Small heterocyclic molecules are in interminable demand due to their wide range of applications in many areas of chemistry. The synthesis of these privileged structures gains additional significance when these are used as building blocks of complex molecular scaffolds. For applications spanning from pharmaceuticals, materials science, nanotechnology and others, as the requirement of new chemical entities with varied substitution pattern on a molecular scaffold increases, the traditional methods available for their construction may lack practicability. Additionally, synthesis of substituted scaffolds requires multistep sequences and repeated use of solvents. Further, reagents are invariably not fully incorporated into the products and the reactions suffer from diminishing overall yields. Straightforward approaches enabling rapid synthesis of the functionalized compounds, avoiding multi-step syntheses as well as repeated construction of the core-structure offers synthetic advantage. A viable alternative to the multistep syntheses for the synthesis of complex macromolecules would be to stitch the available building blocks, prefunctionalized with the required substituents or better, following a post-decoration approach, a pre-formed macroring core can’t be functionalized. In this investigation, our aim has been to develop new strategies for the synthesis of meso-elaborated di(heterocyclyl)methane derivatives which are important synthons. Also, we have undertaken regioselective meso-functionalization of sulfur bridged 5,16-dihydro[22]annulene(2.1.2.1)s and hexamethoxycalix[6]arenes to obtain functionally decorated molecules of considerable significance.

Chapter 2. Review of literature

This chapter presents a brief discussion on the synthesis of di(pyrrol-/furan-/thien-2-yl)methanes and summarizes the scope and limitations of the most relevant synthetic methodologies furnishing these products in a variety of reaction conditions.

Chapter 3. Synthesis of meso-substituted di(heterocyclyl)methane building blocks

Di(heterocyclyl)methanes such as di(pyrrol-2-yl)methanes, di(furan-2-yl)methanes, di(thien-2-yl)methanes and related systems constitute important building blocks for the synthesis of important cyclic conjugated chemical entities as well as fluorescent boron-
dipyrrromethene (BODIPY) dyes. For example, di(pyrrol-2-yl)methanes are key intermediates of synthetic porphyrins as well as their core-modified analogues (Figure 1). Likewise, di(furan-2-yl)methanes are structural constituents of dicationic tetraoxaporphyrins as well as other categories of macrocycles such as calix[n]furans (Figure 1). Additionally, these are also of interest to food and beverage industry as well as show interesting biological effects. Likewise,

Figure 1. Synthetic porphyrins and core-modified porphyrinoids derived from di(pyrrol-2-yl)methanes, di(furan-2-yl)methanes and di(thien-2-yl)methanes.
Summary

Thiophene analogues are widely used as intermediates for sulfur bridged annulenes and porphyrinoids (Figure 1), pharmaceuticals, conducting polymers, liquid crystals, novel porphyrinoids, molecular machines, molecular switches and a variety of material science applications.

Di(indol-3-yl)methane and their derivatives have received significant attention due to their presence in bioactive metabolites, marine origin and are also known for their biological activity. Their oxidized forms are utilized as dyes as well as colorimetric sensors for the detection of different analytes.

Generally, two types of methods have been used for the synthesis of di(heterocyclyl)methane derivatives. The widely used approach for the synthesis of di(heterocyclyl)methane derivatives, relies on a one-pot condensation of heterocycles and desired aldehydes in acidified solvents. Essentially, in these methods, the condensation reaction completes only when large excess of the expensive heterocycle is employed to drive the reaction to completion and to suppress the formation of unwanted linear/cyclic oligomers and/or by-products of carbonyl counterparts. Another method involves the use of different protic acids and Lewis acids which are known to catalyse these types of condensations. The protic acids (e.g. HCl and H₂SO₄) and Lewis acids (e.g. BBr₃ and BF₃) which are generally used as catalysts are hazardous and difficult to handle and remove from the reaction mixture. Several other catalysts are not readily available or are expensive.

Keeping in mind limitations (i.e. limited availability of carbonyl components for the condensation process, use of expensive heterocycles in excess (upto 400 equiv.) which leads to the formation of oligomeric products and lower yields of products) of many synthetic methodologies reported in the literature, we planned to synthesise di(heterocyclyl)methane derivatives using:

(i) Addition of Grignard reagents to pyrrole/furan-2-carboxaldehydes followed by Lewis acid catalysed condensation with pyrrole/N-methyl pyrrole.

(ii) Recyclable Amberlyst-15 catalysed condensation of heterocycles or electron rich arenes with aldehydes under solvent-less reaction conditions.

The outcome of these reactions is briefly mentioned below.
(i) **Addition of Grignard reagents to pyrrole/furan-2-carboxaldehydes and condensation with pyrrole/N-methyl pyrrole**

Pyrrole/furan-2-carboxaldehydes 1/2 were prepared in near quantitative yield through Vilsmeier-Haack formylation [DMF/POCl$_3$] of pyrrole and furan respectively. We envisaged that a Grignard reagent upon reaction with pyrrole/furan-2-carboxaldehydes would yield carbinol 3 which could be condensed with pyrrole 4 or N-methyl pyrrole 5 under acid catalysed reaction conditions to obtain corresponding di(heterocyclyl)methanes 6 (Scheme 1).

![Scheme 1](image)

**Scheme 1.** Outline of synthesis of di(heterocyclyl)methane derivatives.

It was observed that the best optimal condition for the formation of carbinol 3 was found to be the addition of 2.0 mmol of Grignard reagent to pyrrole/furan-2-carboxaldehydes at 0 °C. The attempted isolation of the carbinol revealed instability as it readily decomposed during work-up procedure. Therefore, 3 was not isolated and was condensed *in situ* with pyrrole 4/5 (10 mmol) at 10 °C under acid (BF$_3$OEt$_2$) catalysed conditions to obtain 6 in synthetically useful manner. All products have been fully characterized using spectroscopic as well as microanalytical data.

The key findings of this investigation are summarized below:

(i) In general, the reactions were quite smooth when performed using the optimized reaction conditions.

(ii) The yields in general were comparable or even superior to the methods reported in literature.

(iii) The reactions proceeded in a regioselective manner without using larger (400 fold) excess of pyrrole in the condensation with aldehydes which is an established route for synthesising di(pyrrol-2-yl)methanes.
(iv) Further, the reaction conditions are mild and the method has operational simplicity. No oligomer formation was detected under the optimized reaction conditions in most of the cases.

(v) A number of aliphatic chains have been incorporated at the meso-positions which are otherwise difficult to append through aldehyde condensation approach.

(ii) Recyclable Amberlyst-15 catalysed condensation of heterocycles or electron rich arenes with aldehydes under solvent-less reaction conditions

The Grignard addition method described in the preceding section addresses many limitations of the conventional methods using aldehyde condensation routes. However, to drive the condensation reaction of the carbinol 3 (Schemes 1) with 4/5 to completion, using BF$_3$.OEt$_2$ as catalyst, excess of 4/5 (nearly 10 mmol) was required which furnished uncharacterized oligomeric products in some reactions along with the desired product which indirectly decreased the yield of the required products. Although, the reaction conditions are mild but the limited availability of Grignard reagents of alkyl halides limits the scope of the method. In order to overcome such limitations, synthesised meso-elaborated di(heterocyclal)methanes through the use of easily available, cheap, recyclable catalyst Amberlyst-15 in the condensation of large number of easily available aromatic aldehydes with electron rich heterocycles.

Using optimized reaction conditions, we employed Amberlyst-15 ion exchange resin as a catalyst for performing condensation reaction of thiophene, pyrrole, N-methyl pyrrole, furan, indole, N-methyl indole with a number of aldehydes (Scheme 2) to obtain di(heterocyclal)methanes, in a synthetically useful manner. The reactions (vide infra) were performed under

Scheme 2. Condensation of electron rich heterocycles with aldehydes.
mild conditions, using stoichiometric amounts of the reactants without any solvent. The products (14-19) (Table 1) have been isolated after column chromatographic purification and characterized using spectroscopic techniques as well as microanalytical analysis.

Table 1. Amberlyst-15 catalysed condensation of heterocycles (7-12) with aldehydes 13.

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<tr>
<th>ArCHO Ar</th>
<th>Thiophene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Pyrrole&lt;sup&gt;b&lt;/sup&gt; 8</th>
<th>N-Me Pyrrole&lt;sup&gt;b&lt;/sup&gt; 9</th>
<th>Furan&lt;sup&gt;c&lt;/sup&gt; 10</th>
<th>Indole&lt;sup&gt;d&lt;/sup&gt; 11</th>
<th>N-Me Indole&lt;sup&gt;d&lt;/sup&gt; 12</th>
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<sup>a</sup> (3.0 mmol), <sup>b</sup> (1.0 mmol), Amberlyst-15 (0.02 g), 80 °C, 20-30 min; <sup>c</sup> (3.0 mmol), <sup>d</sup> (1.0 mmol), Amberlyst-15 (0.02 g), 80 °C, 2-3 min.; <sup>c</sup> (5.0 mmol), <sup>d</sup> (1.0 mmol), Amberlyst-15 (0.02 g), 25 °C, 3h; <sup>d</sup> (3.0 mmol), <sup>d</sup> (1.0 mmol), Amberlyst-15 (0.02 g), 80 °C, 15 min.

The recyclability of the catalyst was also noted for these reactions and it was found that the catalyst could be recycled for at least five batches without significant loss in its activity, an observation which is relevant to commercial applications.

Extending the synthetic utility of the meso-functionalization approach, we planned to undertake synthesis of meso-bridged di(heterocycl) methane derivatives by single-step
condensation reaction of terephthalaldehyde 13y with electron rich species such as thiophene 7, pyrrole 8, N-methyl pyrrole 9, furan 10, indole 11 and N-methyl indole 12. Such intermediates are of immense synthetic significance in the synthesis of meso-linked novel porphyrinoids and other categories of cyclic conjugated entities. However, direct condensation of 1.0 mmol of 13y with 3.0-4.0 mmol of 7-12 using Amberlyst-15 as catalyst furnished corresponding di(heterocyclyl)methanes 20-25. Condensation of the 20, with heterocycles furnished both symmetrical as well as unsymmetrical meso-linked di(heterocyclyl)methane derivatives 26-30 (Scheme 3). All products have been fully characterized using spectroscopic as well as microanalytical data.


The outcome of this investigation can be summarized as under:

(i) Synthetically useful applicability of Amberlyst-15 catalysed, solvent-free protocol for the synthesis of 5-substituted di(heterocyclyl)methanes and meso-linked di(heterocyclyl)methanes has been demonstrated.
Chapter 5

(ii) The method showed considerable tolerance to the substitution variation on the aromatic aldehydes.

(iii) The products were obtained in high yields and without noticeable formation of side products such as oligomers.

(iv) Near stoichiometric amounts of the reactants were used in the condensation reactions and reactions completed in reasonably shorter time.

(v) The catalyst is recyclable and is economical, a feature of considerable concern in the industrial processes.

Chapter 4. Regioselective, direct meso-functionalization of macrocyclic entities

Small sized macrocyclic entities constitute key structural elements in applications ranging from host-guest chemistry, supramolecular analyte recognition, diversity oriented synthesis of biomolecules and opto-electronic applications. However, using classical macrocyclization reactions, efficient and systematic access of suitably substituted macrocycles face many limitations. One of the attractive approaches for obtaining differently functionalized macrocycles is to start with the macrocyclic core and to decorate it with appropriate substituents in a single-step chemical transformation. However, it is usually considered a formidable task owing to vulnerability of the macrocycle sub-units to the reagents used and/or issues related to regioselectivity of the functionalization step.

In this investigation, we have undertaken structure elaboration of two types of macrocyclic entities, which are important in their own right and, herein, the results are presented in the form of two sections.

(i) Regioselective lithiation-substitution of sulfur bridged 5,16-dihydro[22]annulene (2.1.2.1)

Porphyrinoids have attained undisputed status in the supramolecular chemistry and material science. Compared to the corresponding linear oligomers and polymers, cyclic conjugated compounds have outstanding characteristics, combining the well-defined structure of the oligomers and the infinite \( \pi \)-conjugated chain of the polymers, but excluding perturbing end-effects. Consequently, such compounds possess interesting optical and electronic properties in areas such as photodynamic therapy, artificial photosynthesis, dye sensitized solar cells, organic semiconductors, organic light emitting diodes, two photon absorbing materials and non-linear
optical materials etc. Aromaticity of these cyclic conjugated chemical entities in terms of cyclic
delocalization of the mobile electrons is a distinctive feature implicated in the understanding of
structural, photophysical, electronic and magnetic properties.

![Scheme 4](image)


Starting material i.e. *meso*-unsubstituted sulfur bridged 5,16-dihydro[22]annulene (2.1.2.1) 31 was prepared by the most commonly employed route i.e. through McMurry coupling (Scheme 4) of *meso*-unsubstituted diformylated di(thien-2-yl)methanes using Zn dust with TiCl₄ and pyridine in refluxing THF.

It was observed that using dimsyl anion (2.5 mmol) [generated from DMSO (2.5 mmol) and *n*-BuLi (2.5 mmol) in anhydrous THF] at 0 °C, under inert atmospheric reaction conditions, *meso*-dianion could be generated, which upon quenching with suitable electrophile (3.0 mmol)

![Scheme 5](image)

Scheme 5. Lithiation-substitution of *meso*-unsubstituted sulfur bridged 5,16-dihydro[22] annulene(2.1.2.1).
Chapter 5

furnished corresponding *meso*-functionalized sulfur bridged 5,16-dihydro[22]annulene(2.1.2.1) derivatives (Scheme 5), in a synthetically useful manner.

The outcome of this investigation can be summarized as under:

(i) A highly efficient and useful method for the *meso*-elaboration of the sulfur bridged 5,16-dihydro[22]annulene(2.1.2.1)s using dimethyl anion (obtained from *n*-BuLi and DMSO) has been achieved.

(ii) The reactions proceed with good regioselectivity and furnished product in good yield (50-55%).

(iii) Good understanding of the lithiation process of these macrocycles was revealed and the methodology avoided the use of vulnerable carbonyl components in the process to synthesised various *meso*-substituted di(thien-2yl)methane building blocks.

(iv) On the whole, this work represents unprecedented direct functionalization of heteroannulene framework and can be purported to be a general protocol.

Oxidation of the resultant *meso*-functionalized sulfur bridged 5,16-dihydro[22]annulenes 32 (R = Et) (Scheme 6) was attempted using 3,4-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) followed by treatment with hydrazine. The UV-vis. spectrum of the crude product showed sharp bands at λ<sub>max</sub> 434, 603, 782 nm corresponding to the Soret and Q-type bands, typical of porphyrinoids. However, even upon repeated attempts, 33 could not be isolated. We suggest that 33 is not very stable presumably due to the presence of ethyl groups at the *meso*-position of 32b which in turn might slow down the rate of conformational motion making it difficult to access the near planar geometry required for oxidation and aromatization of 32 (R = Et).

![Scheme 6. Attempted oxidation of 5,16-dihydro[22]annulene(2.1.2.1)s using DDQ.](image-url)
Regioselective lithiation-substitution of hexamethoxycalix[6]arenes

Calix[n]arenes are a class of cyclic oligomers formed upon phenol-formaldehyde condensation, with defined upper and lower rims and a central annulus. The increasing interest in these macrocycles is not mainly due to the possibility of shaping their cavities through functionalization at the lower rim (phenolic OH groups) or at the upper rim (aromatic nuclei) and the methylene region. In contrast to the large number of known synthetic routes allowing the chemical modification of the calix scaffold at the upper rim or lower rim, only a handful of methods are known allowing the incorporation of substituents at the methylene bridges. Such modifications are of interest since the substituents at the bridges may modify the physical and chemical properties of the macrocycle, and may pre-organise and rigidify the calix skeleton in a desired conformation. This part of Chapter 4 focuses on the development and applicability of a deprotonative lithiation-substitution reaction sequence for forming new carbon-carbon bonds at meso-carbon of calix[6]arenes which constitute an important synthetic operation.

Starting material i.e. 5,11,17,23,29,35-hexakis(1,1-dimethylethyl)-37,38,39,40,41,42-hexahydroxycalix[6]arene 34 was prepared by the base-catalysed condensation of \( p-t \)-butylphenol with formaldehyde (Scheme 7).


It was observed that use of \( n \)-BuLi:TMEDA (8 mmol) in THF, at ambient temperature generated meso-dianion which upon quenching with electrophiles (8.1 mmol) furnished the 2,20-disubstituted calix[6]arenes 36 (Scheme 8) in good yield. The structure of 2,20-diethyl substituted calix[6]arene \( 36a \) was further confirmed from 2D-NMR experiments, single-crystal X-ray analysis as well as supported by quantum mechanical calculations. All these reactions
have been conducted under inert atmospheric conditions and at room temperature using hypodermic syringes, single necked, septum capped and flame dried flasks. The products 36a-f have been isolated after column chromatographic purification and characterized using spectroscopic techniques as well as microanalytical analysis.


In summary,

(i) We have developed a direct and short route to synthesise meso-disubstituted calix[6]arenes.

(ii) Reactions proceed with high regioselectivity as only the desired 2,20-disubstituted products were formed in good yields (60-75%).

(iii) This investigation presents a good understanding of the lithiation process of these important macrocycles and an effective alternative to obtain meso-elaborated calix[6]arenes.

Thus, overall in this thesis, we have reported straightforward approaches to synthesise meso-elaborated di(pyrrol-2-yl)methanes building blocks for porphyrinoids, as well as a number of di(heterocyclyl)methanes using different heterocycles. We have also reported single-step, highly regioselective functionalization of sulfur bridged 5,16-dihydro[22]annulene (2.1.2.1)s and hexamethoxycalix[6]arenes in a synthetically useful manner.