

First Description of a Guanidine-embedded Pillar[5]arene: Opening New Avenues for Biological Applications

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Abstract: Guanidine functionality embedded in macrocyclic framework provides intriguing and tunable chemical and physical characteristics to molecular structures. We describe in this paper the first example of guanidine-containing pillar[5]arene and their potential applications in biology and material science. The reaction of O-alkylated *p*-aminopillar[5]arene with guanylating reagent, amidinopyrazole hydrochloride, gives first ever synthesis of a new generation of guanidine-embedded pillararene **2** under mild reaction conditions.

Introduction

Biologically relevant functional groups play a central role in life. Amongst these fundamental groups, guanidine has been one of the most attractive organic compounds despite its simple chemical composition. The guanidine group has been found to control chemical and physicochemical characteristics of numerous bio-active compounds and guanidine-containing derivatives represent a very important and a promising class of therapeutic agents for a wide spectrum of diseases. The first description of the synthesis of guanidine from guanine has opened avenues for the development of methodologies. Guanidine is described as nucleosuperbase groups and their derivatives have been widely used in organic synthesis¹, catalysis², asymmetric functionalization³, polymer chemistry,

coordination chemistry (several potential coordination modes)⁴, medicinal chemistry (*Rosuvastatin*, *Guanabenz*, *Imanitib*, *Cimetidine*, *Zanamivir*) and found in many natural products such as creatine, palau'amine, satitoxin, purines, marine microorganisms, marine and terrestrial invertebrates, and marine sponges, guanidiniums-the protonated form of guanidines, and the anionic derivatives, guanidates⁵. The wide scope of applications explains need for their in-depth studies, especially in the area of macrocyclic chemistry. The main drawback of guanylation reactions is quite highly limited making their synthesis challenging.

Guanidinium are the conjugated acid-form of guanidine which is a strong organic base. Moreover, these key functional groups are found in a wide of range of natural products such as creatine, saxitoxin etc.

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Guanidinium-based compounds play a key role in the biological processes due to their high solubility in water, interaction with negatively-charged compounds, host-guest interactions, antimicrobial properties, and capability to enhance cell penetration. They are part of arginine residues which are present on the surface of proteins improving their water solubility and are involved in different interactions. Guanidinium-containing calixarenes were reported and displayed relevant biological use in enhancing calixarene transfection within cells⁶, DNA delivery⁷, and triggering the p53-protein enhancer complex formation which increased the p53 gene expression⁸.

Pillar[n]arenes are a new generation of pillar-shaped macrocycles comprised of hydroquinone derivatives linked through the 2- and 5-positions by methylene bridges⁹. Their particular scaffold and architecture provide important properties in host-guest interaction. This inspired us to prepare the guanidine-functionalized pillar[5]arene. The unique characteristics of guanidine and pillar[5]arene promises crucial developments in biological studies. Herein, we report the synthesis and characterization of a new generation of versatile guanidine-based pillar[5]arene (**Figure 1**) which may be useful for further transformations and biological studies.

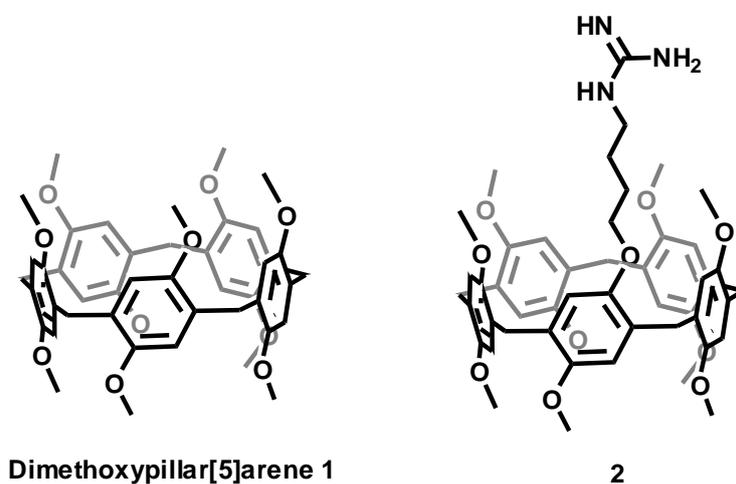
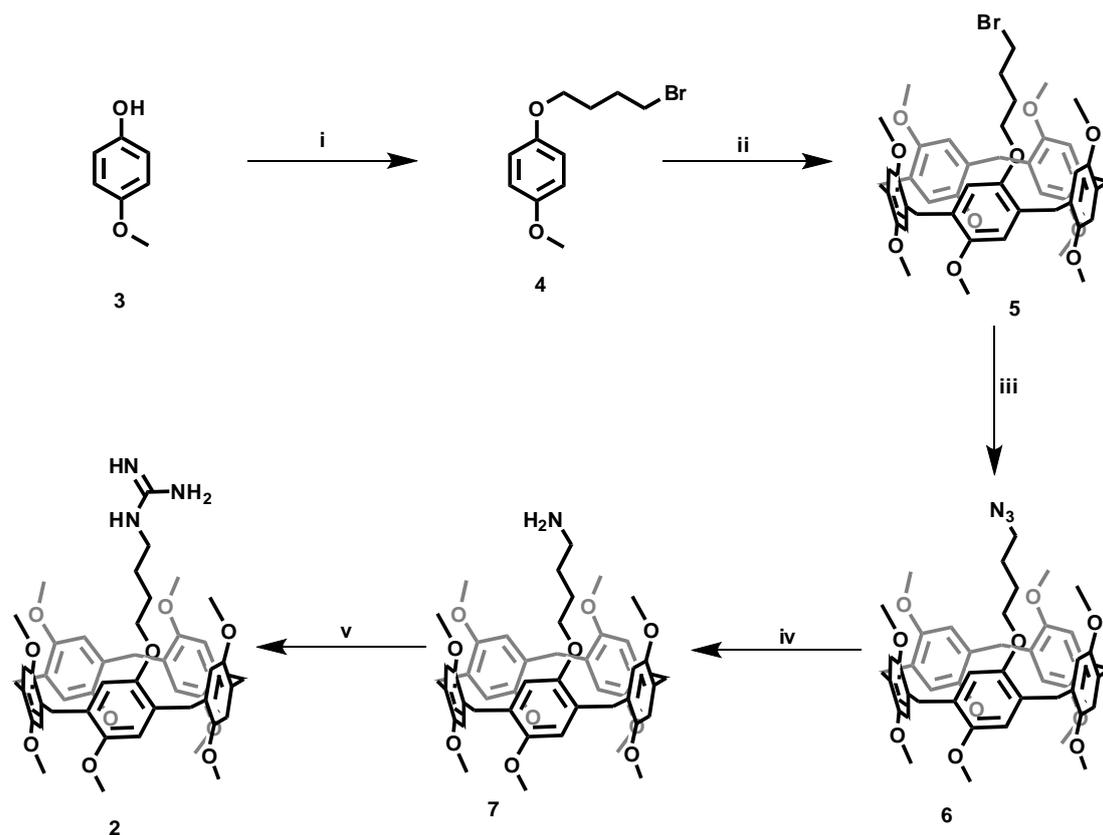


Figure 1. An example of pillar[n]arene family: dimethoxypillar[5]arene 1 and depicting representation of the first synthesized guanidine-based copillar[5]arene 2.

Results and Discussion

Several strategies are available for synthesizing guanidines from various starting materials. Guanidines are generally prepared via guanidinylation reactions of amines¹⁰. Reaction of thioureas and amine to give guanidines also represents a viable process that is usually carried out in the presence of a coupling reagent¹¹. We were interested in the use of azide as the source of amine as introduction of azide functionality in co-pillar[5]arene was rather easy. The general sequence of our guanidinium-based co-pillar[5]arene is illustrated in **Scheme 1**. At first, the alkylation of 4-methoxyphenol **3** with 1, 4-dibromobutane was performed to produce **4**. The acid-dependent

synthesis of bromo-functionalized co-pillar[5]arene **5** was carried out with compound **4** and 1, 4-dimethoxybenzene in presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$. The substitution of bromine by sodium azide proceeded smoothly to give azido-containing co-pillar[5]arene **6** which was subsequently reduced under H_2 and catalytic amount of Pd/C in MeOH:DCM (1:1, v/v) at room temperature to give amino-functionalized co-pillar[5]arene **7**. The use of guanylating reagent 1-amidinopyrazole hydrochloride provided co-pillar[5]arene **2** in one step under mild reaction conditions. More importantly, the gram-scale reaction could be carried out successfully and efficiently to give desired product **2** in high yield under mild reaction conditions.



Scheme 1. Synthesis of Compound 2 (i) 1,4-dibromobutane, K_2CO_3 and KI in acetonitrile, $81^\circ C$; (ii) 1,4-dimethoxybenzene, $(CH_2O)_n$ and $BF_3 \cdot Et_2O$ in DCM, $0^\circ C$; (iii) NaN_3 in DMF, $90^\circ C$; (iv) Pd/C (10%), H_2 in methanol and DCM, R.T.; (v) 1-Amidinopyrazole Hydrochloride, DIPEA in methanol and DCM, R.T.

Since many of biological processes take place in water, the synthesis of water-soluble receptors is of great interest in biological sciences. This first description of synthesis of compound **2** makes water soluble, guanidinium-based pillar[*n*]arenes attractive for studies related to understanding of biological processes. The pillar[*n*]arenes are cavity containing compounds and can easily be functionalized at both rims and thus, they represent a molecular scaffold that can be used to build artificial receptors. We have been investigating the biological applications of this new generation of pillar[*n*]arenes to understand the biological processes. Further studies in this direction are undergoing in our research laboratory and new findings will be reported in coming days.

Conclusions

In conclusion, we have synthesized the first generation of guanidine-containing pillar[5]arene that can be acidified into guanidinium-based

pillar[5]arene. The synthesis represented in this paper is simpler and uses mild reaction conditions which open new avenues for gram-scale synthesis of different class of guanidinium-based pillar[*n*]arenes. The guanidinium-based pillar[*n*]arenes represent a milestone development due to their pillar-structure which increases the number of functionality, and capacity to drive the directionality and specificity of the interactions with a wide range of biomolecules. Furthermore, guanidine-based pillar[*n*]arenes can also be used as catalysts for various chemical transformations. The new findings will establish the wide applicability of guanidine-based pillar[*n*]arenes in the areas of chemical biology and catalysis.

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Supplementary Information: The experimental details, ¹H-NMR, ¹³C-NMR and Mass data are available via the “Supplementary Content” section of this article’s webpage.

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