1**. The single-step formation of the 42-membered macrocycle **1** is another example of an efficient, and atom-economy approach to large macrocycles using the [3+3] cyclocondensation strategy. The study of coordination and supramolecular chemistry of both hexa Schiff base **1** and hexaamine **4**, which has been obtained upon reduction of **1**, is the focus of our forthcoming research.

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Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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