4.1 Introduction

In parallel with the developments in the chemistry of synthetic porphyrins and derivatives, as presented in chapter 3, structural variations of the pyrrolic macrocycles by way of using furan, thiophene and imidazole subunits, in such a manner that the π-electron conjugation pathway is maintained, has given rise to potentially rich family of neutral as well as charged isologues (Figure 1).

![Figure 1](image)

Diverse electrochemical and physio-chemical properties\(^2\) of these molecules prompted investigations varying from the development of new synthetic methodologies, to the study of molecular complexation of charged or neutral guests, development of ion recognition and binding selectively particularly of furan analogues to various metal cations.\(^3\) However, the chemistry of furan containing macrocycles has received little attention. Especially compounds of type 1-5 are extremely less understood.\(^3,5\) Further, no general route for meso-functionalization of 2-4 are known. The synthesis of 1-3 has been achieved by standard McMurry coupling reaction\(^6\) and/or Witting reaction\(^5,7\) of
Chapter 4

Bis(furan-2-yl)methane derivatives constitute key intermediates for the synthesis of all 2-5 derivatives. Additionally, bis(furan-2-yl)methane derivatives are of interest to food industry as they are present as natural compounds in food and beverage items such as licorice. These are also flavor agents in coffee. Such derivatives find various industrial applications. Some derivatives e.g. polyketides, exhibit interesting biological effects also. Furthermore, bis(furan-2-yl)alkanes are important intermediates in the synthesis of various macromolecules. Bis(furan-2-yl)methanes have also been found to be good substrates for cycloaddition reactions with oxyallyl cations.

The first report on the synthesis of bis(furan-2-yl)methane appeared in 1932 in which furylmagnesium bromide was reacted with 2-cyanofuran to obtain difurfylketone derivative (Scheme 1), which upon metal reduction furnished bis(furan-2-yl)methane 6 (R² = R³ = H).

![Scheme 1](image)

Likewise, 2-chloromercury furan reacts with furfuryl chloride, possessing highly reactive halogen to furnish 6 (R¹ = R² = R³ = H). Another method employed for the synthesis of 6 involves treatment of ethyl furate with trioxane in the presence of sulfuric acid. Subsequent saponification, hydrolysis and decarboxylation furnishes 6 (R¹ = R² = R³ = H). Bis(furan-2-yl)methane has also been isolated as a product during the acid catalyzed resinification of furfuryl alcohol. Formation of 2,2-difurylpropane 6 (R¹ = H, R² = R³ = Me) has been reported through the condensation of furan with acetone in the presence of hydrochloric acid. Furan also condenses with aldehydes and ketones to furnish corresponding 6 (R¹ = H, R² = R³ = H, alkyl). The synthesis through reaction of a (heteroaryl)lithium with a (heteroaryl)methyl chloride requires severe conditions. However, all these synthetic methods are low yielding, requiring lengthy procedures. The first high yielding synthesis of 6 (R¹ = R² = R³ = H) was reported in 1989 wherein 6 (R¹ = R² = R³ = H) was obtained in 60% yield through the
use of strongly acidic cation exchanger, Amberlyst 15, as catalyst in the condensation of furfuryl alcohol and furan.\textsuperscript{20}

In the context of structural diversification at the inter ring carbon (meso-position),\textsuperscript{*} the first general synthesis was achieved only through the condensation of 2-methyl furan with different aldehydes;\textsuperscript{21} but the approach has not been extended to unsubstituted furan derivatives. Thus condensation of 2-methyl furan and aldehydes in the presence of a macroporous resins either in the phosphonic, carboxylic or sulphonic forms proceed with facility. In a related acid catalyzed condensation reaction using a mineral acid (HCl, 35%), furan and formaldehyde were condensed to obtain 6 (R\textsubscript{1} = R\textsubscript{2} = R\textsubscript{3} = H) albeit in 13\% poor yield.\textsuperscript{8b} Using a benzotriazole as a synthetic auxiliary, Katritzky has reported\textsuperscript{22} a convenient method for the synthesis of bis(furan-2-yl)methane derivatives 6 (R\textsubscript{1} = Me, R\textsubscript{2} = i-Pr, Ph, R\textsubscript{3} = H).

Reaction of furan and 2-hydroxyethyl furan using lewis acidic conditions yielded 6 (R\textsubscript{1} = R\textsubscript{2} = R\textsubscript{3} = H) along with oligomers.\textsuperscript{23} 6 (R\textsubscript{1} = R\textsubscript{2} = R\textsubscript{3} = H) was also obtained via the reaction of 2-furyl lithium with bromochloromethane or reaction with 2-furaldehyde followed by \textit{in situ} reduction of the resulting lithium alkoxide with NaBH\textsubscript{4} and TFA.\textsuperscript{23} Use of catalysts such as BF\textsubscript{3}OEt\textsubscript{2}, TiCl\textsubscript{4}, TFA, AlCl\textsubscript{3} etc. has been reported for obtaining 6 (R\textsubscript{1} = H, R\textsubscript{2} = Ph, R\textsubscript{3} = H) through the condensation of furan and aldehydes.\textsuperscript{12a,24} Similarly AuCl\textsubscript{3} promoted condensation of 2-methyl furan and various aldehydes furnished \textit{meso}-aryl substituted bis(furan-2-yl)methane 6 (R\textsubscript{1} = Me, R\textsubscript{2} = Ph, R\textsubscript{3} = H), in practically good yield.\textsuperscript{25} Recently, bis(furan-2-yl)methane 6 (R\textsubscript{1} = Me, R\textsubscript{2} = Aryl, R\textsubscript{3} = H) derivatives have been synthesized through the condensation of 2-methyl furan and benzaldehyde using Yb(OTf)\textsubscript{3} as catalyst under solvent-free conditions.\textsuperscript{26}

This brief but complete update on the methods of synthesis of bis(furan-2-yl)methane derivatives 6 (R\textsubscript{1} = Me, mainly) points to the limitation of availability of a general and practicable method for \textit{meso}-elaboration of bis(furan-2-yl)methanes, especially in the context of appending alkyl substituents at the \textit{meso}-position. Also all these methods involve use of aldehydes under a variety of acid catalysts which not only provide the desired compounds in low yields but also are prone to oligomer formation in some cases.

\textsuperscript{*}See footnote, page 71 (Chapter 3).
In light of this, and our past experience on meso-elaboration of dipyrromethane (Chapter 3), we envisaged an analogous approach involving meso-lithiation of preformed bis(furan-2-yl)methane (Scheme 2), followed by quenching using a variety of electrophiles to obtain meso-elaborated bis(furan-2-yl)methane derivatives in high yields.

![Scheme 2]

The results of this hypothesis are presented in the following three sections.

4.2 Optimization of reaction conditions for meso-lithiation of bis(furan-2-yl)methane

4.3 Synthesis of meso-functionalized bis(furan-2-yl)methane derivatives

4.4 Formation of C-5 functionalized bis(furan-2-yl)methane derivatives

4.2 Optimization of reaction conditions for meso-lithiation of bis(furan-2-yl)methane

meso-Unsubstituted bis(furan-2-yl)methane 6 (R1 = R2 = R3 = H) was synthesized through condensation of furan and formaldehyde in an acid catalyzed reaction.24 6 has been well characterized using spectroscopic and other techniques (vide experimental).

With an experience of meso-lithiation of dipyrromethane (Chapter 3), we analogously examined the metalation of 6 with lithium bases and subsequent quenching with electrophiles to determine the optimal conditions for meso-metalation. To achieve this aim, 6 was treated with n-BuLi (1.0 equiv.) at low temperature (-78°C and 0°C), under the blanket of purified anhydrous N2 gas, followed by quenching with benzaldehyde (1.5 equiv.). In both of these cases, unreacted 6 (50-60%) along with uncharacterized polymeric material was obtained after aqueous workup of the reaction mixture with saturated ammonium chloride solution. Change of solvent (Table 1) from anhydrous THF to diethylether or replacing n-BuLi with lithium diisopropylamide (LDA) did not show the required result. The use of high complexing agents (in equimolar quantity or even excess) such as diisopropylamine (DIPA), tetramethylethylenediamine (TMEDA), the later used in combination with n-BuLi or in THF, also did not produce desired outcome, although successful metalation of the
Central carbon in tris(2-thienyl)methane has been reported to proceed with ease using DIPA in THF at 0°C. A correlation of the pKa values of carbon acids: diphenylmethane (pKa = 32.2), 2-benzylfuran (pKa = 30.2) suggested that upon replacing a phenyl group with furan lowers the pKa. We envisaged a further decrease in pKa if both the aryl rings of diphenylmethane were replaced with furan rings to obtain 6. Thus pKa of 6 could well be lower than pKa of 2-benzylfuran (30.2), which certainly is less than pKa of furan (pKa = 35). We chose to employ THF-DMSO as solvent to generate more basic methylsulfinyl (dimsyl) anion, which being ‘soft’ should effect metalation of the relatively ‘soft’ meso-carbon of 6 as compared to the ‘hard’ C-5 position. Thus, 6 was expected to be metalated at the more acidic and ‘soft’ meso-position prior to the ring CH. Dimsyl anion could be generated in situ by the reaction of n-BuLi and excess DMSO (pKa = 35), the excess DMSO assisting in dispersion of anion aggregates as previous literature suggests. Moreover, the meso-position in 6 may also draw rings of diphenylmethane were replaced with furan rings to obtain 6. Thus pKa of 6 could well be lower than pKa of 2-benzylfuran (30.2), which certainly is less than pKa of furan (pKa = 35). We chose to employ THF-DMSO as solvent to generate more basic methylsulfinyl (dimsyl) anion, which being ‘soft’ should effect metalation of the relatively ‘soft’ meso-carbon of 6 as compared to the ‘hard’ C-5 position. Thus, 6 was expected to be metalated at the more acidic and ‘soft’ meso-position prior to the ring CH. Dimsyl anion could be generated in situ by the reaction of n-BuLi and excess DMSO (pKa = 35), the excess DMSO assisting in dispersion of anion aggregates as previous literature suggests. Moreover, the meso-position in 6 may also draw

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**Table 1.** Optimization of reaction conditions for metalation of 6 with lithium bases.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Solvent&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Reaction Temp. (°C)</th>
<th>Yield (%) 7a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi</td>
<td>THF</td>
<td>-78</td>
<td>---</td>
</tr>
<tr>
<td>2</td>
<td>n-BuLi</td>
<td>THF</td>
<td>-20</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td>n-BuLi</td>
<td>THF</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>4</td>
<td>n-BuLi</td>
<td>Ether</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>5</td>
<td>LDA</td>
<td>THF</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>6</td>
<td>n-BuLi</td>
<td>THF-DIPA (5:5 v/v) THF</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>7</td>
<td>n-BuLi-TMEDA (1.5 equiv.)</td>
<td>THF</td>
<td>-60</td>
<td>---</td>
</tr>
<tr>
<td>8</td>
<td>n-BuLi-TMEDA (1.5 equiv.)</td>
<td>THF</td>
<td>0</td>
<td>---</td>
</tr>
<tr>
<td>9</td>
<td>n-BuLi</td>
<td>THF-TMEDA (5:5 v/v)</td>
<td>-78</td>
<td>---</td>
</tr>
<tr>
<td>10</td>
<td>n-BuLi</td>
<td>THF-DMSO (1:1 v/v)</td>
<td>0</td>
<td>65</td>
</tr>
</tbody>
</table>

<sup>a</sup>1.2 equiv of n-BuLi (2.2 N in hexanes) and LDA (freshly prepared) were used. <sup>b</sup>10 ml.
activation as depicted in figure 2. Further, this type of activation shall impede the deprotonation and subsequent substitution of the furan (C-5) ring positions, imparting regioselectively to the process in favor of meso-substitution. The failure of the non-coordinative LDA to deprotonate (Table 1) either the meso- or C-5 (furan) positions has further supported this hypothesis. Thus, when 6 was treated with n-BuLi (1.2 equiv.) in anhydrous THF/DMSO (1:1 v/v) solution at 0°C, under anhydrous N₂ gas, turbid reddish brown colored solution was generated. Upon addition of benzaldehyde (1.5 equiv.) (Scheme 3) at the same temperature, formation of a product at Rf: 0.27 (ethyl acetate:hexane/10:90) (TLC) was observed.

Scheme 3

The ¹H NMR (CDCl₃) spectrum (Figure 3) of the product depicted signals at δ 2.44 (s, 1H, OH, exchanged with D₂O), 4.41 (d, 1H, J 7.2 Hz, meso-CH), 5.28 (d, 1H, J 7.2 Hz, CH(OH)), 6.01-6.02 (m, 1H, CH), 6.20-6.26 (m, 2H, 2 x CH), 6.34-6.35 (m, 1H, CH), 7.15-7.25 (m, 5H, ArH), 7.28-7.29 (m, 1H, CH), 7.40-7.41 (m, 1H, CH). The disappearance of singlet at δ 3.97 corresponding to meso-CH₂ of 6 and appearance of doublet at δ 4.41, as well as appearance of signals corresponding to the phenyl group

Figure 3. ¹H NMR (300 MHz, CDCl₃) spectrum and ¹³C NMR (75 MHz, CDCl₃) assignments of 7a.
suggested the incorporation of PhCH(OH)- at the meso-position of 6. Its $^{13}$C NMR (CDCl$_3$) spectrum showed corresponding signals at $\delta$ 47.7, 107.7, 108.2, 110.2, 110.4, 126.1, 127.7, 128.0, 141.5, 142.0 and 151.8. In its EIMS, parent ion peak appeared at $m/z$ 276.8, corresponding to molecular formula C$_{16}$H$_{14}$O$_3$+Na for the expected product. Based on the spectral as well as microanalytical data (vide experimental), the product has been assigned the structure, 2,2'-di(furan-2-yl)1-phenylethanol 7a. It was formed in 72% (Table 2) isolable yield.

Further, it was observed that increasing the equivalents of n-BuLi from 1.2 to 3.2, the yield of 7a did not change significantly. However, upon altering the DMSO:THF ratio (Table 2) the isolated yield of 7a varied significantly, and showed a decreasing trend with the increase in the proportions of DMSO keeping the equivalent of base (2.0 equiv.) constant.

**Table 2.** Optimization of reaction conditions for meso-functionalization of 6 with benzaldehyde.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents of base</th>
<th>DMSO:THF (v/v)</th>
<th>Isolated yield 7a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>3:7</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>3:7</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>3.2</td>
<td>3:7</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>2.0</td>
<td>5:5</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>7:3</td>
<td>42</td>
</tr>
</tbody>
</table>

Thus, the optimized conditions, for meso-elaboration of 6 were found to be: n-BuLi 1.2 equiv., DMSO:THF 3:7 v/v, temperature 0°C.

### 4.3 Synthesis of meso-functionalized bis(furan-2-yl)methane derivatives

Using the optimized reaction conditions (n-BuLi, 1.2 equiv./0°C, DMSO:THF/3:7 v/v), we investigated the reaction of metalated 6 with a range of electrophiles (Scheme 4) to obtain meso-elaborated bis(furan-2-yl)methane 7 derivatives.

* See footnote at page 77 (Chapter 3).
Typically, when metalated 6 was quenched with 4-chlorobenzaldehyde, a single product [Rf: 0.30 (ethyl acetate:hexane/10:90)] (TLC) was isolated. The $^1$H NMR (CDCl$_3$) spectrum depicted the signals at $\delta$ 2.42 (d, $J$ 3.3 Hz, 1H, OH, exchanged with D$_2$O), 4.28 (d, 1H, $J$ 7.5 Hz, meso-CH), 5.88 (dd, 1H, $J$ 6.3, 4.8 Hz, CH), 5.94-6.02 (m, 1H, CH), 6.15-6.24 (m, 2H, 2 x CH), 6.26-6.28 (m, 1H, CH), 7.00-7.04 (m, 2H, ArH), 7.12-7.18 (m, 2H, ArH), 7.26 (m, 1H, CH), 7.32-7.33 (m, 1H, CH). Its $^{13}$C NMR (CDCl$_3$) spectrum showed signals at $\delta$ 47.8, 74.9, 107.9, 108.4, 110.3, 110.5, 127.4, 128.1, 141.7, 142.1 and 151.4. In its EIMS analysis, a parent ion peak at $m/z$ 311.5 (M$^+$+23) corresponding to the molecular formula C$_{16}$H$_{13}$ClO$_3$+Na was observed. Based on the spectral and microanalytical data (vide experimental) structure, 1-(4-chlorophenyl)-2,2-di(furan-2-yl)ethanol 7b (Table 3) (65%) has been assigned to this compound.

Likewise, 3,4-dimethoxybenzaldehyde was used as electrophile for reaction with the metalated 6, following the same procedure. The product, 1-(3,4-dimethoxyphenyl)-2,2-di(furan-2-yl)ethanol 7e was obtained in 70% yield (Table 3) and the structure was established from the spectral and microanalytical data (vide experimental).

The behaviour of metalated 6 toward bulky electrophiles was also checked. Thus, when $\beta$-napthaldehyde was used for quenching the metalated 6, and the product 2,2-di(furan-2-yl)-1-(naphthalene-2-yl)ethanol 7d was obtained in 65% yield. The
structure of 7d was established from the spectral and microanalytical data (vide experimental).

Table 3. Synthesis of meso-substituted bis(furan-2-yl)methane derivatives 7.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-Cl-C\textsubscript{6}H\textsubscript{4}CHO</td>
<td>7b</td>
<td>65</td>
</tr>
<tr>
<td>2</td>
<td>3,4-(MeO)\textsubscript{2}-C\textsubscript{6}H\textsubscript{5}CHO</td>
<td>7c</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>β-C\textsubscript{10}H\textsubscript{2}CHO</td>
<td>7d</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>MeCOMe</td>
<td>7e</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>PhCOCH\textsubscript{3}</td>
<td>7f</td>
<td>45</td>
</tr>
<tr>
<td>6</td>
<td>2-Acetylthiophene</td>
<td>7g</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>C\textsubscript{2}H\textsubscript{5}Br</td>
<td>7h</td>
<td>65\textsuperscript{b}</td>
</tr>
<tr>
<td>8</td>
<td>n-C\textsubscript{3}H\textsubscript{3}Br</td>
<td>7i</td>
<td>56\textsuperscript{b}</td>
</tr>
<tr>
<td>9</td>
<td>n-C\textsubscript{4}H\textsubscript{3}Br</td>
<td>7j</td>
<td>83\textsuperscript{b}</td>
</tr>
<tr>
<td>10</td>
<td>BnCl</td>
<td>7k</td>
<td>69</td>
</tr>
<tr>
<td>11</td>
<td>PhNCO</td>
<td>7l</td>
<td>51</td>
</tr>
<tr>
<td>12</td>
<td>PhNCS</td>
<td>7m</td>
<td>30</td>
</tr>
<tr>
<td>13</td>
<td>n-PrSSPr</td>
<td>7n</td>
<td>68</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Isolated purified yields.
\textsuperscript{b}Based on \textsuperscript{1}H NMR (unreacted 6 in entry 7: 35%, entry 8: 44% and entry 9: 17%)

The scope of the current methodology was further extended by using ketones as electrophiles. Using typical reaction conditions, when metalated 6 was quenched with acetone, a product [Rf: 0.36 (ethyl acetate:hexane/10:90)] (TLC) was obtained. In its \textsuperscript{1}H NMR (CDCl\textsubscript{3}) spectrum (Figure 4), signals were observed at δ 1.21 (s, 6H, 2 x CH\textsubscript{3}), 1.61 (s, 1H, OH, exchanged with D\textsubscript{2}O), 4.19 (s, 1H, meso-CH), 6.25-6.26 (m, 2H, 2 x C4-H), 6.33-6.35 (m, 2H, 2 x C3-H), 7.38-7.39 (m, 2H, 2 x C5-H). The presence of singlet at δ 1.21 corresponding to two CH\textsubscript{3} groups ensured the substitution process. Its \textsuperscript{13}C NMR (CDCl\textsubscript{3}) spectrum displayed signals at δ 27.6, 50.4, 108.2, 110.3, 141.6 and 152.6. Its IR (KBr) spectrum was characteristic with the appearance of bands of OH at 3510 cm\textsuperscript{-1} in addition to other absorptions. Additionally, microanalytical data and mass spectrum (m/z 289, M\textsuperscript{+}+23) peaks, corresponded to the molecular formula C\textsubscript{13}H\textsubscript{14}O\textsubscript{3}+Na, and thus led to the assignment of structure, 1,1-di(furan-2-yl)-2-methylpropan-2-ol 7e to this compound isolated in 72% yield (Table 3).
Similar reaction of metalated 6 (Scheme 4) with acetophenone under standardized reaction conditions furnished a product [Rf: 0.30 (ethyl acetate:hexane/20:80)] (TLC). In its $^1$H NMR (CDCl$_3$) spectrum, signals were observed at $\delta$ 1.55 (s, 3H, CH$_3$), 4.00 (s, 1H, OH, exchanged with D$_2$O), 4.54 (s, 1H, meso-CH), 6.02 (m, 1H, CH), 6.19-6.22 (m, 2H, 2 x CH), 6.32 (s, 1H, CH), 7.18-7.25 (m, 5H, ArH), 7.27-7.37 (m, 2H, 2 x CH). Its IR (KBr) spectrum was characteristic with the appearance of bands of OH at 3030 cm$^{-1}$ in addition to other absorptions. On the basis of NMR assignments, EIMS ($m/z$ 291, corresponding to the molecular formula C$_{17}$H$_{16}$O$_3$+23) and correct microanalytical data (vide experimental), structure, 1,1-di(furan-2-yl)-2-phenylpropan-2-ol 7f (45%) has been assigned to this product (Table 3).

Likewise, when 2-acetyl thiophene was used for quenching the metalated 6, product 1,1-di(furan-2-yl)-2-(thiophen-2-yl)propan-2-ol 7g (Table 3) was obtained in 40% yield. The structure of 7g was established from the spectral and microanalytical data (vide experimental).

Use of alkyl halides as electrophiles, to quench metalated 6, also furnished corresponding meso-elaborated products with ease. For example, when ethyl bromide was used, the product [Rf: 0.93 (hexane)] in its $^1$H NMR (CDCl$_3$) spectrum showed the signals at $\delta$ 0.88 (t, 3H, $J$ 7.5 Hz, CH$_3$), 2.02 (m, 2H, CH$_2$), 3.96 (t, 1H, $J$ 7.5 Hz, meso-CH), 6.07-6.09 (m, 2H, 2 x C4-H), 6.29-6.32 (m, 2H, 2 x C3-H), 7.32-7.34 (m, 2H, 2 x C5-H). The appearance of a triplet at $\delta$ 0.88 and a multiplet at $\delta$ 2.02 suggested the
incorporation of ethyl unit. Appearance of a triplet at δ 3.96 supported the meso-substitution of 6. However, due to the low polarity of the product and matching Rf (TLC) with 6, its separation from 6 was tedious and the isolated product was invariably accompanied by varying amount of 6. The contamination could not be removed despite repeated chromatographic purifications and was visible from the persistence of singlet of meso-CH₂ of 6 at δ 4.0 in its ¹H NMR (CDCl₃) (Figure 5) spectrum. Its ¹³C NMR (CDCl₃) spectrum showed corresponding signals at δ 11.9, 25.9, 40.5, 105.6, 110.0, 141.2 and 155.4 with the additional signal at δ 25.9 corresponding to meso-C of 6. Further, in its mass spectrum, a parent ion peak at m/z 199 (M⁺+23) corresponding to molecular formula C₁₁H₁₂O₂+Na was observed. Also a peak at m/z 180.8 (M⁺+23) corresponding to 6 was observed. Based on this data and correct microanalytical analysis (vide experimental) structure, 2,2’-(propane-1,1-diyl)difuran, 7h (Scheme 4) has been assigned to this compound which was obtained in 65% yield (Table 3).

![Figure 5](image)

**Figure 5.** ¹H NMR (300 MHz, CDCl₃) spectrum and ¹³C NMR (75 MHz, CDCl₃) assignments of 7h.

The product isolated after quenching the metalated 6 with n-propyl bromide in its ¹H NMR (CDCl₃) spectrum depicted signals at δ 0.91 (t, 3H, J 7.5 Hz, CH₃), 1.29 (m, 2H, CH₂), 1.97 (m, 2H, CH₂), 4.00 (s, 2H, meso-CH₂), 4.06 (t, 1H, J 7.5 Hz, meso-CH), 6.08 (m, 2H, 2 x C4-H), 6.30 (m, 2H, 2 x C3-H), 7.32 (m, 2H, 2 x C5-H). Based on ¹H NMR spectral assignments and other spectral/analytical data (vide experimental) structure, 2,2’-(butane-1,1-diyl)difuran 7i (56%), (Table 3) was assigned to this compound.
Similar reaction of lithiated 6 with n-butyl bromide furnished 2,2’-(pentane-1,1-diyl)difuran 7j, (Scheme 4) in 83% yield. The structure of 7j was established on the basis of spectral as well as microanalytical data (vide experimental).

Attachment of a benzyl group at the meso-position of 6, gains significance in view of possibility of generation of anion at the benzylic carbon for further elaboration through reaction with electrophiles. Upon using benzyl chloride as electrophile for quenching the metalated 6, a single product was obtained which in its $^1$H NMR (CDCl$_3$) spectrum (Figure 6) depicted signals at $\delta$ 3.30 (d, 2H, $J$ 2.7 Hz, CH$_2$), 4.31 (t, 1H, $J$ 7.5 Hz, meso-CH), 6.01-6.02 (m, 2H, 2 x C4-H), 6.26-6.27 (m, 2H, 2 x C3-H), 6.99-7.02 (m, 2H, ArH), 7.15-7.23 (m, 3H, ArH), 7.34-7.36 (m, 2H, 2 x C5-H), indicative of incorporation of benzyl group at the meso-position analogously to the earlier reactions. The $^{13}$C NMR (CDCl$_3$) spectrum displayed the corresponding signals at $\delta$ 39.1, 41.0, 106.3, 110.1, 126.2, 128.1, 128.8, 141.4 and 154.4. Based on this data as well as spectral/analytical data (vide experimental) structure, 2,2’-(2-phenylethane-1,1-diyl)difuran 7k was assigned to this compound. It was obtained in 69% (Table 3) yield.

Figure 6. $^1$H NMR (300 MHz, CDCl$_3$) spectrum and $^{13}$C NMR (75 MHz, CDCl$_3$) assignments of 7k.

Deviating from the more traditional electrophiles and to append functionalized fragments at the meso-position of 6, we chose to employ isocyanates as electrophiles. Thus, when metalated 6 was quenched with phenyl isocyanate under the optimized reaction conditions, smooth formation of a single product was observed. The $^1$H NMR (CDCl$_3$) spectrum (Figure 7), depicted the signals at $\delta$ 5.17 (s, 1H, meso-CH), 6.36-6.41
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(m, 4H, 4 x CH), 7.10-7.13 (m, 1H, ArH), 7.25-7.33 (m, 4H, ArH), 7.45-7.48 (m, 2H, 2 x CH), 7.53 (s, 1H, NH, exchanged with D₂O). Appearance of resonance for 5 additional aromatic protons along with the disappearance of meso-H proton and downfield shifted meso-H signal at δ 5.17 (s, 1H, meso-CH) indicated the incorporation of carbomyl moiety at meso-position. The \(^{13}\)C NMR (CDCl₃) spectrum displayed the signals at δ 48.4, 108.9, 110.8, 119.8, 124.6, 128.9, 142.8, 149.2, 168.2 and the structure, 2,2-di(furan-2-yl)-N-phenylacetamide \(7l\) (51%) was assigned to this compound, which has been corroborated by the correct EIMS and microanalytical analysis (vide experimental).

![Figure 7](image)

**Figure 7.** \(^1\)H NMR (300 MHz, CDCl₃) spectrum and \(^{13}\)C NMR (75 MHz, CDCl₃) assignments of \(7l\).

Likewise, phenyl isothiocyanate was used as electrophile for reaction with the metalated \(6\), following the same procedure. The \(^1\)H NMR (CDCl₃) spectrum of the product depicted the signals at δ 5.17 (s, 1H, meso-CH), 6.36-6.41 (m, 4H, 4 x CH), 7.08-7.18 (m, 3H, ArH), 7.26-7.46 (m, 2H, ArH), 7.49-7.63 (m, 2H, 2 x CH), 8.94 (br, 1H, NH, exchanged with D₂O). Based on \(^1\)H NMR spectral assignments and other spectral/analytical data (vide experimental) structure, 2,2-di(furan-2-yl)-N-phenylethanethioamide \(7m\) (30%) was assigned to this compound.

In order to further broaden the scope of the meso-elaboration protocol, reaction of metalated \(6\) was performed with other electrophiles such as disulfides. Quenching of metalated \(6\) with di-\(n\)-propyl disulfide furnished a single product at Rf: 0.80 (ethyl acetate:hexane/2:98) (TLC). Its \(^1\)H NMR (CDCl₃) spectrum (Figure 8) displayed the signals at δ 0.94 (t, 3H, J 7.2 Hz, CH₃), 1.54 (m, 2H, CH₂), 2.48 (t, 2H, J 7.2 Hz, CH₂),
5.22 (s, 1H, *meso*-CH), 6.27-6.34 (m, 4H, 4 x CH) and 7.38-7.39 (m, 2H, 2 x CH). The $^{13}$C NMR displayed the signals at $\delta$ 13.4, 22.5, 33.7, 40.1, 107.8, 110.4, 142.2 and 151.6. Further, in its mass spectrum, a parent ion peak was observed at $m/z$ 245 (M$^+$+23), corresponding to the molecular formula C$_{12}$H$_{14}$O$_2$+Na. Based on this data and correct microanalytical analysis (*vide experimental*), structure, 2,2'-((propylthiomethylene)difuran 7n (Scheme 3) was assigned to this compound which was obtained in 68% yield (Table 3).

![Figure 8](image)

**Figure 8.** $^1$H NMR (300 MHz, CDCl$_3$) spectrum and $^{13}$C NMR (75 MHz, CDCl$_3$) assignments of 7n.

Thus these few reactions demonstrate validity of regioselective generation of carbanion at the *meso*-position of 6 followed by reaction with a variety of electrophiles. Mechanistically, the reactions are visualized to be proceeding through the transition state suggested in figure 2. Thus our initial rationalization of preferential *meso*-metalation, based upon pKa comparison stands validated.

### 4.4 Formation of C-5 functionalized bis(furan-2-yl)methane derivatives

From the above discussion, we have found that bis(furan-2-yl)methane undergo regioselective metalation at the *meso*-position with alkyl lithium base in the presence of DMSO as co-solvent. To see if the metatalation could be directed to the ring upon blocking the *meso*-position, we have performed some reactions. For this, 2,2’-((propane-2,2-diyl)difuran 8 (Scheme 5), was synthesized by acid catalyzed condensation of furan and acetone$^8$ and was well characterized using spectral as well as microanalytical data, presented in the experimental section.
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Scheme 5. Synthesis of 2,2’-(propane-2,2-diyl)difuran 8.

When 8 was treated with \( n \)-BuLi (1.2 equiv.) at -78°C (Scheme 6), under the blanket of purified nitrogen gas, red colored solution was obtained, indicating the generation of carbanion. After stirring for 30 min. at the same temperature, anion was quenched with benzaldehyde (1.2 equiv.). Upon completion (TLC), potassium tert-butoxide (1.2 equiv.) was added followed by methyl iodide (1.5 equiv.). A single product Rf: 0.70 (ethyl acetate/hexane:10:90) was isolated. The \(^1\)H NMR (CDCl\(_3\)) spectrum (Figure 9) showed the signals at \( \delta \) 1.61 (s, 6H, 2 x CH\(_3\)), 3.35 (s, 3H, OCH\(_3\)), 5.21 (s, 1H, CH(OCH\(_3\))), 5.90 (d, 1H, \( J \) 2.4 Hz, CH), 5.96-5.97 (m, 2H, 2 x CH), 6.24-6.25 (m, 1H, CH), 7.22-7.29 (m, 2H, ArH), 7.31-7.33 (m, 2H, ArH), 7.34-7.38 (m, 1H, CH), 7.40 (m, 1H, ArH). The \(^{13}\)C NMR (CDCl\(_3\)) spectrum displayed the corresponding signals at \( \delta \) 26.2, 26.4, 37.5, 56.9, 78.9, 104.1, 104.7, 109.1, 109.9, 126.7, 127.2, 127.8, 128.3, 139.3, 160.1, 160.4, 161.0.


Figure 9. \(^1\)H NMR (300 MHz, CDCl\(_3\)) spectrum and \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) assignments of 10a.
Additionally the corrected microanalytical data and mass spectrum (m/z 319, M^+23), corresponding to the molecular formula C_{19}H_{20}O_{3}Na, led to the assignment of structure, 2-(2-(furan-2-yl)propan-2-yl)-5-(methoxy(phenyl)methyl)furan 10a to this compound.

Likewise, 3,4-dimethoxybenzaldehyde was used as electrophile for reaction with the metalated 8, following the same procedure as for 10a. The ^1H NMR (CDCl₃) spectrum of the product depicted the signals at δ 1.63 (s, 6H, 2 x CH₃), 3.34 (s, 3H, OCH₃), 3.85 (s, 3H, OCH₃), 3.87 (s, 3H, OCH₃), 5.15 (s, 1H, CH(OCH₃)), 5.91 (m, 1H, CH), 5.97-6.00 (m, 2H, 2 x CH), 6.25-6.26 (m, 1H, CH), 6.80-6.91 (m, 2H, ArH), 7.00 (m, 1H, ArH) and 7.29 (m, 1H, CH). Based on ^1H NMR spectral assignments and other spectral/analytical data (vide experimental) structure, 2-[(3,4-dimethoxyphenyl)(methoxy)methyl]-5-(2-(furan-2-yl)propan-2-yl)furan 10b (70%) was assigned to this compound. These two reactions demonstrate the possibility of furan ring elaboration when the meso-position was blocked and hence establish unequivocally the proposed decreasing order of acidity of bis(furan-2-yl)methane as: meso-CH > ring CH.

4.5 Conclusions
(i) A highly efficient method for meso-functionalized bis(furan-2-yl)methane derivatives has been devised, which are otherwise difficult to get due to lack of appropriate aldehyde precursors.
(ii) Reaction proceeds with good selectivity and furnished product in good yield (30-72%).
(iii) Apart from simplicity of procedure, no side product formation has been observed during any reaction.
(iv) The elaboration could be diverted to furan ring when meso-position was blocked.

4.6 Experimental
4.6.1 General information
Melting points were determined in open capillaries and are uncorrected. ^1H NMR (300 and 400 MHz) spectra were recorded on multinuclear Jeol FT-AL-300 and Bruker-400 MHz spectrometers using commercial deuterated solvents. The chemical shifts are reported in parts per million (ppm, δ unit) relative to tetramethylsilane (TMS,
δ 0.0) used as internal standard. Data are reported as follows: chemical shifts (multiplicity [singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), broad (br), and multiplet (m)], integration, coupling constant [Hz], assignment). $^{13}$C NMR spectra* were recorded at 75 MHz on Jeol FT-AL-300 and 100 MHz on Bruker-400 instruments, and the chemical shifts are reported in parts per million (ppm, δ unit) downfield from the signal of tetramethylsilane used as the internal standard. The electron ionization/impact (EI) mass spectra were recorded on Bruker Daltonics esquire 3000 spectrometer at Indian Institute of Integrated Medicine (IIIM), Jammu. IR spectra were recorded on Shimadzu FTIR 8400 S spectrophotometer. Elemental analyses were performed on FLASH EA 112 (Thermo Electron Corporation) analyzer and the results are quoted in %.

For monitoring the progress of the reactions and for the comparison purpose, thin layer chromatography (TLC) was performed on pre-coated aluminium sheets (Merck) (60F$_{254}$, 0.2 mm) using an appropriate solvent system. The chromatograms were visualized under UV light. The compounds were purified using flash chromatography using silica gel-G (60-120 mesh) and mixtures of ethyl acetate/hexane etc. as eluent.

4.6.2 Materials and methods

The solvents and reagents: diethyl ether/hexane/tetrahydrofuran (THF) (Nα-benzophenone ketyl), dichloromethane (DCM)/acetophenone/alkyl halides (CaCl$_2$), acetone (K$_2$CO$_3$), diisopropylamine (KOH pellets) were adequately dried and drawn under N$_2$ atmosphere using hypodermic glass syringes. Low boiling reagents were invariably distilled over 4Å molecular sieves. Freshly prepared n-BuLi (2.0-2.3 N in hexane) was titrated against diphenylacetic acid$^{31}$ before use. Lithium diisopropyl amide (LDA) was generated by reaction of equimolar quantities of diisopropyl amine and n-BuLi at 0°C.

Reactions were run under a blanket of dry nitrogen gas in round-bottomed flasks, sealed with rubber septum (Aldrich). Organometallic reagents were transferred using cannula. The low temperature (-78°C, -20°C) was achieved by using slush of liquid nitrogen with appropriate solvent.

* Kindly see footnote, page 98 (Chapter 3).
4.6.3 Synthesis of bis(furan-2-yl)methane derivatives

To an ice cooled solution of furan (2.5 mol) in ethanol (75 ml), aqueous hydrochloric acid (50 ml, 35% w/v) mixture, formaldehyde (37% w/v) (1.25 mol) was added dropwise with stirring at under 10°C. The mixture after stirring for 18 h at room temperature, was extracted with ether, washed with 5% aqueous sodium bicarbonate solution until the washings were neutral, and then with water, dried over anhydrous sodium sulphate, and filtered. After evaporation of the solvent, the residue was chromatographed over silica gel-G (60-120 mesh) using hexane as eluent to isolate bis(furan-2-yl)methane 6 as viscous liquid. Rf: 0.96 (hexane). Yield: 15%. IR (KBr): $\nu_{\text{max}}$ 1785 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$, 25°C): $\delta$ 3.97 (s, 2H, meso-CH$_2$), 6.03-6.14 (m, 2H, 2 x C4-H), 6.29 (m, 2H, 2 x C3-H), 7.34 (m, 2H, 2 x C5-H). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): $\delta$ 26.8, 106.7, 110.6, 142.1 and 151.9. Anal. Calcd. for C$_9$H$_8$O$_2$: C, 72.97; H, 5.40; Found: C, 72.69; H, 5.27. EIMS: $m/z$ 171 (M$^+$+23).

Similar reaction of furan and acetone furnished 2,2’-(propane-2,2-diyl)difuran 8 as viscous liquid. Rf: 0.92 (hexane). Yield: 23%. IR (KBr): $\nu_{\text{max}}$ 1794 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$, 25°C): $\delta$ 1.63 (s, 6H, 2 x CH$_3$), 6.02 (m, 2H, 2 x C4-H), 6.28 (m, 2H, 2 x C3-H), 7.31 (m, 2H, 2 x C5-H). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): $\delta$ 26.7, 37.2, 103.9, 109.8, 141.1 and 160.1. Anal. Calcd. for C$_{11}$H$_{12}$O$_2$: C, 75.00; H, 6.82; Found: C, 75.16; H, 6.67. EIMS: $m/z$ 199 (M$^+$+23).

4.6.4 General procedure for elaboration of meso-unsubstituted bis(furan-2-yl)methane

To a clear solution of 6 (R$^1$ = R$^2$ = R$^3$ = H) (3.37 mmol) in a mixture (3:7, v/v) of DMSO and THF (7 ml) under a blanket of dry nitrogen gas, a solution of n-BuLi (1.2 equiv.) was added dropwise at 0°C. After the addition, reaction mixture was stirred for 15 min. whereupon turbid reddish brown colored solution was obtained. Dropwise addition of appropriate electrophile (1.5 equiv.), dissolved in anhydrous THF (10 ml) was made at the same low temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, it was quenched with cold aqueous saturated solution of NH$_4$Cl at the same low temperature. The reaction was extracted with ethyl acetate (3 x 25 ml) and the organic extract washed with brine, dried over anhydrous
Na$_2$SO$_4$ and concentrated under reduced pressure. The products were purified by flash chromatography using silica gel-G (60-120 mesh) and mixtures of ethyl acetate/hexane as eluent.

2,2-Di(furan-2-yl)-1-phenylethanol (7a)

Yellow oil. Rf: 0.27 (ethyl acetate:hexane/10:90). Yield: 72%. IR (DCM): $v_{\text{max}}$ 3620 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$, 25$^\circ$C): $\delta$ 2.44 (s, 1H, OH, exchanged with D$_2$O), 4.41 (d, 1H, J 7.2 Hz, meso-CH), 5.28 (d, 1H, J 7.2 Hz, CH(OH)), 6.01-6.02 (m, 1H, CH), 6.20-6.26 (m, 2H, 2 x CH), 6.34-6.35 (m, 1H, CH), 7.15-7.25 (m, 5H, ArH), 7.28-7.29 (m, 1H, CH), 7.40-7.41 (m, 1H, CH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25$^\circ$C): $\delta$ 47.7, 107.7, 108.2, 110.2, 110.4, 126.1, 127.7, 128.0, 141.5, 142.0 and 151.8. Anal. Calcd. for C$_{16}$H$_{14}$O$_3$: C, 75.59; H, 5.51; Found: C, 75.32; H, 5.24. EIMS: $m/z$ 276.8 (M$^+$+23).

1-(4-Chlorophenyl)-2,2-di(furan-2-yl)ethanol (7b)

Colorless oil. Rf: 0.30 (ethyl acetate:hexane/10:90). Yield: 65%. IR (DCM): $v_{\text{max}}$ 3500 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$, 25$^\circ$C): $\delta$ 2.42 (d, 1H, OH, J 3.3 Hz, exchanged with D$_2$O), 4.28 (d, 1H, J 7.5 Hz, meso-CH), 5.18 (dd, 1H, J 6.3 Hz, J 4.8 Hz, CH(OH)), 5.94-6.02 (m, 1H, CH), 6.15-6.24 (m, 2H, 2 x CH), 6.26-6.28 (m, 1H, CH), 7.00-7.04 (m, 2H, ArH), 7.12-7.18 (m, 2H, ArH), 7.26 (m, 1H, CH), 7.32-7.33 (m, 1H, CH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25$^\circ$C): $\delta$ 47.8, 74.9, 107.9, 108.4, 110.3, 110.5, 127.4, 128.1, 141.7, 142.1 and 151.4. Anal. Calcd. for C$_{16}$H$_{13}$ClO$_3$: C, 66.55; H, 4.50; Found: C, 66.34; H, 4.64. EIMS: $m/z$ 311.5 (M$^+$+23).

1-(3,4-Dimethoxyphenyl)-2,2-di(furan-2-yl)ethanol (7c)

White solid. Rf: 0.43 (ethyl acetate:hexane/10:90). Yield: 70%. m.p. 73-75$^\circ$C (DCM). IR (KBr): $v_{\text{max}}$ 3560 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$, 25$^\circ$C): $\delta$ 1.61 (br, 1H, OH, exchanged with D$_2$O), 3.77 (s, 3H, OCH$_3$), 3.84 (s, 3H, OCH$_3$), 4.37 (d, 1H, J 7.5 Hz, meso-CH), 5.23 (d, 1H, J 7.5 Hz, CH(OH)), 6.03 (d, 1H, J 3.0 Hz, CH), 6.22-6.26 (m, 2H, 2 x CH), 6.35-6.37 (m, 1H, CH), 6.63 (s, 1H, CH), 6.74 (s, 2H, 2 x CH), 7.26-7.42 (m, 3H, ArH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25$^\circ$C): $\delta$ 47.9, 55.7, 75.3, 107.7, 108.1, 109.1, 110.3, 110.4, 118.3, 134.0, 141.5, 141.9, 148.5 and
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151.9. Anal. Calcd. for C$_{18}$H$_{18}$O$_3$: C, 68.79; H, 5.73; Found: C, 68.36; H, 5.69. EIMS: m/z 337 (M$^+$+23).

2,2-Di(furan-2-yl)-1-(naphthalene-2-yl)ethanol (7d)
White solid. Rf: 0.35 (ethyl acetate:hexane/10:90). Yield: 65%. m.p. 82°C (DCM). IR (KBr): $\nu_{\text{max}}$ 3560 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$, 25°C): $\delta$ 2.54 (br, 1H, OH, exchanged with D$_2$O), 4.52 (d, 1H, $J$ 6.9 Hz, meso-CH), 5.44 (br, 1H, CH(OH)), 6.02 (m, 1H, CH), 6.19-6.34 (m, 3H, 3 x CH), 7.25-7.33 (m, 4H, ArH), 7.41-7.45 (m, 3H, ArH), 7.72-7.76 (m, 2H, 2 x CH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): $\delta$ 47.7, 75.5, 107.8, 108.3, 110.3, 110.4, 124.0, 125.2, 125.8, 125.9, 127.5, 127.7, 128.0, 132.9, 133.0, 138.8, 141.6, 142.0 and 151.7. Anal. Calcd. for C$_{20}$H$_{16}$O$_3$: C, 78.95; H, 5.26; Found: C, 78.76; H, 5.58. EIMS: m/z 327 (M$^+$+23).

1,1-Di(furan-2-yl)-2-methylpropan-2-ol (7e)
Viscous oil. Rf: 0.36 (ethyl acetate:hexane/10:90). Yield: 72%. IR (KBr): $\nu_{\text{max}}$ 3600 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$, 25°C): $\delta$ 1.21 (s, 6H, 2 x CH$_3$), 1.61 (s, 1H, OH, exchanged with D$_2$O), 4.19 (s, 1H, meso-CH), 6.25-6.26 (m, 2H, 2 x C4-H), 6.33-6.35 (m, 2H, 2 x C3-H), 7.38-7.39 (m, 2H, 2 x C5-H). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): $\delta$ 27.6, 50.4, 108.2, 110.3, 141.6 and 152.6. Anal. Calcd. for C$_{12}$H$_{14}$O$_3$: C, 69.90; H, 6.80; Found: C, 69.62; H, 6.64. EIMS: m/z 229 (M$^+$+23).

1,1-Di(furan-2-yl)-2-phenylpropan-2-ol (7f)
Viscous oil. Rf: 0.32 (ethyl acetate:hexane/10:90). Yield: 45%. IR (KBr): $\nu_{\text{max}}$ 3570 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$, 25°C): $\delta$ 1.55 (s, 3H, CH$_3$), 4.00 (s, 1H, OH, exchanged with D$_2$O), 4.54 (s, 1H, meso-CH), 6.02 (m, 1H, CH), 6.19-6.22 (m, 2H, 2 x CH), 6.32 (s, 1H, CH), 7.18-7.25 (m, 5H, ArH), 7.27-7.37 (m, 2H, 2 x CH). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): $\delta$ 28.1, 50.9, 76.8, 108.5, 108.7, 110.1, 110.4, 124.8, 126.6, 127.7, 141.4, 141.6, 145.8 and 151.9. Anal. Calcd. for C$_{17}$H$_{16}$O$_3$: C, 76.12; H, 5.97; Found: C, 76.34; H, 5.92. EIMS: m/z 291 (M$^+$+23).
1,1-Di(furan-2-yl)-2-(thiophen-2-yl)propan-2-ol (7g)
Yellow oil. Rf: 0.27 (ethyl acetate:hexane/10:90). Yield: 40%. IR (KBr): \( \nu_{\max} \) 3250 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 1.64 (s, 3H, CH\(_3\)), 2.57 (s, 1H, OH, exchanged with D\(_2\)O), 4.54 (s, 1H, meso-CH), 6.15 (m, 1H, CH), 6.20 (m, 1H, CH), 6.26-6.30 (m, 1H, CH), 6.31-6.32 (m, 1H, CH), 6.68-6.69 (m, 1H, CH), 6.84-6.87 (m, 1H, CH), 7.12-7.14 (m, 1H, ArH), 7.33-7.37 (m, 2H, ArH). \(^13\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 21.3, 59.9, 98.0, 124.1, 130.0, 139.1, 149.1, 152.7 and 164.6. Anal. Calcd. for C\(_{15}\)H\(_{14}\)O\(_3\)S: C, 65.69; H, 5.11; S, 11.68; Found: C, 65.45; H, 5.32; S, 11.53. EIMS: \( m/z \) 297 (M\(^+\)+23).

2,2’-(Propane-1,1-diyl)difuran (7h)
Viscous oil. Rf: 0.93 (hexane). Yield: 65%. IR (CHCl\(_3\)): \( \nu_{\max} \) 1240 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 0.88 (t, 3H, \( J \) 7.5 Hz, CH\(_3\)), 2.02 (m, 2H, CH\(_2\)), 3.96 (t, 1H, \( J \) 7.5 Hz, meso-CH), 6.07-6.09 (m, 2H, 2 x C4-H), 6.29-6.32 (m, 2H, 2 x C3-H), 7.32-7.34 (m, 2H, 2 x C5-H). \(^13\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 11.9, 25.9, 40.5, 105.6, 110.0, 141.2 and 155.4. EIMS: \( m/z \) 199 (M\(^+\)+23).

2,2’-(Butane-1,1-diyl)difuran (7i)
Viscous oil. Rf: 0.94 (hexane). Yield: 56%. IR (CHCl\(_3\)): \( \nu_{\max} \) 1245 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 0.91 (t, 3H, \( J \) 7.5 Hz, CH\(_3\)), 1.30 (q, 2H, \( J \) 7.8 Hz, CH\(_2\)), 1.96 (q, 2H, \( J \) 7.5 Hz, CH\(_2\)), 4.06 (t, 1H, \( J \) 7.5 Hz, meso-CH), 6.08 (m, 2H, 2 x C4-H), 6.30 (s, 2H, 2 x C3-H), 7.32 (m, 2H, 2 x C5-H). \(^13\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 13.4, 22.4, 34.8, 38.8, 105.5, 106.4, 110.0, 110.3, 141.2 and 141.5. EIMS: \( m/z \) 213 (M\(^+\)+23).

2,2’-(Pentane-1,1-diyl)difuran (7j)
Viscous oil. Rf: 0.95 (hexane). Yield: 83%. IR (CHCl\(_3\)): \( \nu_{\max} \) 1246 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\), 25°C): \( \delta \) 0.85 (t, 3H, \( J \) 6.9 Hz, CH\(_3\)), 1.23 (m, 4H, 2 x CH\(_2\)), 1.98 (q, 2H, \( J \) 7.5 Hz, CH\(_2\)), 4.04 (t, 1H, \( J \) 7.5 Hz, meso-CH), 6.06-6.09 (m, 2H, 2 x C4-H), 6.28-6.31 (m, 2H, 2 x C3-H), 7.31-7.33 (m, 2H, 2 x C5-H). \(^13\)C NMR (75 MHz, CDCl\(_3\), 25°C): \( \delta \) 21.3, 29.3, 30.4, 38.7, 40.6, 61.4, 73.2, 110.0, 110.3, 141.2 and 141.4. EIMS: \( m/z \) 231 (M\(^+\)+23).
MHz, CDCl$_3$, 25°C): δ 13.9, 22.4, 29.5, 32.4, 38.8, 105.5, 110.0, 141.2 and 155.6. EIMS: m/z 227 (M$^+$+23).

$2,2'$(2-Phenylethane-1,1-diyl)difuran (7k)

Viscous oil. Rf: 0.85 (ethyl acetate:hexane/2:98). Yield: 69%. IR (CHCl$_3$): $\nu_{\text{max}}$ 1240 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$, 25°C): δ 3.30 (d, 2H, $J$ 2.7 Hz, CH$_2$), 4.31 (t, 1H, $J$ 7.5 Hz, meso-CH), 6.01-6.02 (m, 2H, 2 x C4-H), 6.26-6.27 (m, 2H, 2 x C3-H), 6.99-7.02 (m, 2H, ArH), 7.15-7.23 (m, 3H, ArH), 7.34-7.36 (m, 2H, 2 x C5-H). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): δ 39.1, 41.0, 106.3, 110.1, 126.2, 128.1, 128.8, 141.4 and 154.4. Anal. Calcd. for C$_{16}$H$_{14}$O$_2$: C, 80.67; H, 5.88; Found: C, 80.42; H, 6.05. EIMS: m/z 261 (M$^+$+23).

$2,2$-Di(furan-2-yl)-N-phenylacetamide (7l)

White solid. Rf: 0.25 (ethyl acetate:hexane/15:85). Yield: 51%. m.p. 119-120°C (DCM). IR (CHCl$_3$): $\nu_{\text{max}}$ 1720 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$, 25°C): δ 5.17 (s, 1H, meso-CH), 6.36-6.41 (m, 4H, 4 x CH), 7.10-7.13 (m, 1H, ArH), 7.25-7.33 (m, 4H, ArH), 7.45-7.48 (m, 2H, 2 x CH), 7.53 (s, 1H, NH, exchanged with D$_2$O). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): δ 48.4, 108.9, 110.8, 119.8, 124.6, 128.9, 142.8, 149.2 and 168.2. Anal. Calcd. for C$_{16}$H$_{13}$NO$_3$: C, 71.91; H, 4.87; N, 5.32; Found: C, 71.65; H, 4.74, N, 5.35. EIMS: m/z 290 (M$^+$+23).

$2,2$-Di(furan-2-yl)-N-phenylethanethioacetamide (7m)

White solid. Rf: 0.25 (ethyl acetate:hexane/15:85). Yield: 51%. m.p. 119-120°C (DCM). IR (CHCl$_3$): $\nu_{\text{max}}$ 1350, 1280 cm$^{-1}$. $^1$H NMR (300 MHz, CDCl$_3$, 25°C): δ 5.17 (s, 1H, meso-CH), 6.36-6.41 (m, 4H, 4 x CH), 7.08-7.18 (m, 3H, ArH), 7.26-7.46 (m, 2H, ArH), 7.49-7.63 (m, 2H, 2x CH), 8.94 (br, 1H, NH, exchanged with D$_2$O). $^{13}$C NMR (75 MHz, CDCl$_3$, 25°C): δ 48.4, 108.9, 110.8, 119.8, 124.6, 128.9, 142.8 and 149.2. Anal. Calcd. for C$_{16}$H$_{13}$NO$_2$S: C, 67.84; H, 4.59; N, 4.95; S, 11.31; Found: C, 67.74; H, 4.53; N, 4.78; S, 11.53. EIMS: m/z 306 (M$^+$+23).
2,2’-(Propylthiomethylene)difuran (7n)

Viscous oil. Rf: 0.88 (hexane). Yield: 68%. IR (CHCl₃): ν_max 1235 cm⁻¹. ¹H NMR (300 MHz, CDCl₃, 25°C): δ 0.94 (t, 3H, J 7.2 Hz, CH₃), 1.54 (m, 2H, CH₂), 2.48 (t, 2H, J 7.2 Hz, CH₂), 5.22 (s, 1H, meso-CH), 6.27-6.34 (m, 4H, 4 x CH), 7.38-7.39 (m, 2H, 2 x CH). ¹³C NMR (75 MHz, CDCl₃, 25°C): δ 13.4, 22.5, 33.7, 40.1, 107.8, 110.4, 142.2 and 151.6. Anal. Calcd. for C₁₂H₁₄O₂S: C, 64.86; H, 6.31; S, 14.41; Found: C, 64.68; H, 6.19; S, 14.58. EIMS: m/z 245 (M⁺+23).

4.6.5 General procedure for the elaboration of meso-substituted bis(furan-2-yl)methane

To a clear solution of 2,2’-(propane-2,2-diyl)difuran 8 (2.84 mmol) in dry THF (10 ml), n-BuLi (2.1 N, 1.2 equiv.) was added dropwise at -78°C under a blanket of dry nitrogen gas. After the addition, the reaction mixture was stirred for 30 minutes, whereupon red colored anion was generated. Dropwise addition of appropriate aldehyde (1.5 equiv.), dissolved in 10 ml dry THF was made at the same low temperature. The progress of the reaction was monitored by TLC. Upon completion, potassium tert-butoxide (1.35 mmol) was added and the temperature of the reaction mixture was allowed to rise to -20°C and methyl iodide (2.12 mmol) dissolved in 10 ml dry THF was added dropwise. The reaction was stirred for additional 30 minutes, followed by quenching with saturated solution of NH₄Cl at the same low temperature. The reaction was extracted with ethyl acetate (3 x 25 ml) and the organic extract washed with brine, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The following products were obtained after purification by flash chromatography using silica gel-G (60-120 mesh) and mixtures of ethyl acetate/hexane as eluent.

2-(2-(Furan-2-yl)propan-2-yl)-5-(methoxy(phenyl)methyl)furan (10a)

Yellow viscous oil. Rf: 0.70 (ethyl acetate:hexane/10:90). Yield: 68%. IR (CHCl₃): ν_max 1130 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C): δ 1.61 (s, 6H, 2 x CH₃), 3.35 (s, 3H, OCH₃), 5.21 (s, 1H, CH(OCH₃)), 5.90 (d, 1H, J 2.4 Hz, CH), 5.96-5.97 (m, 2H, 2 x CH), 6.24-6.25 (m, 1H, CH), 7.22-7.29 (m, 2H, ArH), 7.31-7.33 (m, 2H, ArH), 7.34-7.38 (m, 1H, CH), 7.40 (m, 1H, ArH). ¹³C NMR (100 MHz, CDCl₃, 25°C): δ 26.2, 26.4, 37.5, 56.9, 78.9, 104.1, 104.7, 109.1, 109.9,
126.7, 127.2, 127.8, 128.3, 139.3, 141.1, 153.0, 159.9 and 160.1. Anal. Calcd. for C_{19}H_{20}O_{3}: C, 77.03; H, 6.76; Found: C, 76.84; H, 6.68. EIMS: m/z 319 (M^+ +23).

2-((3,4-Dimethoxyphenyl)(methoxy)methyl)-5-(2-(furan-2-yl)propan-2-yl)furan (10b)

Yellow viscous oil. Rf: 0.74 (ethyl acetate:hexane/10:90).
Yield: 70%. IR (CHCl$_3$): $\nu_{\text{max}}$ 1120 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C): $\delta$ 1.63 (s, 6H, 2 x CH$_3$), 3.34 (s, 3H, OCH$_3$), 3.85 (s, 3H, OCH$_3$), 3.87 (s, 3H, OCH$_3$), 5.15 (s, 1H, CH(OCH$_3$)), 5.91 (d, 1H, J 3.2 Hz, CH), 5.97-6.00 (m, 2H, 2 x CH), 6.25-6.26 (m, 1H, CH), 6.80-6.91 (m, 2H, ArH), 7.00 (m, 1H, ArH), 7.29 (m, 1H, CH). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C): $\delta$ 26.3, 37.4, 55.8, 55.9, 56.7, 78.7, 104.1, 104.6, 109.0, 109.9, 110.6, 111.9, 120.3, 131.8, 141.1, 148.6, 148.9, 153.0, 159.9 and 160.1. Anal. Calcd. for C$_{21}$H$_{24}$O$_5$: C, 70.79; H, 6.74; Found: C, 70.56; H, 6.69. EIMS: m/z 379 (M$^+ +23$).

4.7 References


