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Synthesis of macrocyclic and linear benzylimidazolidine oligomers from solvent free aromatic Mannich-type reaction

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ABSTRACT

The reaction between the phenolic Mannich bases 1,3-bis[2′-hydroxybenzyl]imidazolidines and the Mannich intermediary macrocyclic aminal 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) was studied under solvent-free conditions. It was established that the major product is a heterocalixarene-type Mannich base, and three linear benzylimidazolidine oligomers were identified as minor products. The formation of these oligomers is analyzed in the present Letter, and the reaction mechanism is proposed.

Introduction

Aminophenol-type Mannich bases are of great chemical and industrial interest due to their growing applicability for the production of new polymeric materials with excellent mechanical, thermal, photophysical, and catalytic properties.[1–4] Previous studies of (aminomethyl)phenol synthesis, both in solution and in the absence of a solvent, employing the Mannich intermediary macrocyclic aminal 1,3,6,8-tetraazatricyclo [4.4.1.1^{3,8}]dodecane (TATD) **1** and phenols showed that the formation of benzylimidazoline oligomers, similar to compound **4**, plays a decisive role in the reaction efficiency. In addition, in certain cases, the reaction products in the absence of the solvent differ from those obtained in solution.[5] It has also been shown that the solvent-free Mannich-type aromatic reaction between the macrocyclic aminal TATD 1 and Mannich phenolic bases of the type 1,3-bis[2′-hydroxybenzyl]imidazolidine **2** is a useful synthetic strategy for the high-efficiency production of heterocalixarene-type macrocyclic compounds **3** and linear oligomers **4** formed by three benzylimidazolidine units (Scheme 1).[5,6]

Considering that aminophenol-type Mannich bases are of interest due to their potential uses, as described above, that the reaction yields polycondensation products when occurs under solvent-free conditions and that the formation of linear or macrocyclic oligomers appears to depend exclusively on the stoichiometric ratio, it becomes necessary to know the reaction mechanism in depth. For this reason, a study of the minor products was undertaken employing spectroscopic techniques and mass spectrometry.

This work identified several subproducts that provide insight into the reaction course, justifying the need to perform the reactions in the absence of a solvent, and the development of a mechanistic proposal that shows the oligomerization and macrocyclization processes (Scheme 1). In addition, the results obtained make it possible to present the synthesis of benzylimidazoline-derived macrocycles as a new example of a macrocyclization reaction assisted by complementary intermolecular hydrogen bonds between phenolic hydroxyls and amino groups.

The starting reagents for the experiments were the macrocyclic aminal TATD **1**, synthesized from formaldehyde and ethylenediamine,[7] and the Mannich bases **2a**–**2d**, previously synthesized from the aminal TATD **1** and the phenols *p*-chlorophenol (**2a**), phenol (**2b**), *p*-cresol (**2c**), and methyl *p*-hydroxybenzoate (**2d**) by heating the reactants in aqueous dioxane solution for variable time at 40–42 °C. The crude product thus obtained was further purified by CC on silica gel eluting with benzene/ethyl acetate mixtures (Scheme 2).[8]

It has been proposed that the initial formation of an intermolecular hydrogen bond between one of the TATD **1** nitrogens and the phenolic hydroxyl is necessary for the formation of 1,3-bis[2′-hydroxybenzyl]imidazolidines **2** through the reaction between the aminal TATD **1** and phenols. This hydrogen bond increases the electrophilicity of the aminal carbons and favors

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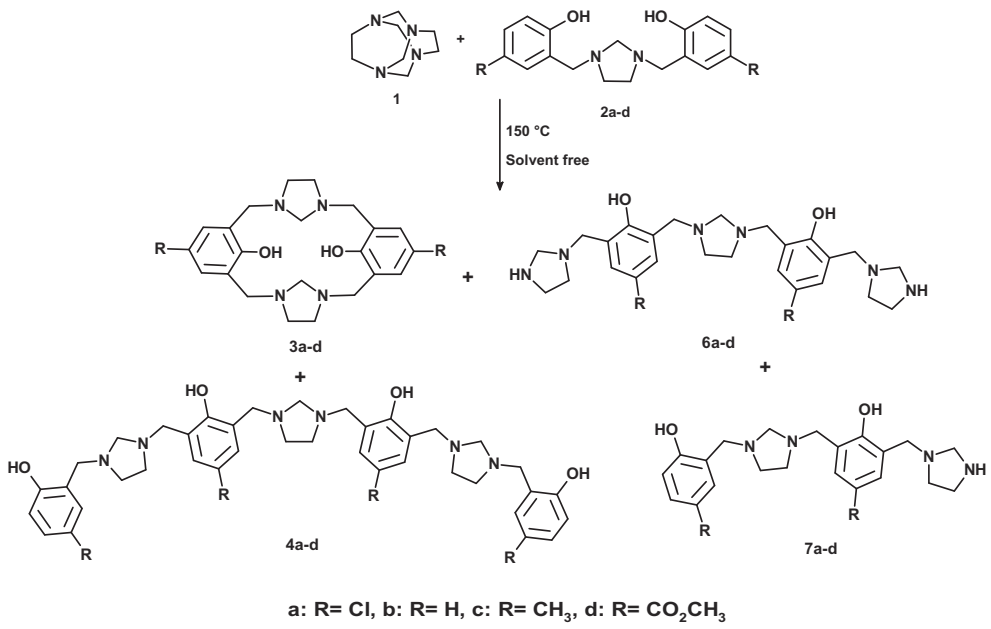
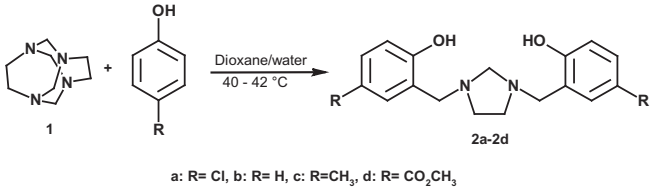
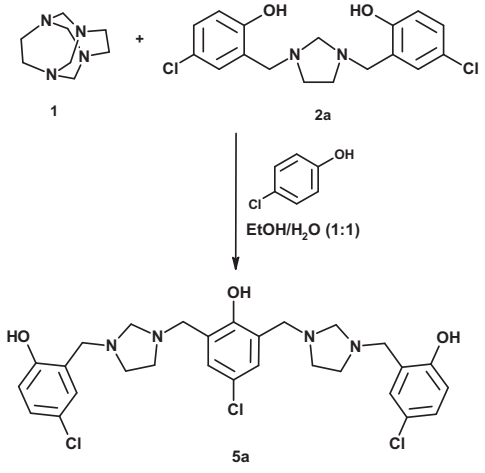


Scheme 1. Reaction of TATD **1** with 1,3-bis[2′-hydroxybezyl]imidazolidines **2**.



Scheme 2. Synthesis of 1,3-bis[2′-hydroxybenzyl] midazolidines **2a**–**2d**.



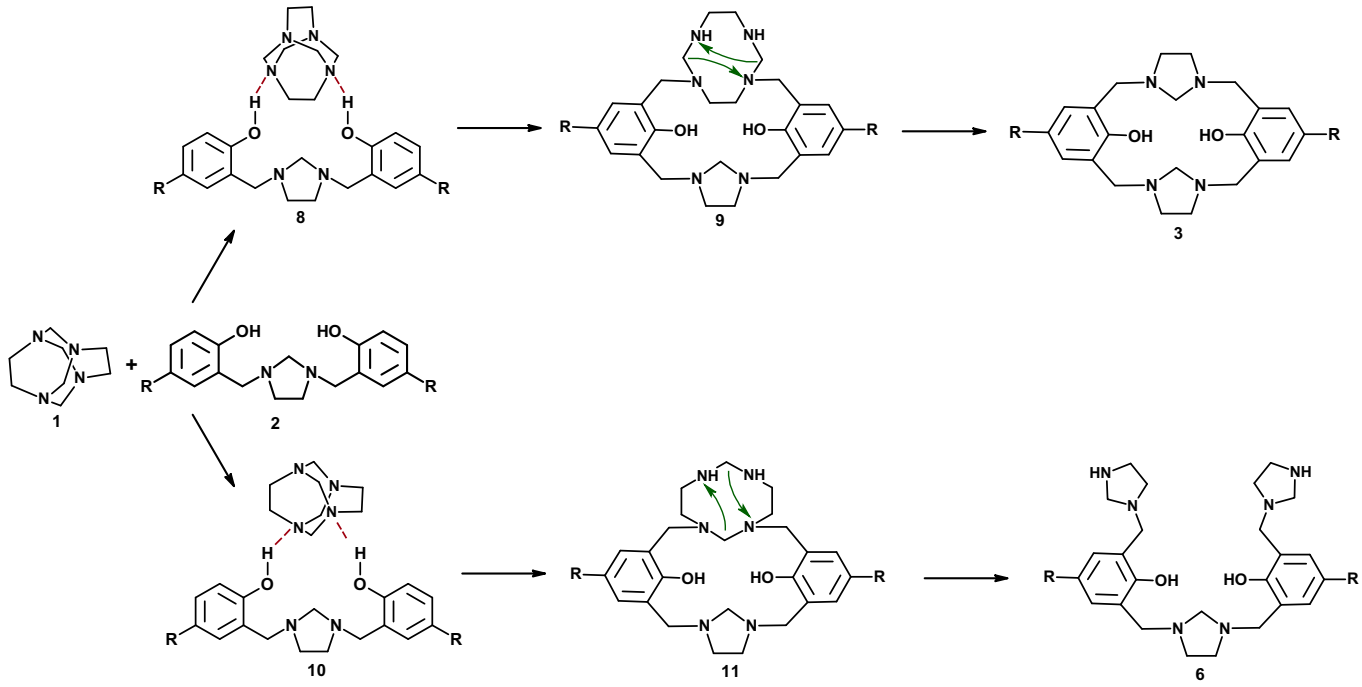
Scheme 3. Reaction of TATD **1**, 1,3-bis[2′-hydroxy-5′-chlorobenzyl]imidazolidine and *p*-chlorophenol in solution.

aromatic electrophilic substitution. It is known that (aminomethyl) phenol-type Mannich bases, such as **2**, form very strong intramolecular hydrogen bonds.[9] In solution, these intramolecular hydrogen bonds prevent the intermolecular interaction of **2** with TATD **1**, and consequently formation of imidazolidine containing products **5** does not occur. When a phenol is present in the reaction medium in addition to the aminal TATD **1** and the Mannich base **2**, the TATD **1**–phenol interaction activates the aminal carbon. Upon activation, the aminal reacts both with a phenol molecule and with a Mannich base to form a linear dimer of benzylimidazolidine, consisting of three aromatic rings joined by two imidazolidines **5** (Scheme 3).[8]

The solvent-free conditions for the reaction between TATD **1** and Mannich bases **2** are necessary to reach higher reaction temperatures, which provide the necessary energy to break the intramolecular hydrogen bond. After this bond breaks, a new interaction appears between the phenolic hydroxyl of the Mannich base **2** and one of the nitrogens from the TATD **1**—nitrogens that are probably more alkaline than those present in the Mannich base (Scheme 1).

The experiments performed showed that when the mixture of TATD **1** and the Mannich bases **2a**–**2d** at a molar ratio of 1:1 is heated to 150 °C, the heterocalixarene-type macrocyclic compound **3a**–**3d** as major product is obtained in less than 9 min. The reaction time is reduced with increased activation degree of the aromatic ring. Reactions at various temperatures from 110 to 200 °C showed higher efficiencies in the formation of **3** when working in the range from 140 to 160 °C. The use of microwave radiation (in a CEM Discover instrument with 250 W maximum power) as a heat source did not modify the course or the efficiency of the reaction (conventional heating: **3a** = 40%; microwave irradiation: **3a** = 49%), but the reaction times decreased. In all cases, the necessary time for the full disappearance of the reagents was less than 1 min.

After the working temperature (150 °C) was established, the crude products of the reaction between TATD **1** (0.3 mmol) and the Mannich bases **2a**–**d** (0.3 mmol) were analyzed, both in the case of conventional heating and in the case of microwave irradiation. The ^{1}H NMR and ESI-(+) MS (using a cone voltage of 10 V, in order to ionize molecules avoiding its fragmentation) spectra showed that with both heating processes, the major product obtained is the macrocyclic compound **3a**–**d**. In the ^{1}H NMR spectrum, in addition to the singlet corresponding to the ethylenic hydrogens present in **3**, appearing at approximately 3 ppm, two triplets are observed: one at 3.12 ppm (J = 7.2 Hz), and the other at 2.72 ppm (J = 7.2 Hz). These signals also correspond to ethylenic hydrogens but, due to their multiplicity, can be attributed to the presence of linear oligomers.[10] The analysis of all the lower-intensity signals in the ^{1}H NMR spectrum led to the



Scheme 4. Formation of the oligomers **3** and **6**.

conclusion that in addition to the macrocyclic compound **3**, linear oligomers with different numbers of (hydroxybenzyl)imidazolidine-type units were obtained.

The fragmentation pattern analysis by mass spectrometry (ESI-(+)MS/MS) enabled the determination and identification of the minor compounds present in the crude reaction product. In the case of the reaction between the aminal **1** and the Mannich base **2a**, an ion was observed at $m/z = 449.2$, corresponding to the ion $[M+H]^+$ of the macrocycle **3a** $3^5,7^5$-dichloro-1,5(1,3)-diimidazolidine-3,7(1,3)-dibenzenacyclooctaphane-$3^2,7^2$-diol. An ion was observed at $m/z = 521.2$, corresponding to $[M+H]^+$ of the molecular formula $C_{25}H_{35}Cl_2N_6O_2$. The fragmentation pattern in the ESI-(+)MS/MS spectrum allowed us to determine that the compound has a linear structure formed by three imidazoline and two phenol units $3^5,7^5$-dichloro-1(1),5(1,3)-diimidazolidine-3(1,3),7(1)-dibenzenaheptaphane-$3^2,7^2$-diol **6a** (Scheme 1).

A linear oligomer formed by three imidazolidine and four phenol units $1^5,5^5,9^5,13^5$-tetrachloro-3,7,11(1,3)-triimidazolidine-1,13(1),5,9(1,3)-tetrabenzenatridecaphane-$1^2,5^2,9^2,13^2$-tetraol **4a** was recently reported when the reaction between the aminal TATD **1** and the Mannich base **2a** was performed solvent-free at a ratio of 1:2 in the absence of a solvent.[5] This antecedent and the fragmentation pattern of the ion at $m/z = 801.2$ showed that the linear oligomer **4a** is also formed when the reaction is performed at the ratio 1:1 (TATD **1**/Mannich base **2**). Analysis of the ESI-(+)MS/MS mass spectrum of the ion at $m/z = 437.1$ showed the formation of a third linear oligomer formed by two phenol and two imidazolidine units $3^5,7^5$-dichloro-1(1),5(1,3)-diimidazolidine-3(1,3),7(1)-dibenzenaheptaphane-3^2-7^2-diol **7a**.

The results showed that the reaction course and the obtained products are independent of the substituent on the aromatic ring (Scheme 1).

The formation of an intermolecular hydrogen bond between one of the TATD **1** nitrogens and the phenolic hydroxyl has been proposed as an initial step for the reaction of TATD **1** and phenols, which activates the aminal carbons. For the formation of the oligomers presented in this Letter, both cyclic and linear, the first step also consists of the formation of intermolecular hydrogen bonds between the two hydroxyls of the Mannich base **2** and two nitrogens of the aminal TATD **1**. When the stoichiometric ratio is 1:1, the hydrogen bonds involve two nitrogens from the same unit of the aminal TATD **1**. If both nitrogens are part of the same ethylenediamine unit, a macrocyclization process assisted by the formation of templates through noncovalent interactions is favored (Scheme 4)[9,11] this induces electrophilic aromatic substitution due to the increased electrophilicity of the aminal carbons for the formation of the intermediate perhidrotetrazecine **9** or **11**.[11] This pre-organization is favored by the stoichiometric ratio utilized (1:1) and by the higher alkalinity of the ethylenic nitrogens due to the electronic effects characteristic of the 1,2-diamines. If the intermolecular hydrogen bond is formed by two nitrogens that belong to different ethylenediamine units, an opening process of the aminal TATD **1** is favored, which leads to the formation of the linear oligomer **6** (Scheme 4). The lower alkalinity of the 1,1-diamines does not favor the formation of this hydrogen bond, and compound **6** is only obtained as a minor product.

The formation of the linear oligomers **4** and **7** follows a similar mechanism to that proposed for the formation of oligomers **3** and **6**. The products are formed when an interaction occurs between two Mannich base **2** molecules and one aminal TATD **1** molecule. The intermolecular hydrogen bonds formed with nitrogens from a 1,2-diamine lead to the formation of **4**, and the hydrogen bonds formed with the nitrogens from a 1,1-diamine lead to the formation of compound **7** (Scheme 5). Despite using the Mannich base/TATD ratio (1:1), oligomers **4** and **7** are always formed due to the fast sublimation of TATD **1** under the selected experimental conditions, which alter the stoichiometric ratio.

In conclusion, this Letter presents the results of a study on the solvent-free reaction of 1,3-bis[2′-hydroxybenzyl]imidazolidines-type Mannich bases **2** and the Mannich intermediary aminal 1,3,6,8-tetraazatricyclo [4.4.1.1^{3,8}]dodecane (TATD) **1**. When microwave radiation is employed, the reaction times are lower, the sublimation decreases, the major product corresponds to a heterocalixarene-type compound **3**, and in all cases, unavoidable formation of oligomeric benzylimidazolidine subproducts was observed. The products formed depend on the initial interaction of hydrogen bonds between the phenolic hydroxyls of the Mannich base with the nitrogens of the aminal TATD **1**.

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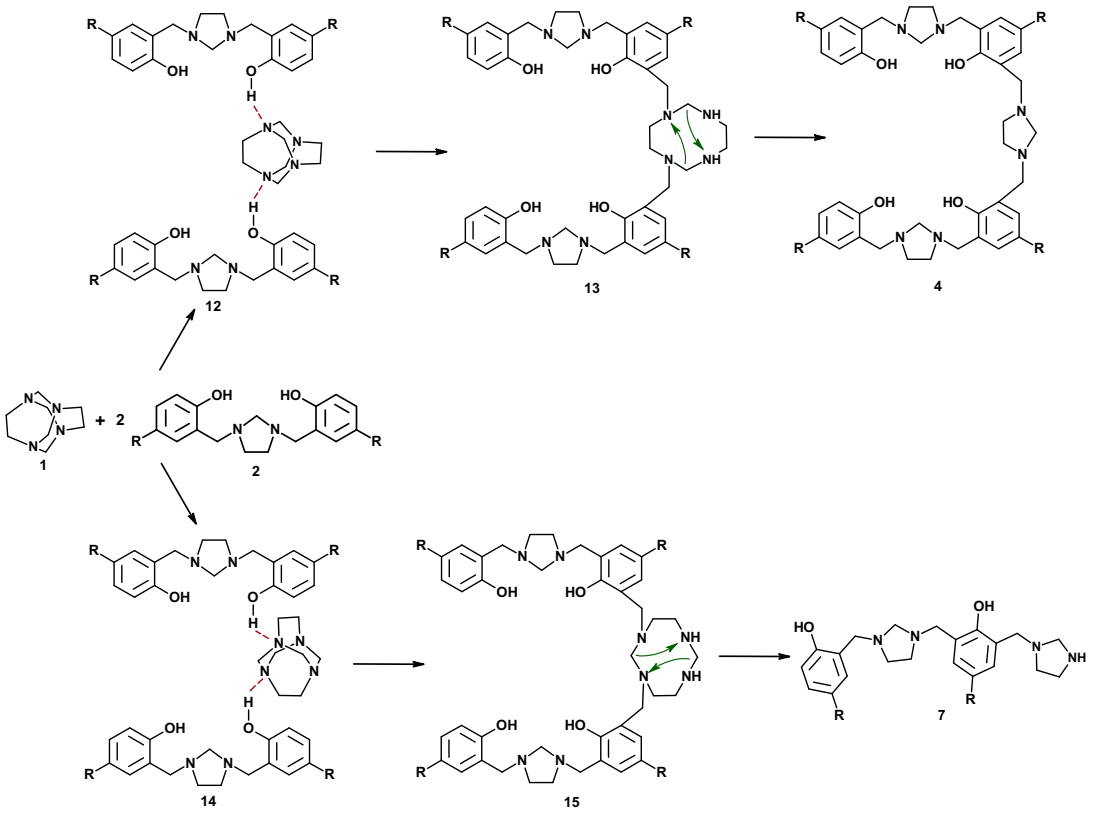

Scheme 5. Formation of oligomers **3** and **6**.

Acknowledgments

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