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Thiophene-based macrocycles via the Suzuki–Miyaura cross coupling reaction

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ABSTRACT

Suzuki–Miyaura cross coupling reaction was used for access to new macrocycles exhibiting oligoethyleneoxide bridges and embedding bithiophene, terthiophene or 3,7-bis(thiophen-2-yl)-*N*-ethyl-10*H*-phenothiazine units. The synthesis was performed under various reaction conditions and different coupling types in order to establish the correlation between yields and employed solvents and bases. The structure of the compounds was supported by single crystal X-ray diffractometry, NMR, and MS experiments.

1. Introduction

The aryl–aryl cross coupling reactions has a spectacular development in recent decades, becoming arguably the most important and easiest way to access new C–C bonds.[1] Despite the increasing interest in the classic Suzuki reaction and its improvements,[2] and the continuously larger number of macrocyclic compounds,[3] there are relatively few works dedicated to the synthesis of macrocycles using the Suzuki-type (cross-)coupling procedure.

To date, the groups of D. A. Schlüter,[4] T. J. J. Müller,[5] R. Jasti,[6] and Z. Bo[7] have reported many successful Suzuki cross coupling procedures for access to macrocyclic compounds, all of them with rigid structures. In other cases, procedures inspired by the Suzuki reaction were used for intramolecular macrocyclizations, but access to the appropriate substrates (for the coupling reactions) was quite difficult requesting several synthetic steps.[8] Palladium (Pd^0) mediated synthesis of some cyclophanes was also reported.[9] The reaction of alkylidene diboronic esters with dihalogenoaromatic derivatives in order to give [*n*]cyclophanes (1+1 reaction) led also to the corresponding [*n.n*]cyclophanes (2+2 reaction), however in both cases, the reported yields were low.[9a] The cyclophane with two porphyrin units connected by two phenothiazine bridges obtained in the reaction of a bis(bromoaryl)porphyrin with the 3,7-diboronic-dipinacolate of *N*-methylphenothiazine revealed a high ability for the formation of host guest complexes with C_{60}.[9d]

On the other hand, thiophene derivatives have emerged as important targets for materials science, as they can easily electropolymerize to give conducting polymers. Macrocyclic thiophenes or polythiophenes were developed in order to take advantage of the specific binding ability of macrocycles towards different cations and to examine the possibility of the development of new electrochemical sensors. The main investigated structures reported in the literature are compounds bearing macrocycles attached through a chain to the thiophene units,[10] thiophenomacrocycles,[11] or macrocyclic compounds embedding bithiophene,[12] terthiophene,[13] quaterthiophene or sexithiophene entities.[14]

The dibrominated derivatives of thiophene itself,[15] of bi- and terthiophene[16] as well as of 10-ethyl-3,7-dithienyl-10*H*-phenothiazine (see Supplementary data) are easily accessible and thus, considered as attractive candidates for macrocyclization reactions by Suzuki cross-coupling procedures.

In this context, we considered it to be of interest to investigate different strategies for the synthesis of macrocycles I, II, and III (Chart 1) using Suzuki–Miyaura cross coupling reaction and to

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obtain new host molecules through direct connection of different aromatic building blocks.

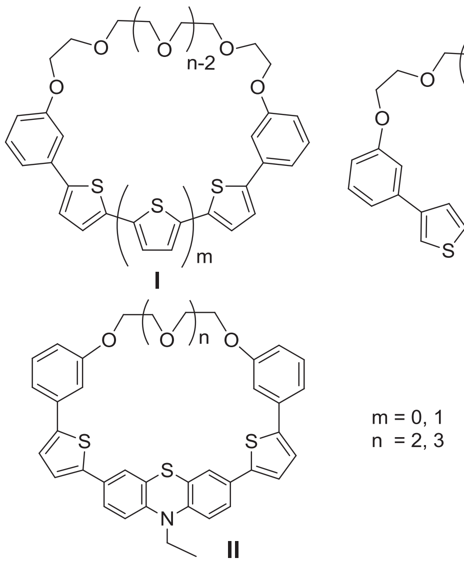
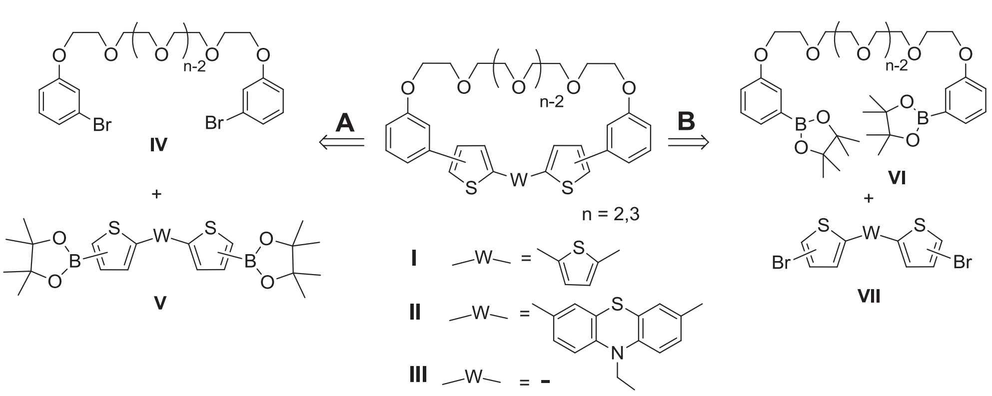


Chart 1.

2. Results and discussion

Two approaches for the rapid access to thiophene-based macrocycles I–III were considered (A and B; Scheme 1). One of the strategies (A) envisaged the preparation of the corresponding diboronic diester of thiophene derivatives V, followed by their reaction with the dibrominated compounds bearing oligo(ethylene-oxide) units IV. The other approach (B), which appears to be more tempting, was based on the cross-coupling reaction of diboronic diesters containing oligo(ethylene oxide) bridges VI with dibrominated thiophenes VII (Scheme 1). In both cases high-dilution was employed and the concentrations of the reagents were of 5 mM. The MS investigations of the row products did not reveal the formation of oligomers (dimers, trimers).



Scheme 1. Strategies for access to macrocycles **I**–**III**.

The macrocyclization reactions using approach A are shown in Schemes 2–4. In order to determine the most favorable conditions for the aryl–aryl cross-coupling reactions of these substrates, different experimental conditions for the Suzuki–Miyaura reaction (strategy A), generated by the modification of the employed solvents and bases (Table 1), were studied for the target macrocycles **6**, **7**, and **11**. The investigated mixtures of solvents were diglyme/water and DMF/water and the considered bases (playing also the template role) were Cs_2CO_3 and K_2CO_3 (both recommended in the literature).[5a,17] Analysis of data of Table 1 reveals better results for all investigated substrates when diglyme/water and Cs_2CO_3 were used. These reaction conditions were further used for all syntheses, following either A or B strategies.

Table 1
Yields of macrocycles **6**, **7**, and **11**, obtained under different reaction conditions using strategy A

No.	Reaction conditions		Yields (%)		
	Solvent	Base	**6**	**7**	**11**
1	Diglyme/H_2O (5/1)	K_2CO_3	13	22	17
2	Diglyme/H_2O (5/1)	Cs_2CO_3	27	33	34
3	DMF/H_2O (5/1)	Cs_2CO_3	19	26	20

The cross-coupling reaction of thiophene diboronic diester **1** with dibrominated derivatives **4** or **5** failed and no macrocyclic coupling product could be isolated (Scheme 2). The reaction of bithiophene diboronic diester **2** with the larger podand **5** successfully led to macrocycle **6**, while its reaction with the shorter podand **4** failed to form the macrocyclic compound. Contrarily, the larger diboronic diester **3** gave the target macrocycles **7** and **8** in its coupling reaction with both podands **4** and **5**, respectively. The different results recorded for macrocyclization of bithiophene and terthiophene diboronic diesters **2** and **3** with podands **4** and **5** can be correlated with the geometry of the diphenyl-polythiophene entities and the better fitting between the size of the thiophene substrates and the length of the chains in podands **4** or **5**.

This assumption was further confirmed by the synthesis of macrocycles **11** and **12** (Scheme 3), which were obtained from 3,7-dithiophenyl-*N*-ethyl-10*H*-phenothiazine diboronic diester **10** with both considered dibrominated podands **4** and **5**, higher yields being recorded for macrocycle **11** having the smaller cavity.

The 4,4′-bithiophene diboronic diester **13** reacted with podands **4** and **5** in a manner similar to that observed for its isomer **2**. No formation of macrocycle was recorded for the shorter podand **4**, while the reaction with **5** gave macrocycle **14** in 18% yield.

In addition to the investigations of the reaction conditions (Table 1), the ‘one pot’ reaction (strategy A) was tested starting from dibrominated compound **9** (see Supplementary data). During this procedure, the diboronic diester **10** was not isolated, while THF was