


Communication

Synthesis of Diastereomeric 2,6-bis{[3-(2-Hydroxy-5-substitutedbenzyl)octahydro-1*H*-benzimidazol-1-yl]methyl}-4-substituted Phenols (R = Me, OMe) by Mannich-Type Tandem Reactions

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Abstract: The synthesis and characterization of two novel diastereomeric Mannich bases was carried out from the reaction of the cyclic aminal (2*R*,7*R*,11*S*,16*S*)-1,8,10,17-tetraazapentacyclo[8.8.1.1.1.^{8,17}0.2.⁷0.11,16]icosane **1** and *p*-cresol **2a** and 4-methoxyphenol **2b** in a water/dioxane mixture. The title compounds (**4a–b**) are interesting because bearing two 3-(2-hydroxy-5-substitutedbenzyl)octahydro-1*H*-benzimidazol-1-yl]methyl substituents joined to an arenol ring. The formation of these new Mannich bases in the reaction mixture can be explained by aminomethylation of previously reported *di*-Mannich base 2,2'-((hexahydro-1*H*-benzo[d]imidazole-1,3(2*H*)-diyl)bis(methylene))bis(4-substituentphenol) **3a–b**. NMR analysis demonstrated that compounds **4a–b** were formed as diastereomeric mixtures. Subsequent experiments revealed that at longer reaction times, the percentage yield of these new products increased considerably (yield percentages up to 22–27%), suggesting a nucleophilic competition between the *p*-substituted phenols and Mannich bases of type **3** for aminal **1**.

Keywords: poly-Mannich bases; cyclic aminal; phenol; NMR; diastereomeric Mannich bases; cascade; tandem reaction



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1. Introduction

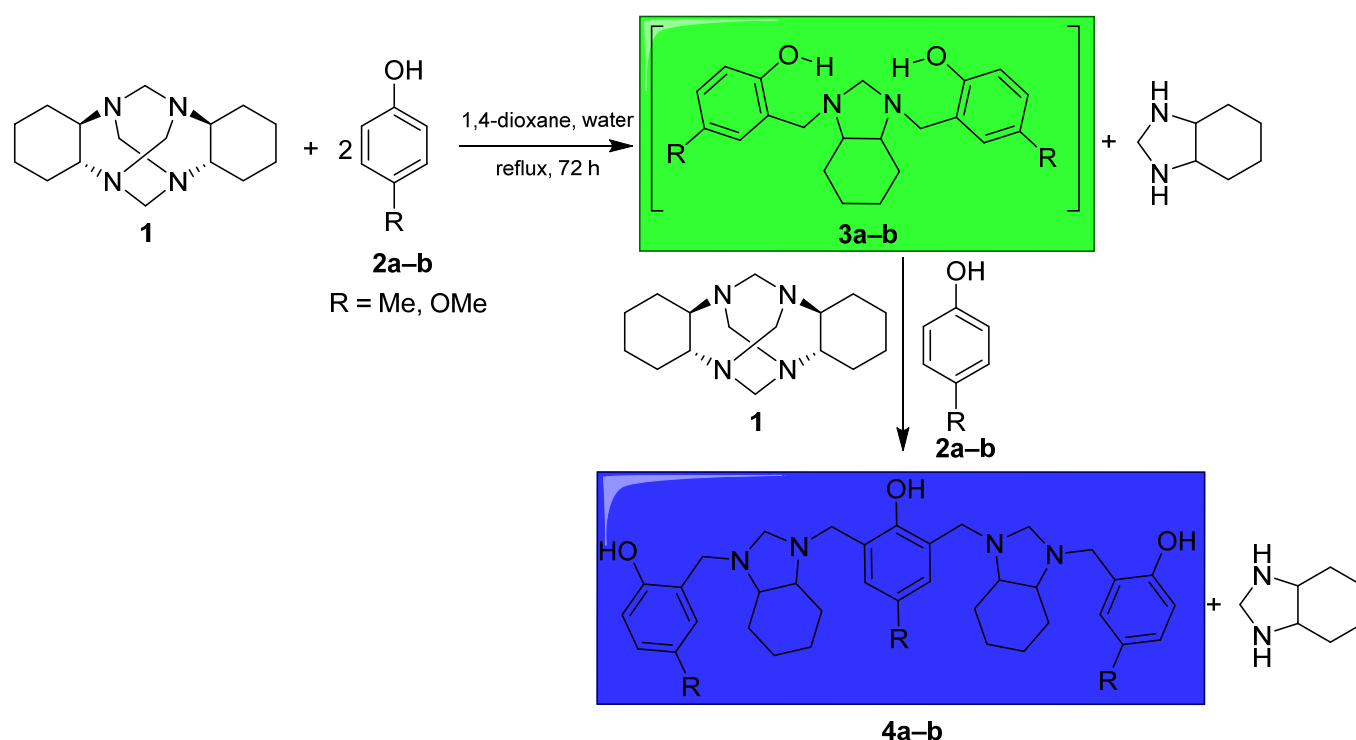
Mannich bases are compounds widely known for their affordable preparation and application versatility [1]. It is known that this class of compounds has demonstrated numerous biological activities [2,3]. Although they are highly explored compounds, multiple investigations continue to be carried out for their application. Recently, four series of Mannich bases were synthesized, incorporating phenothiazines, a pharmacophore used to treat severe mental and emotional disorders and reduce nausea [4]. The reaction of 10-methyl-10*H*-phenothiazine-3-sulfonamide with some secondary amines and formaldehyde afforded the respective Mannich bases, which showed inhibition of growth in vitro against *P. aeruginosa*, *E. coli*, and *S. aureus* (MIC between 3.125–12.5 µg/mL) [5]. The synthesis of Mannich bases of the benzimidazole type was carried out, and the in vitro evaluation of their antituberculous activity was performed [6]. These compounds were synthesized by condensation reaction between 1-(1*H*-benzo[d]imidazol-1-yl)ethanone and some amines, showing significant antituberculosis activity against the cell wall enzyme of *Mycobacterium tuberculosis* (M.tb), enoyl acyl reductase carrier protein (InhA), and regulatory protein of EthR in strain H73Rv. Functionalized bicyclo[3.1.1]heptane-type Mannich bases showed behavior as a human ornithine aminotransferase inhibitor [7], and isatin-containing *N*-Mannich base derivatives of primaquine with heterocyclic scaffolds were able to act against the dihydrofolate reductase receptor (DHFR) [8]. Protein kinase C (PKC)-epsilon

inhibitors to treat alcohol disorders were also obtained through a highly enantioselective nitro-Mannich reaction using a dual-reactant catalysis system [9]. The synthesis of the Mannich bases of the *N,N'*-bis(3-oxo-3-phenylpropyl)ethane-1,2-diamine dihydrochloride type has been reported to afford corrosion inhibitors of N80 steel. This report demonstrated that the inhibition performance was significantly improved by combining these Mannich bases and allicin [10].

Although the Mannich reaction has been widely explored, numerous modifications and improvements have been reported trying to improve yields and stereoselectivity [11]. An example is the chemical synthesis of chiral compounds of the β -aminocarbonyl type, which are usually used as synthetic precursors [12]. These compounds have been obtained through Mannich-type organocatalytic reactions of glyoxylate imines using organocatalysts that operate through covalent activation of enamines, such as catalysts derived from pyrrolidine, as well as in the catalysts based on other structural motifs, and non-covalent organocatalysts, such as thioureas, squaramides, and chiral Brønsted acids [13]. An enantioselective vinylogenic Mannich reaction was carried out using 2-methoxyfuran under chiral catalysis with spiroposphoric acid, involving 4-isoxazoline derivatives as cyclic ketimine substitutes and providing γ -butenolide structures [14]. Additionally, the enantioselective Mannich reaction of α -fluoroindanones with *N*-Boc-ketimines derived from isatin, catalyzed by a phase transfer catalyst based on quinine, yielded 3-substituted 3-amino-2-oxindole compounds featuring vicinal tetrasubstituted stereocenters. This reaction achieved high yields (83–95%), moderate to excellent enantioselectivities (66–91%), and high diastereoselectivities (up to >99:1) [15]. Moreover, the use of trypsin or α -chymotrypsin immobilized on titanate nanotubes to synthesize β -amino carbonylated compounds, specifically 2-[phenyl(phenylamino)methyl] cyclohexanone, has also been reported, indicating that the use of this system allowed high conversions and diastereomeric ratios [16]. The synthesis of bicyclic γ -ureasultams, possible analogs of biotin and containing two consecutive chiral centers, was carried out through an intramolecular cascade of Mannich addition and aza-Michael of alkenyl sulfonamides [17]. Moreover, the use of a photochemical synthetic protocol to afford polyfunctionalized dihydro-2-oxypyrroles using Michael–Mannich cyclocondensation of amines, dialkyl acetylenedicarboxylates, and formaldehyde was recently reported. This methodology adopted a photocatalyst as a single-electron redox mediator in an ethanol solution under exposure to blue light of the perovskite halide type [18].

One of our research lines mainly uses cyclic amins with asymmetric centers as preformed Mannich reagents in reactions with phenols in basic media [19,20]. This reaction between these interesting precursors and active-hydrogen compounds continues to be studied, and it is considered a potential synthetic route. The cyclic aminal 4,9-dimethyl-1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane, synthesized by the reaction of *rac*-1,2-propanediamine with paraformaldehyde, was used in a Mannich-type reaction against *p*-chlorophenol, resulting in 2,2'-[(4-methylimidazolidine-1,3-diyl)dimethanediyl]bis(4-chlorophenol) as a racemic mixture in moderate yields [19]. Another well-explored aminal, with the presence of chiral centers, corresponds to (2*S*,7*R*,11*S*,16*R*)-1,8,10,17-tetraazapentacyclo[8.8.1.1^{8,17}0^{2,7}0^{11,16}]icosane, derived from *cis*-(*meso*)-1,2-diaminocyclohexane and formaldehyde. Its use as a suitable substrate for the preparation of a series of *cis*-*meso* Mannich bases of the 4,4'-disubstituted-2,2'-{[(3*aR*,7*aS*)-2,3,3*a*,4,5,6,7,7*a*-octahydro-1*H*-1,3-benzimidazol-1,3-diyl]bis(methylene)}diphenols type was demonstrated [20]. Its diastereoisomer, the aminal (2*R*,7*R*,11*S*,16*S*)-1,8,10,17-tetraazapentacyclo[8.8.1.1^{8,17}0^{2,7}0^{11,16}]icosane 1, has also been proven to be a potential precursor of *di*-Mannich bases. Notably, the reaction against *p*-cresol 2*a* and 4-methoxyphenol 2*b* apparently only led to the formation of the racemic bases *di*-Mannich 4,4'-dimethyl-2,2'-{[(3*aRS*,7*aRS*)-2,3,3*a*,4,5,6,7,7*a*-octahydro-1*H*-1,3-benzimidazole-1,3-diyl]bis(methylene)}diphenol 3*a* and 4,4'-dimethoxy-2,2'-{[(3*aRS*,7*aRS*)-2,3,3*a*,4,5,6,7,7*a*-octahydro-1*H*-1,3-benzimidazole-1,3-diyl]bis(methylene)}diphenol 3*b*, respectively [21,22]. However, subsequent studies have shown that the reaction between the Mannich phenolic bases 1,3-bis[2'-hydroxybenzyl]imidazolidines and the cyclic aminal 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD), in addition to allowing the formation of heterocalixarene-type Mannich bases, leads to the

formation of linear benzylimidazolidine oligomers as minority products [23]. Performing experiments between aminal **1** and phenols **2a–b**, we observed that in addition to **3a–b**, other very minor products were formed based on what was reported. Then, we hypothesized that in our reaction, the same thing would occur in situ, and once **3a–b** were formed, they would react with aminal **1** in competition with phenols **2a–b**. For this reason, we decided to study the variables that govern this reaction, seeking to improve the yields of these minor products, to know them, characterize them, and understand their formation mechanism. Continuing this deep exploration, this manuscript presents the study of the reaction between aminal **1** and the active phenols **2a–b**, identifying that depending on the conditions of the reaction, oligomers of type 2,6-bis{[3-(2-hydroxy-5-substitutedbenzyl)octahydro-1*H*-benzimidazol-1-yl]methyl}-4-substituted phenols **4a–b** can also be obtained as diastereomeric mixtures (Scheme 1). The results obtained are described below.



Scheme 1. Sequential synthesis of **4a–b**.

2. Results

The study of the reactivity of cyclic aminal **1** against *p*-cresol **2a** and 4-methoxyphenol **2b** has been previously addressed [21,22]. The reaction between aminal **1**, **2a**, and **2b** was carried out under conventional heating conditions and in the presence of a dioxane: water mixture as solvent. The main products corresponded to the previously reported *di*-Mannich base 2,2'-((hexahydro-1*H*-benzo[d]imidazole-1,3(2*H*)-diyl)*bis*(methylene))*bis*(4-substituentphenol) **3a–b** (yield percentages 45 and 34%, respectively) [21,22]; however, a close inspection of the crude reaction mixture by NMR made evident the formation of the entitled compounds as diastereomeric mixtures **4a–b**. Considering the main variables that affect the reaction, such as temperature, concentration, and polarity of the solvent, a series of experiments was carried out to optimize these conditions towards the total consumption of the respective aminal **1** and to increase the yields of oligomeric products **4a–b** (Table 1). Solvents of varying polarities—low (benzene, toluene, 1,4-dioxane), medium (ethyl acetate, chloroform), and high (methanol, ethanol)—were tested. Based on the background information on chemical reactivity reported by Rivera [23], the reactions were carried out with a stoichiometric ratio of 1:2 of aminal **1** to phenol **2** to allow the formation of

di-Mannich bases via double-aminomethylation reaction. Temperatures between 20 °C and 30 °C with constant stirring were evaluated for up to 40 h until the reagent concentrations were stabilized or the reagents were consumed entirely. Initial tests showed that both aminal **1** and phenol **2** were mostly recovered unchanged at temperatures between 20 °C and 40 °C. Therefore, further tests were conducted by varying the temperature. It was found that, using medium- to high-polarity solvents, the concentrations of the reactants decreased over 40 h of heating and stirring, indicating the formation of product **3**. However, complete conversion was not achieved. In 1,4-dioxane, 65% of the starting aminal **1** was recovered despite its low polarity, suggesting some reaction occurred. Polar solvents were expected to enhance reaction kinetics. In ethanol, 45% of aminal **1** was recovered after 40 h at optimal temperatures, indicating partial conversion. This suggests that the reaction depends significantly on both temperature and solvent polarity. It was proposed that increasing these factors would enhance reactant conversion. Further tests involved using mixtures of ethanol and 1,4-dioxane with water to vary polarity and temperature. 1,4-Dioxane is miscible with water, which allows for manipulation of the dielectric constant, while ethanol–water mixtures create a highly polar medium through hydrogen bonding. Reactions were performed at 90 °C for 40 h using these solvent mixtures. The results showed that increasing the proportion of water in the solvent mixtures decreased the recovery percentage of aminal **1**. Using mixtures of 1,4-dioxane and water, in addition to increasing the polarity of the medium, allowed the reaction temperature given by the medium under reflux conditions to be higher, increasing the reaction rate and ensuring that **1** was consumed entirely. The hypothesis was supported by a high conversion of the reagents employing a 60:40 1,4-dioxane–water mixture, with conversion rates enhanced by higher temperatures. Thus, the reactions between aminal **1** and phenol **2** were carried out in a prolonged reaction time of 72 h. Although the main products corresponded to **3a–b**, a decrease in yields of 15–30% was observed, and the concentration of the new products increased progressively (22–27% yield), identified as the titled compounds. The results of the characterization by NMR and HR-ESI-MS are presented in the Supplementary Materials.

Table 1. Summary of the reactivity assays of aminal **1** vs. phenols **2a–b** varying solvent, temperature, and reaction times to afford compounds **4a–b**.

Tested Solvent System	Solvent Polarity	Temperature/°C	Reaction Time/h	Recovery of Aminal 1 /%	Yield for Compounds 4a–b /%
Benzene or toluene	Low	20–40 °C	Up to 40	>99	0
1,4-Dioxane	Intermediate	40 °C	40	65	<2
Ethanol	High	77 °C	40	0,45	<2
1,4-Dioxane/water	Intermediate–high	90 °C	40	0,1	13–15
1,4-Dioxane/water	Intermediate–high	94–97 °C	72	0	22–27

The ¹H NMR spectrum of compound **4a** (Figure S1a) is characterized by several multiplet signals between 1.00 and 2.50 ppm, integrating 40 hydrogen atoms. These signals are similar to those observed for compounds **3a** and were assigned to the diastereotopic hydrogens of two cyclohexane rings in the *meso*-(3*a*R,7*a*R,3*a*'S,7*a*'S) and enantiomers (3*a*S,7*a*S,3*a*'S,7*a*'S) and (3*a*R,7*a*R,3*a*'R,7*a*'R). The *meso*-(3*a*R,7*a*R,3*a*'S,7*a*'S) stereoisomers present a plane of symmetry through the central aromatic ring, to which the (methylene)-(1*H*-benzo[*d*]imidazole-3,1-(2*H*,3*H*,3*a**H*,4*H*,5*H*,6*H*,7*H*,7*a**H*)-diyl)-bis-(methylene)-4-substituted aryl groups are attached in positions 2 and 6. Enantiomers (3*a*S,7*a*S,3*a*'S,7*a*'S) and (3*a*R,7*a*R,3*a*'R,7*a*'R) possess a C₂ symmetry axis, also through the central aromatic ring, but without a plane of symmetry. These symmetry elements influence the simplicity of the spectrum concerning the signals of the diastereotopic cyclohexane rings (Figure 1).

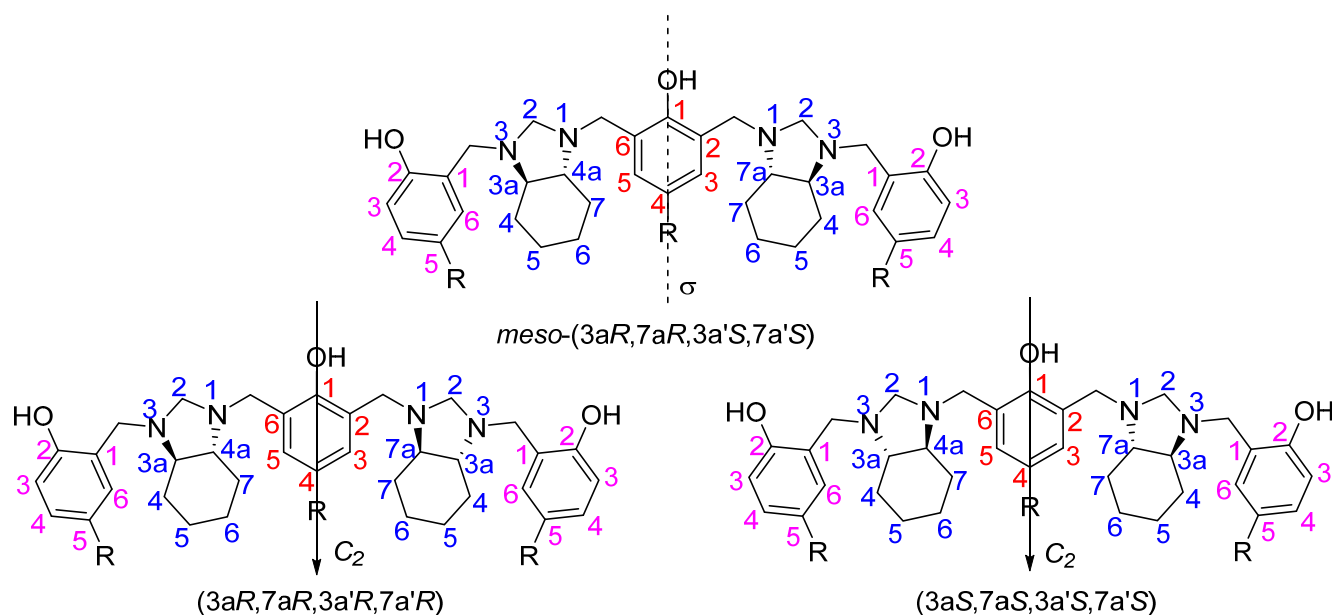


Figure 1. Labeled chemical structures of the formed diastereoisomers for the title compounds **4a–b**.

The integration of the signals between 3.20 and 4.20 ppm suggests the presence of 24 hydrogen atoms grouped in two signals of 12 hydrogens corresponding to the pairs of stereoisomers of compound **4a**. The observed multiplicity seems complex and unexpected compared to *trans*-1,2-diaminocyclohexane-derived compound **3**. Around these chemical shift values, the signals from the benzylic hydrogens ArCH₂ and the hydrogens on the amino carbon N-CH₂-N were expected. However, the apparent multiplicity of these signals and the difficulty in calculating the coupling constants complicated the analysis. Through two-dimensional COSY, HMQC, and HMBC experiments (Figure 2), the nature of these signals was clarified so that eight signals appeared, each integrating two hydrogens, with doublet multiplicity and a geminal coupling constant of 14.0 Hz, overlapping each other, and with a molar ratio of 1:1 between the enantiomer mixture and *meso* compounds. The signals were grouped into two sets of four and were assigned to the hydrogens of the ArCH₂N group, which acted as a bridge between the aromatic rings and the perhydrobenzimidazolidin system. For the *meso*-(3aR,7aR,3a'S,7a'S) compounds, the signals at 4.16 ppm and 4.07 ppm appeared as doublets, with a geminal coupling constant of 14.0 Hz. These doublets coupled with the signals at 3.52 ppm and 3.47 ppm, which had the same multiplicity, and were assigned to the benzylic protons. In the ¹³C NMR spectrum (Figure S1b), the benzylic carbons were identified by signals around 56.7 ppm, indicating that these hydrogens behaved as diastereotopic protons. For the enantiomers (3aS,7aS,3a'S,7a'S) and (3aR,7aR,3a'R,7a'R), a similar pattern was observed. The doublet signals at 4.14 ppm and 3.97 ppm coupled with the signals at 3.51 ppm and 3.41 ppm, correlating with the signals from the benzylic carbons around 56.7 ppm. Additionally, hydrogens were observed on the amino carbon at 3.60 ppm and 3.59 ppm with singlet multiplicity, correlating with the carbons around 76.3 ppm. The ¹H NMR spectrum of compound **4a** showed signals above 6.50 ppm, indicating the presence of aromatic ring systems as ABX coupling systems (with doublets and a singlet at 6.72 ppm, 7.09 ppm, and 6.92 ppm). The two-dimensional HMBC experiment (Figure 2) confirms the assignment of these aromatic hydrogens and their correlation with the signals of the benzylic hydrogens. The proposed structure for compound **4a** was confirmed by the HR-ESI-MS mass spectrum in its positive mode (Figure S3), which showed a signal with *m/z* of 625.4086 for [M + H]⁺ (calculated for C₃₉H₅₃N₄O₃: 625.4112). The results of the spectroscopic characterization using uni- and two-dimensional NMR experiments of compound **4b** reflected a similar behavior for the signals of both the ¹H and ¹³C nuclei, as previously discussed for the results for compound **4a**. As expected, CH₃O groups attached to the aromatic rings appeared as singlet signals around 3.69 ppm in the ¹H

NMR spectrum and around 56.0 ppm in the ^{13}C NMR spectrum (Figure S3). These results confirm the formation of the title compounds **4a–b** from the synthetic route described in this report.

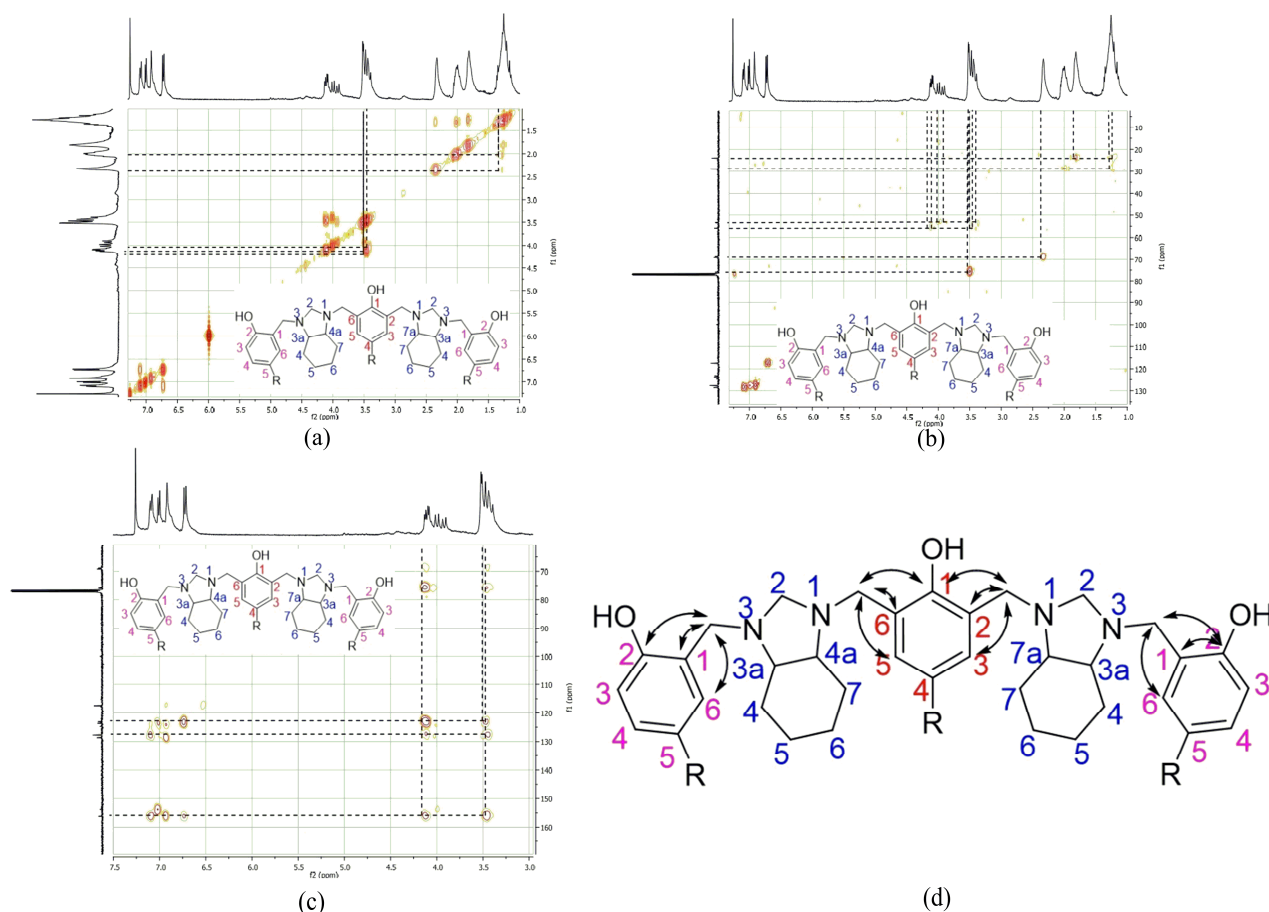


Figure 2. Two-dimensional nuclear magnetic resonance experiments of compound **4a**. (a) COSY, (b) HMQC, (c) HMBC, (d) schematic representation of the connectivity between resonances of ^1H and ^{13}C atoms in **4a**.

3. Materials and Methods

3.1. General

All reagents and chemicals were commercially acquired (Merck KGaA and/or Sigma-Aldrich, Darmstadt, Germany). They were employed without additional refinement. As a result, the purity of dry solvents was sufficiently defined during purchase. The products' progression of reaction and purification were monitored by thin-layer chromatography (TLC) on silica gel 60 F254 plates (Merck KGaA) under detection at 254 nm. Nuclear magnetic resonance (NMR) experiments were conducted using a Bruker Avance AV-400 MHz spectrometer. TMS was used as a reference to give chemical shifts in δ (ppm). Typical splitting patterns were implemented to define the signal multiplicity (i.e., s, singlet; d, doublet; t, triplet; m, multiplet).

3.2. General Procedure: Reaction between Aminoal and *p*-Substituted Phenols

To a solution of aminoal **1** (1.00 mmol, 0.276 g) in 1,4-dioxane (3.0 mL), the respective *p*-substituted phenol **2a–b** (2.00 mmol; *p*-cresol and 4-methoxyphenol) dissolved in 1,4-dioxane (3.0 mL) was slowly added. The reaction mixture was kept at room temperature for 10 min. Water (4.0 mL) was added and heated to reflux with constant stirring for 72 h. Once the reaction was completed, the solvent was removed under reduced pressure, and products **3a–b** and **4a–b** were purified by column chromatography (silica gel), eluting with

mixtures of hexanes: ethyl acetate in a polarity gradient. ^1H and ^{13}C NMR spectroscopy, HR-ESI-MS, and FT-IR spectroscopy were used to characterize compounds **4a–b**. The results are presented in the Supplementary Materials (Figures S1–S3).

4. Conclusions

The study on the reactivity of cyclic aminal **1** with *p*-cresol **2a** and 4-methoxyphenol **2b** showed that under specific conditions, the formation of di-Mannich bases **3a–b** or oligomers **4a–b** could be favored. Variables such as the polarity of the medium, the temperature, and the time of reaction presumably determined the mechanism pathway. These reaction conditions influence the competition between **2** and **3** to attack the aminal **1**. Structural characterization of **4a** via NMR and HRMS confirmed the proposed structures, underscoring the importance of reaction conditions in product yield and conversion.

Supplementary Materials: Figure S1: ^1H and ^{13}C NMR spectra of compound **4a**; Figure S2: HR-ESI-MS spectrum of compound **4a**; Figure S3: ^1H and ^{13}C NMR spectra of compound **4b**.

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