CHAPTER 3

Study on Lewis acid catalyzed benzylolation reactions:
   TMSOTf catalyzed benzylolation

Part-1

Benzylation reactions in organic synthesis
3.1.1. Introduction

Carbon-carbon bond formation is fundamental to organic synthesis and the nucleophilic displacement plays main role in this area. Lewis acid-catalyzed benzylolation reactions are of great current interest and one of most powerful methods to form carbon-carbon bond in organic synthesis because of the unique reactivities and selectivities that can be achieved as well as for the mild conditions. Various kinds of Lewis acid-promoted benzylolation reactions including application in industry have been developed, and especially Friedel-Crafts benzylolation reaction is of great synthetic significance in industrial processes.\(^1\) On the other hand, many of asymmetric Lewis-acid catalyzed benzylolation reactions have also been developed. Benzylated products are important building blocks for the synthesis of many pharmaceuticals, agro-and fine chemicals, for example, piritrexim, trimethoprim, avrainvilleol, papaverine, beclabrate, anastrozole, and letrozole, have been shown to possess interesting biological activity.\(^2-^6\) (Fig.3.1).

![Examples of bio-active benzylated molecule.](image)

Figure 3.1: Examples of bio-active benzylated molecule.
Initially, the benzylation reactions are carried out by employing a benzyl halide and a catalytic amount of the Lewis acid. But these reactions have their own limitation, such as toxic benzyl halides have to be utilized leading to vast amounts of salt side products. With the need for more environmentally and economically benign processes, the benzylation using catalytic amounts of Lewis acid catalyst and more environmental friendly benzylation agents are highly desirable. To this end, substantial progress has been made and different benzyl halide substitutes, including free and protected benzyl alcohols as well as tosylamides, benzyl carboxylates, and styrene derivatives have been introduced.

In particular benzyl alcohols have become valuable alternatives due to their availability, lower toxicity, and the fact that only stoichiometric amount of water is generated as the side product. Thus, the benzylation with benzyl and propargyl alcohols presented a first and important step toward an environmental friendly process.

3.1.2. Review of literature

Uemura et al. (1986)\(^7\): They had investigated the chlorination of benzyl and alkyl alcohols mediated by SeCl\(_4\) and TeCl\(_4\). While the reaction performed in non-aromatic solvents yielded the desired benzyl chlorides in good yields, an unexpected side reaction was observed in aromatic solvents such as toluene resulting in the 1,1-diarylalkane in 83% yield. The authors explained this observation with chlorination of 1-phenylethanol and subsequent FC alkylation of the formed benzyl chloride and toluene. However, more surprisingly the reaction yield could be improved to 93% if only catalytic amount (10 mol%) of TeCl\(_4\) was present (Scheme 3.1). Although the reaction was found by accident, this was probably the first description of a catalytic FC alkylation utilizing a benzyl alcohol.
Fukuzawa (1996)\textsuperscript{9} and Shimizu et al. (1997)\textsuperscript{10}: The first systematic investigations of catalytic FC benzylations were performed independently by Fukuzawa and Shimizu. While the latter used 10 mol\% Mo(CO)\textsubscript{6} as the Lewis acid catalyst under the strict exclusion of air and moisture, the Fukuzawa group utilized Sc(OTf)\textsubscript{3} as a water and air tolerant catalyst. Various arenes, including benzene, p-xylene, or mesitylenes were alkylated with benzyl alcohols to afford the desired 1,1-diarylalkanes in high yields.

Gyochang Keum et al (2000)\textsuperscript{11}: They have reported indium catalyzed Friedel-Crafts benzylation of aromatic compounds using benzyl halides. They have treated various aromatic compounds with benzyl halides in presence of catalytic amount of indium resulting in the corresponding diarylmethane products in good yields.

Beller et al. (2005)\textsuperscript{12-15}: They have systematically tested the activity of various Lewis- and Brønsted acids in FC benzylations and found that compounds of late transition metals such as H\textsubscript{2}PtCl\textsubscript{6} \textsuperscript{13}, H\textsubscript{2}PdCl\textsubscript{4}, [MesW(CO)\textsubscript{3}], IrCl\textsubscript{3}, H\textsubscript{2}RhCl\textsubscript{3}, H\textsubscript{2}AuCl\textsubscript{4}, 12
and FeCl$_3$\textsuperscript{14} were the most effective. FeCl$_3$, in particular, is an attractive alternative to rare-earth triflates since it is non-toxic, cheap and readily available. Different benzyl alcohols and acetates (Scheme No 3.4, $R^1 = H$) and 1-aryl alcohols ($R^1 = \text{Me}$) were tolerated in the reaction if 10 mol\% FeCl$_3$ catalyst is applied. Even fairly unstable thiophene- and furan-2-carbaldehyde derived benzyl alcohols, cyano(phenyl)methyl acetate or 3-hydroxy-3-phenylpropanoates and benzyl methyl ethers have been successfully applied as benzylaion reagents.$^{15}$

\[
\begin{array}{c}
\text{Ar} + R^1 \text{R} \rightarrow 10 \text{mol\% FeCl}_3 \\
50-80 \degree \text{C}, 20 \text{h} \\
\end{array}
\]

Scheme 3.4

Later, the same authors used gold(III) as a catalyst for an efficient one-pot synthesis of beclobrate, a well known fibric acid derivative with a potent hypolipidemic activity.$^{13}$ The straightforward synthesis was accomplished by the reaction of readily available p-chlorobenzyl acetate with 2-methyl-2-phenoxybutyrate to give beclobrate in 90\% yield. However, 10 mol\% of HAuCl$_4$ had to be used.

\[
\begin{array}{c}
\text{Cl} + \text{OAc} \rightarrow 10 \text{mol\% HAuCl}_4 \\
\text{MeNO}_2, 80 \degree \text{C}, 20 \text{h} \\
\end{array}
\]

Scheme 3.5

Zhang et al. (2010)$^{16}$: An efficient Fe/CuBr$_2$-catalyzed benzylaion of arenes and thiophenes with benzyl alcohols under mild condition was developed.
Hikawa et al. (2011): They have developed the new methodology for achieving the palladium-catalyzed benzylation of unprotected anthranilic acid with benzyl alcohols in water.

![Scheme 3.7](image)

Palladium-catalyzed reactions with both allylic and benzylic alcohols proceeded smoothly in aqueous media.

Mukai et al. (2010): They have described an effective palladium catalyst system for the direct benzylation of the aromatic sp² C-H bond of azoles with benzyl carbonates derived from the corresponding benzyl alcohols. In addition, the removal of the external base allowed the same palladium complex to catalyze the benzylic sp³ C-H benzylation.

![Scheme 3.8](image)

Ackermann et al. (2009): They have reported a broadly applicable Ruthenium catalyst for highly regioselective direct benzylation of various arenes under remarkably mild, nonacid reaction conditions.

![Scheme 3.9](image)
Shih et al. (2010)\textsuperscript{20}: The first enantioselective aldehyde \(\alpha\)-benzylation using electron-deficient aryl and heteroaryl substrates has been accomplished. The productive merger of novel imidazolididione organocatalyst and commercially available iridium photoredox catalyst directly allows the stereocontrolled formation of homobenzylic stereogenicity in good to excellent yield.

\[
\text{Scheme 3.10}
\]

Keglevich et al. (2008)\textsuperscript{21}: They have reported chemoselectivity in the microwave solvent-free solid-liquid phase benzylation of phenol (O- versus C-alkylations).

\[
\text{Scheme 3.11}
\]

3.1.3. General mechanism for Benzyl reaction

Most of the benzylation reactions of organic compounds were carried out using benzylation reagents such as benzyl halides or benzyl alcohols in presence of catalytic amount of Lewis acid catalyst. Generally, the benzylic carbocation was generated from the benzylation reagents in the presence of Lewis acid catalyst which then reacts with different kinds of nucleophiles to give corresponding benzylated products. In this reactions, water or stoichiometric amount of salts were formed as side products (Scheme 3.12).
Scheme 3.12

X = halogen, OH, OR, NHR''
Side product = HX, H₂O, HO-R', NH₂-R''

R¹ = R² = alkyl or aryl

Nu-H = Ar-H, [Other structures are shown]

R¹, TMS-CN, \( \text{SiMe}_3 \), \( \text{OSiMe}_3 \)
CHAPTER 3

Study on Lewis acid catalyzed benzylolation reaction

Part-2

TMSOTf–catalyzed benzylolation of β-dicarbonyl compounds
3.2.1. Introduction

The benzylation of 1,3-dicarbonyl compounds represents one of the most important and very useful transformation in the organic synthesis. Generally, these transformations are performed using alkyl halides, and at least equimolar amounts of base or Lewis acid are required, resulting in large amounts of salt byproducts which can be a significant drawback. In this contest, direct substitution of the hydroxyl group in alcohols by nucleophiles could be considered as an ideal process because of the generation of water as the only side product. Recently, considerable interest has been focused on benzylation of 1,3-dicarbonyl compounds using alcohols as electrophiles.

3.2.2. Review of literature

Roberto Sanz et al. (2006)\textsuperscript{22}: They have found that the simple Brønsted acids such as p-toluenesulfonic acid monohydrate or polymer-bound p-toluenesulfonic acid efficiently catalyze the direct nucleophilic substitution of the hydroxyl group of allylic and benzylic alcohols with 1,3-dicarbonyl compounds.

\[ \text{ArOH} + \text{R}^1\text{RCOR}^2 \xrightarrow{\text{PTS (10 mol%) \text{CH}_2\text{Cl}_2 \text{ reflux}} } \text{R}^1\text{ArC}=\text{O} \]

\( R = \text{aryl or alkyl} \quad R^1=R^2=\text{alkyl} \)

Scheme 3.13

Magnus Rueping et al. (2007)\textsuperscript{23}: A highly effective new bismuth triflate catalyzed direct benzylation of 1,3-dicarbonyl compounds has been developed by the authors.

\[ \text{R} + \text{R}^1\text{RCOR}^2 \xrightarrow{1 \text{ mol\% Bi(OTf)}_3 \text{CH}_3\text{NO}_2, 100 \degree \text{C}} \text{R}^1\text{R}^2\text{ArC}=\text{O} \]

\( R = \text{Me or H} \quad R^1=R^2=\text{alkyl or aryl} \)

Scheme 3.14
Masahiro Noji et al. (2007): The authors have reported the rare earth metal and hafnium triflate-catalyzed secondary benzylation and allylation of 1,3-diketones. The procedure was carried out under normal conditions. Various 1-phenylethyl cations were generated from substituted 1-phenylethanols using 0.5 mol % of metal triflates in nitromethane. The cations reacted with 1,3-diketones to give benzyolated products in high yields.

![Scheme 3.15](image)

Qureshi et al. (2009): They have studied the benzylation of 1,3-dicarbonyl compounds using Amberlyst-15 immobilized in ionic liquid[Bmim][PF₆] as an efficient reusable reagent.

![Scheme 3.16](image)

Thirupathi et al. (2010): The authors have described a mild and efficient Fe(ClO₄)₃.xH₂O-catalyzed direct C-C coupling reaction of 1,3-dicarbonyl compounds with electron-rich arenes and heteroarenes having secondary benzylic alcohol groups.

![Scheme 3.17](image)
Huang et al. (2007)\textsuperscript{27}: The have reported Yb(OTf)\textsubscript{3}-catalyzed propargylation and allylation of 1,3-dicarbonyl derivatives with propargylic alcohols. Selective propargylation or allenylation products are obtained depending on the nature of propargylic alcohols.

\[ \text{OH} + R^1=\text{aryl} R^2=CH_3, \text{Ph} \xrightarrow{5 \text{ mol}\% \text{ Yb(OTf)}_3} \text{CH}_3\text{NO}_2, \text{RT} \rightarrow R^2 R^3 \]

Scheme 3.18

Yadav et al. (2008)\textsuperscript{28}: Various 1,3-dicarbonyl compounds reacted readily with benzylic and propargylic alcohols in the presence of 10 mol\% of phosphomolybdic acid on silica gel(PMA/SiO\textsubscript{2}) under mild reaction conditions to produce 2-benzylic and 2-propylic-1,3-dicarboxyl compounds in excellent yields and with high selectivity.

\[ R^1=\text{Ph, Me} \]
\[ R^2=\text{Me, OEt} \]

Scheme 3.19

Roberto Sanz et al. (2007)\textsuperscript{29}: They have described the direct benzylaion of 1,3-dicarbonyl compounds with benzylic alcohols using Brønsted acids such as triflic acid (TfOH) and p-toluenesulfonic acid (PTS) to give rise to monoalkylated dicarboxyl derivatives in high yields. In the absence of the nucleophile, substituted alkenes, generated through a formal dimerization reaction, are obtained.
Bisaro Fabrice et al. (2002)\textsuperscript{30}: They have reported the Lewis acid (BF\textsubscript{3}, OEt\textsubscript{2}) mediated direct benzylation of active methylene compound with benzylic alcohols.

Weidong Rao et al. (2008)\textsuperscript{31}: A highly efficient iodine-catalyzed allylation of 1,3-dicarbonyl compounds with a wide variety of allylic alcohols has been developed. The reaction is operationally straightforward and proceeds under very mild conditions at room temperature in good to excellent yields (up to 99\%) and regioselectivity.

Umasish Jana et al. (2007)\textsuperscript{32}: They have developed FeCl\textsubscript{3}-catalyzed alkylation of various active methylene compounds with various benzylic or allylic alcohols under mild conditions. The reaction was carried out in the presence of a catalytic amount of anhydrous FeCl\textsubscript{3}(10 mol \%) under reflux in methylene chloride. High to excellent yields were obtained.
Makoto Yasuda et al. (2006): The direct coupling reaction of alcohols with active methylenes, alkoxyketones, or indoles catalyzed by InCl₃ proceeding without the formation of metal salts has been discussed. As H₂O was the only by-product of this system, the alkylated products were easily isolated in pure form, and the reaction is suitable for large-scale synthesis.

3.2.3. Objective

Recently, many methods have been reported in the literature for direct benzylolation of 1,3-dicarbonyl compounds. However, the use of high temperature, extended reaction times and harsh condition in many of the above-mentioned methods limit their practical utility in large scale synthesis. Therefore, the development of catalytic versions of this reaction remains as a major objective of the modern organic chemistry. Despite all these negative forewarnings, we decided to develop an alternative method for this transformation using an efficient, cost-effective and environmentally friendly Lewis acid catalyst.
3.2.4. Present work

In view of the demand for ecologically valuable processes to avoid large quantities of waste production,\textsuperscript{3} the catalytic direct alkylation with unmodified electrophiles such as alcohols, that provide water as the only by product, would be a suitable alternative. However, the main limitation of this strategy is due to the poor leaving ability of the hydroxyl group. Direct alkylation of 1,3-dicarbonyl compounds with alcohols using various Lewis acid catalysts have been reported in literature as mentioned above (see 3.2.2).

Alkylation reactions using metal-triflates as heterogeneous catalysts have also been studied.\textsuperscript{11} Inspired by this, we developed a new, mild alkylation of 1,3-dicarbonyl compounds with alcohols, where an organic-triflate could be used as a homogeneous catalyst that leads to reduction of the reaction time and practical difficulties of using the heterogeneous catalyst in large-scale experiments. Trimethylsilyl trifluoromethane sulfonate (TMSOTf) has recently been shown to be a versatile reagent in mediating a wide variety of organic transformations such as aldol and Sakurai alkylation,\textsuperscript{34} bis-silylation,\textsuperscript{35} deprotection,\textsuperscript{36} and Baylis-Hillman reaction.\textsuperscript{37} As part of our ongoing research program in the development of new synthetic methods of important organic products, herein we wish to report the use of TMSOTf as a powerful catalyst for the alkylation of \(\beta\)-dicarbonyl compounds with secondary benzylic alcohols that proceeded in good to excellent yields.

\[
\begin{align*}
\text{Scheme 3.25: Benzylation of } \beta\text{-dicarbonyl compound}
\end{align*}
\]
3.2.5. Results and discussion

Initially, the reaction of 1-phenylethanol (1) with acetyl acetone (2a) in the presence of TMSOTf was selected as a model reaction to develop the optimum reaction conditions. The effect of solvents was also investigated. The rate of the reaction and the yield were highly influenced by the solvent used which may be attributed to the stability of benzylic carbocation and also the stability of the catalyst in the particular solvent.

The reaction of 1-phenylethanol with acetyl acetone in acetonitrile and dichloroethane afforded the product only in moderate yields. However, the corresponding product was obtained in low yields even after 6 h when toluene or tetrahydrofuran was used as solvent. The best result was achieved in nitromethane, affording the desired product in 92% yield within 30 min at room temperature.

Table 3.1. TMSOTf catalyzed alkylation of 1,3-dicarbonyl compounds under the optimum conditions.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Alcohol</th>
<th>Nu-H</th>
<th>Product</th>
<th>Time (h)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="image" /></td>
<td>2a</td>
<td><img src="image2.png" alt="image" /></td>
<td>0.5</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="image" /></td>
<td>2a</td>
<td><img src="image4.png" alt="image" /></td>
<td>0.5</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="image" /></td>
<td>2a</td>
<td><img src="image6.png" alt="image" /></td>
<td>0.5</td>
<td>91</td>
</tr>
</tbody>
</table>

120
<table>
<thead>
<tr>
<th>No.</th>
<th>Structure 1</th>
<th>Structure 2</th>
<th>Value 1</th>
<th>Value 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td><img src="image1.png" alt="Structure 1" /></td>
<td><img src="image2.png" alt="Structure 2" /></td>
<td>1.0</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td><img src="image3.png" alt="Structure 1" /></td>
<td><img src="image4.png" alt="Structure 2" /></td>
<td>0.75</td>
<td>73(^\dagger)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image5.png" alt="Structure 1" /></td>
<td><img src="image6.png" alt="Structure 2" /></td>
<td>0.5</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="Structure 1" /></td>
<td><img src="image8.png" alt="Structure 2" /></td>
<td>0.5</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td><img src="image9.png" alt="Structure 1" /></td>
<td><img src="image10.png" alt="Structure 2" /></td>
<td>0.5</td>
<td>90(^\dagger)</td>
</tr>
<tr>
<td>9</td>
<td><img src="image11.png" alt="Structure 1" /></td>
<td><img src="image12.png" alt="Structure 2" /></td>
<td>0.75</td>
<td>86(^\dagger)</td>
</tr>
<tr>
<td>10</td>
<td><img src="image13.png" alt="Structure 1" /></td>
<td><img src="image14.png" alt="Structure 2" /></td>
<td>0.5</td>
<td>88(^\dagger)</td>
</tr>
<tr>
<td>11</td>
<td><img src="image15.png" alt="Structure 1" /></td>
<td><img src="image16.png" alt="Structure 2" /></td>
<td>1.0</td>
<td>65(^\dagger)</td>
</tr>
<tr>
<td>12(^d)</td>
<td><img src="image17.png" alt="Structure 1" /></td>
<td><img src="image18.png" alt="Structure 2" /></td>
<td>0.5</td>
<td>82</td>
</tr>
<tr>
<td>13</td>
<td><img src="image19.png" alt="Structure 1" /></td>
<td><img src="image20.png" alt="Structure 2" /></td>
<td>0.5</td>
<td>78(^\dagger)</td>
</tr>
<tr>
<td>14</td>
<td><img src="image21.png" alt="Structure 1" /></td>
<td><img src="image22.png" alt="Structure 2" /></td>
<td>0.5</td>
<td>71(^\dagger)</td>
</tr>
<tr>
<td>15</td>
<td><img src="image23.png" alt="Structure 1" /></td>
<td><img src="image24.png" alt="Structure 2" /></td>
<td>1.0</td>
<td>60(^\dagger)</td>
</tr>
<tr>
<td>16</td>
<td><img src="image25.png" alt="Structure 1" /></td>
<td><img src="image26.png" alt="Structure 2" /></td>
<td>0.5</td>
<td>96</td>
</tr>
<tr>
<td>17</td>
<td>2b</td>
<td>0.5</td>
<td>94(^\dagger)</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>2b</td>
<td>0.75</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>2b</td>
<td>0.5</td>
<td>90(^\dagger)</td>
<td></td>
</tr>
<tr>
<td>20(^d)</td>
<td>2b</td>
<td>0.5</td>
<td>87(^\dagger)</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>2b</td>
<td>1.0</td>
<td>80(^\dagger)</td>
<td></td>
</tr>
<tr>
<td>22(^d)</td>
<td>2c</td>
<td>1.0</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>2c</td>
<td>0.5</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>2c</td>
<td>0.75</td>
<td>68(^\dagger)</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>2c</td>
<td>1.0</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>26(^d)</td>
<td>2c</td>
<td>0.5</td>
<td>65(^\dagger)</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>2c</td>
<td>0.5</td>
<td>62</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Alcohol (1 mmol), 1,3-dicarbonyl compound (2 equiv), TMSOTf (15 mol\%) at RT
\(^b\) Reaction monitored by TLC. \(^c\) Isolated yield. \(^d\) Mixture of diastereomers (8:2)
\(^\dagger\) Novel compounds

We then turned our attention to optimize the amount of catalyst. The conversion was very slow at room temperature when 5 mol % of TMSOTf was used.
as catalyst, then it was found that 15 mol % of TMSOTf was optimum amount for this transformation. Encouraged by these results, we next investigated the scope of the reaction to various alcohols and 1,3-dicarbonyl compounds under these optimized conditions and the results are summarized in Table 3.1.

Acetyl acetone with 1-arylethanols in the presence of TMSOTf in nitromethane gave the corresponding benzylated products, in good yields (Table 3.1). However, the reaction of 2a with simple benzyl alcohol did not proceed under the optimized conditions, whereas, while heating at 100 °C yielded only 5-10% of corresponding benzylated product. However the reaction of benzoyl acetone (2b) and ethylacetoacetate (2c) with differently substituted 1-arylethanols proceeded smoothly to give the corresponding products in good yields. The presence of electron-donating substituent in para-position of the benzene ring in 1-phenylethanol can increase the reactivity, while the electron-withdrawing substituent in para-position of benzene ring in 1-phenylethanol seems to have a negative effect on the benzylation reaction (Table 3.1, entries 2 and 15), whereas, such effects of electron-donating/electron-withdrawing substituent are not observed in diphenylmethanol and the reaction proceeded very smoothly to give corresponding benzylated products in good yields (Table 3.1, entries 7 to 10).

3.2.6. Plausible mechanism:

The plausible mechanism of this reaction can be speculated (Scheme 3.26) based on the experimental observations. One of the probable routes could be a direct alkylation of C with a stabilized carbocation derived from the alcohol. Another probable pathway, we and others\(^\text{24,29}\) have previously observed is that, with a
catalytic amount of triflates or other Lewis acid, benzylic alcohols were rapidly converted to dimeric ether (A) by elimination of water. The ether is polarized by triflate to generate the incipient benzylic carbocation which may act as the alkylating species. The nucleophilic attack of the β-dicarbonyl compound onto the resulting, benzyl carbocation produce the final alkylated product after the release of proton. Support for this second mechanism was obtained from the isolation of the symmetric ether at the initial stages (with in 10 min) whose structure was confirmed by NMR and which after appropriate time (mentioned in Table 3.1) was fully converted to the corresponding alkylated products.

Scheme 3.26: Plausible mechanism for the TMSOTf catalyzed benzylation.

3.2.7. Conclusion

In summary we have described a simple, convenient and novel methodology for the direct benzylation of β-dicarbonyl compounds with various benzylic alcohols as benzylation agents, using TMSOTf as catalyst. Operational simplicity and good-to-excellent yields are key features of this protocol.
3.2.8. Experimental section

General experimental procedure for the TMSOTf-catalyzed alkylation of 1,3-dicarbonyl compounds

To a mixture of alcohol (1 mmol) and 1,3-dicarbonyl compound (2 mmol) in nitromethane (10 vol), trimethylsilyl trifluoromethane sulfonate (15 mol%) was added drop wise. The reaction mixture was stirred at room temperature for 30 min. After completion of the reaction (monitored by TLC), water was added and extracted with EtOAc, separated the organic layer and washed with water, brine and dried over anhydrous sodium sulfate, concentrated to furnish the desired compound. When necessary, the obtained crude samples were purified by column chromatography.

3.2.9. Characterization of the products

In the present study, we have encountered some new compounds that have not been already reported in the literature (Table 3.1, entries 5, 8, 9, 10, 11, 13, 14, 15, 17, 19, 20, 21, 24, 26, 27) and were confirmed by their IR, LC-MS and $^1$H-, $^{13}$C-NMR data.

3-(1-(3-Methoxyphenyl)ethyl)pentane-2,4-dione (5): Oil. Isolated yield: 73%, IR (neat): 2963, 1725 cm$^{-1}$.$^1$H NMR (CDCl$_3$): $\delta$ (ppm) 7.19–7.28 (m, 1H), 6.74–6.80 (m, 3H), 4.06 (d, J=11.6 Hz, 1H), 3.80 (s, 3H), 3.52–3.63 (m, 1H), 2.28 (s, 3H), 1.88 (s, 3H), 1.22 (d, J=6.8 3H), $^{13}$C NMR (CDCl$_3$): $\delta$ 203.43, 159.84, 144.73, 129.83, 119.53, 113.32, 112.06, 55.55, 40.43, 29.80, 29.72, 17.36. MS: m/z Calcd for C$_{14}$H$_{18}$O$_3$: 234.29; Found: 233.0 (M$^+$). Anal. Calcd for C$_{14}$H$_{18}$O$_3$: C, 71.77; H, 7.74; O, 20.49%. Found: C, 73.10; H, 7.92%.

3-(Bis(4-fluorophenyl)methyl)pentane-2,4-dione(8): White solid. Isolated yield: 90%, mp: 122–123 °C. IR (neat): 3528, 1727 cm$^{-1}$.$^1$H NMR (CDCl$_3$): $\delta$ (ppm) 7.20–
7.23 (m, 4H), 6.96–7.00 (m, 4H), 4.84 (d, J=12.4 Hz, 1H), 4.67 (d, J=12.4 Hz, 1H),
2.02 (s, 6H), $^{13}$C NMR (CDCl$_3$): $\delta$ 202.28, 162.91, 160.47, 137.09, 136.98, 129.29,
129.21, 115.96, 115.74, 74.67, 49.50, 29.57. MS: m/z Calcd for C$_{14}$H$_{16}$F$_2$O$_2$:
302.32%; Found: 301.1 (M$^-$). Anal. Calcd for C$_{14}$H$_{16}$F$_2$O$_2$: C, 71.51; H, 5.33; F,
12.57, O, 10.58. Found: C, 72.80; H, 5.52%.

3-((3,4-Dichlorophenyl)(phenyl)methyl)pentane-2,4-dione(9): White solid, Isolated
yield: 86%, mp: 101–103 °C. IR (neat): 3058, 3030, 1731 cm$^{-1}$. $^1$H NMR (CDCl$_3$): $\delta$
(ppm) 7.29–7.36 (m, 4H), 7.23–7.24 (m, 3H), 7.14 (d, J=8.4 Hz, 1H), 4.81 (d, J=12.4
Hz, 1H), 4.71 (d, J=12.4 Hz, 1H), 2.08 (s, 3H), 2.00 (s, 3H), $^{13}$C NMR (CDCl$_3$): $\delta$
202.00, 141.73, 140.10, 132.95, 131.24, 130.84, 129.79, 129.22, 127.69, 127.52,
127.04, 74.26, 50.04, 29.80. MS: m/z Calcd for C$_{18}$H$_{16}$Cl$_2$O$_2$: 335.22; Found: 333.0
(M$^-$). Anal. Calcd for C$_{18}$H$_{16}$Cl$_2$O$_2$: C, 64.49; H, 4.81; Cl, 21.15, O, 9.55%. Found:
C, 65.60; H, 5.12%.

3-((3,4-Dimethylphenyl)(phenyl)methyl)pentane-2,4-dione(10): White solid,
Isolated yield: 88%, mp: 103–105 °C. IR (neat): 2969, 2941, 1727 cm$^{-1}$. $^1$H NMR
(CDCl$_3$): $\delta$ (ppm) 7.24–7.26 (m, 4H), 7.14–7.17 (m, 1H), 6.98–7.03 (m, 3H), 4.73 (s,
2H), 2.19 (s, 3H), 2.16 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), $^{13}$C NMR (CDCl$_3$): $\delta$
203.21, 203.15, 141.70, 138.69, 137.10, 135.32, 130.12, 129.12, 128.91, 127.69,
126.89, 124.82, 74.59, 50.94, 29.82, 29.61, 19.88, 19.29. MS: m/z Calcd for
C$_{20}$H$_{22}$O$_2$: 294.39; Found: 293.2 (M$^-$). Anal. Calcd for: C$_{20}$H$_{22}$O$_2$: 81.60; H, 7.53; O,
10.87%. Found: C, 83.30; H, 7.92%.

3-(Phenyl(4-(trifluoromethyl)phenyl)methyl) pentane-2,4-dione(11): White
solid, Isolated yield: 65%, mp: 105–106 °C. IR (neat): 3064, 3036, 1732 cm$^{-1}$. $^1$H
NMR (CDCl$_3$): $\delta$ (ppm) 7.50–7.63 (m, 3H), 7.23–7.43 (m, 6H), 4.94 (d, J=12.4 Hz,
1H), 4.81 (d, J=12.4 Hz, 1H), 2.06 (s, 3H), 2.03 (s, 3H), $^{13}$C NMR (CDCl$_3$): δ 202.19, 146.12, 145.47, 140.97, 140.69, 129.83, 129.17, 128.79, 128.18, 125.89, 125.36, 79.83, 74.31, 50.76, 29.69, 29.50. MS: m/z Calcd for C$_{19}$H$_{17}$F$_3$O$_2$: 334.33; Found: 333.2 (M$^+$). Anal. Calcd for C$_{19}$H$_{17}$F$_3$O$_2$: C, 68.26; H, 5.13; F, 17.05, O, 9.57%. Found: C, 69.78; H, 5.97%.

2-(1-(3-Bromophenyl)ethyl)-1-phenylbutane-1,3-dione(13): Oil, Isolated yield: 78%, IR (neat): 3021, 3011, 1668 cm$^{-1}$. $^1$H NMR (CDCl$_3$): δ (ppm) 8.06–8.10 (m, 2H), 7.59–7.64 (m, 1H), 7.48–7.52 (m, 2H), 7.42–7.48 (m, 1H), 7.32–7.37 (m, 1H), 7.16–7.22 (m, 2H), 4.87 (d, J=11.2 Hz, 1H), 3.80–3.88 (m, 1H), 1.93 (s, 3H), 1.20 (d, J=6.8 Hz, 3H), $^{13}$C NMR (CDCl$_3$): δ 202.57, 194.83, 145.70, 137.05, 133.99, 130.55, 130.41, 130.19, 128.95, 128.90, 128.62, 126.31, 122.84, 70.44, 40.51, 28.12, 21.35. MS: m/z Calcd for C$_{18}$H$_{17}$BrO$_2$: 344.04; Found: 343.0 (M$^+$). Anal. Calcd for C$_{18}$H$_{17}$BrO$_2$: C, 62.62; H, 4.96; Br, 23.15; O, 9.25%. Found: C, 63.55; H, 5.18%.

2-(1-(3-Methoxyphenyl)ethyl)-1-phenylbutane-1,3-dione(14): Oil, Isolated yield: 71%, IR (neat): 2965, 2934, 1711 cm$^{-1}$. $^1$H NMR (CDCl$_3$): δ (ppm) 8.09–8.11 (m, 2H), 7.59–7.63 (m, 1H), 7.49–7.53 (m, 2H), 7.23–7.28 (m, 1H), 6.88–6.90 (m, 1H), 6.85 (s, 1H), 6.78–6.84 (m, 1H), 4.94 (d, J=10.8 Hz, 1H), 3.85–3.89 (m, 1H), 3.81 (s, 3H), 1.95 (s, 3H), 1.23 (d, J=6.8 Hz, 3H), $^{13}$C NMR (CDCl$_3$): δ 202.99, 195.18, 159.86, 144.92, 137.25, 133.81, 129.82, 128.87, 119.80, 113.68, 111.98, 70.68, 55.17, 40.95, 28.00, 21.47. MS: m/z Calcd for C$_{19}$H$_{20}$O$_3$: 296.36; Found: 295.2 (M$^+$). Anal. Calcd for C$_{19}$H$_{20}$O$_3$: C, 77.00; H, 6.80; O, 16.20%. Found: C, 79.13; H, 7.31%.

1-Phenyl-2-(1-(4-(trifluoromethyl)phenyl)ethyl) butane-1,3-dione(15): White solid, Isolated yield: 60%, mp: 67–68 °C. IR (neat): 2970 2928, 1715 cm$^{-1}$. $^1$H NMR (CDCl$_3$): δ (ppm) 8.08–8.06 (m, 2H), 7.55–7.63 (m, 3H), 7.47–7.51 (m, 2H), 7.39–
7.44 (m, 2H), 4.94 (d, J=11.2 Hz, 1H), 3.91–3.99 (m, 1H), 1.90 (s, 3H), 1.22 (d, J=6.8 Hz, 3H). \(^{13}\text{C}\) NMR (CDCl\(_3\)): \(\delta\) 202.41, 194.74, 147.52, 137.04, 134.06, 128.96, 128.86, 127.94, 125.6-12576, 70.29, 40.56, 28.07, 21.19. MS: m/z Calcd for C\(_{10}\)H\(_{27}\)F\(_3\)O\(_2\): 334.33; Found: 333.2 (M\(^+\)). Anal. Calcd for C\(_{10}\)H\(_{27}\)F\(_3\)O\(_2\): C, 68.26; H, 5.13; F, 17.05; O, 9.57%. Found: C, 69.16; H, 6.14%.

2-(Bis(4-methoxyphenyl)methyl)-1-phenylbutane-1,3-dione(17): White solid, Isolated yield: 94%, mp: 161–162 °C. IR (neat): 2956, 1727 cm\(^{-1}\). \(^{1}\text{H}\) NMR (CDCl\(_3\)): \(\delta\) (ppm) 7.95–8.01 (m, 2H), 7.51–7.53 (m, 1H), 7.39–7.43 (m, 2H), 7.24–7.28 (m, 2H), 7.10–7.13 (m, 2H), 6.81–6.85 (m, 2H), 6.64–6.68 (m, 2H), 5.52 (d, J=12 Hz, 1H), 5.02 (d, J=12 Hz, 1H), 3.76 (s, 1H), 3.65 (s, 3H), 2.03 (s, 3H). \(^{13}\text{C}\) NMR (CDCl\(_3\)): \(\delta\) 203.23, 194.45, 158.47, 158.11, 137.02, 134.31, 133.67, 133.61, 129.04, 128.72, 128.60, 114.35, 114.03, 69.41, 55.20, 55.10, 49.95, 27.70. MS: m/z Calcd for C\(_{25}\)H\(_{24}\)O\(_4\): 388.46; Found: 387.2 (M\(^+\)). Anal. Calcd for C\(_{25}\)H\(_{24}\)O\(_4\): C, 77.30; H, 6.23; O, 16.47%. Found: C, 78.86; H, 7.69%.

2-((3,4-Dichlorophenyl)(phenyl)methyl)-1-phenylbutane-1,3-dione(19): White solid, Isolated yield: 90%, mp: 152–153 °C. IR (neat): 3056, 3027, 1713 cm\(^{-1}\). \(^{1}\text{H}\) NMR (CDCl\(_3\)): \(\delta\) (ppm) 7.91–7.99 (m, 2H), 7.53–7.58 (m, 1H), 7.39–7.45 (m, 4H), 7.32–7.33 (m, 1H), 7.15–7.26 (m, 4H), 7.06–7.09 (m, 1H), 5.55 (m, 1H), 5.07 (d, J=12 Hz, 1H), 2.07 (s, 3H). \(^{13}\text{C}\) NMR (CDCl\(_3\)): \(\delta\) 203.05, 193.64, 142.15, 141.74, 140.53, 140.07, 136.07, 136.57, 134.05, 133.88, 132.98, 131.28, 129.97–130.9, 128.87-129.25, 127.07-128.84, 68.48, 68.39, 50.51, 50.43, 28.18, 27.97. MS: m/z Calcd for C\(_{23}\)H\(_{18}\)Cl\(_2\)O\(_2\): 397.29; Found: 397.0 (M\(^+\)). Anal. Calcd for C\(_{23}\)H\(_{18}\)Cl\(_2\): C, 69.53; H, 4.57; Cl, 17.85; O, 8.05%. Found: C, 70.60; H, 5.25%.

¹H NMR (CDCl₃): δ (ppm) 7.97–8.02 (m, 2H), 7.53–7.56 (m, 1H), 7.39–7.47 (m, 3H), 7.30–7.34 (m, 1H), 7.21–7.28 (m, 2H), 7.10–7.17 (m, 3H), 7.0–7.08 (m, 2H), 6.90–6.98 (m, 1H), 5.62–5.67 (m, 1H), 5.08 (d, J=12 Hz, 1H), 2.25 (s, 3H), 2.19 (s, 3H), 2.11 (s, 3H), ¹³C NMR (CDCl₃): δ 203.15, 193.52, 142.09, 141.65, 139.14, 138.63, 137.11, 137.05, 136.73, 135.36, 134.87, 133.56, 130.14, 129.84, 129.46, 129.30, 128.93, 128.72, 128.68, 128.60, 128.09, 127.69, 126.96, 126.54, 125.29, 125.58, 6+9.03, 68.90, 51.19, 51.14, 27.84, 27.74, 19.89, 19.77, 19.32, 19.18. MS: m/z Caled for C₂₅H₂₄O₂: 356.46; Found: 355.0 (M). Anal. Caled for C₂₅H₂₄O₂: C, 84.24; H, 6.79; O, 8.98%; Found: C, 85.37; H, 7.01%.

1-Phenyl-2-(phenyl(4-(trifluoromethyl)phenyl)methyl)butane-1,3-dione (21): 

White solid, Isolated yield: 80%, mp: 95–96 °C. IR (neat): 2971, 2918, 1743 cm⁻¹. 

¹H NMR (CDCl₃): δ (ppm) 7.92–7.97 (m, 2H), 7.55–7.58 (m, 4H), 7.53–7.55 (m, 2H), 7.35–7.48 (m, 2H), 7.13–7.21 (m, 3H), 7.06–7.13 (m, 1H), 5.59–5.63(m, 1H), 5.18 (d, J=12 Hz, 1H), 2.05 (s, 3H), ¹³C NMR (CDCl₃): δ 202.25, 193.79, 145.86, 140.69, 136.6, 133.85, 129.52, 128.82, 128.72, 128.48, 127.76, 125.96, 125.68, 15.36, 168.53, 51.19, 28.03. MS: m/z Caled for C₂₄H₁₉F₃O₂: 396.4; Found: 395.0 (M). Anal. Caled for C₂₄H₁₉F₃O₂: C, 72.72; H, 4.83; F, 14.38; O, 8.07%. Found: C, 73.6; H, 5.85%.

Ethyl-2-(bis(4-methoxyphenyl)methyl)-3-oxobutanoate (24): Oil, Isolated yield: 68%, IR (neat): 2958, 2934, 1711 cm⁻¹. 

¹H NMR (CDCl₃): δ (ppm) 7.14–7.20 (m, 4H), 6.76–6.80 (m, 4H), 4.68 (d, J=12 Hz, 1H), 4.43 (d, J=12 Hz, 1H), 3.95–4.01 (m, 2H), 3.72 (s, 3H), 2.08 (s, 3H), 1.01–1.04 (t, 3H), ¹³C NMR (CDCl₃): δ 202.00,
167.80, 158.36, 158.32, 134.12, 133.70, 128.72, 128.59, 114.20, 113.97, 65.69, 61.40, 55.16, 49.42, 29.85, 13.83. MS: m/z Calcd for C_{21}H_{22}O_3: 356.41; Found: 355.2 (M'). Anal. Calcd for C_{21}H_{22}O_3: C, 70.77; H, 6.79; O, 22.45%; Found: C, 72.24; H, 7.68%.

Ethyl-2-((3,4-dichlorophenyl)(phenyl)methyl)-3-oxobutanoate(26): Low melting solid, Isolated yield: 65%, IR (neat): 3060, 3031, 1713 cm^{-1}. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) (ppm) 7.24–7.40 (m, 4H), 7.21–7.23 (m, 3H), 7.13–7.16 (m, 1H), 4.76 (d, J=12 Hz, 1H), 4.50 (d, J=12 Hz, 1H), 3.98–4.09 (m, 2H), 2.29 (s, 3H), 2.19 (s, 3H), 0.99–1.13 (t, 3H), \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 200.76, 167.25, 143.9, 140.43, 132.78, 130.38, 129.78, 128.40, 128.16, 127.72, 127.41, 127.15, 126.57, 125.80, 64.92, 64.611, 61.8, 61.71, 49.78, 49.58, 30.11, 30.04, 13.85, 13.70. MS: m/z Calcd for C_{19}H_{18}Cl_{2}O_3: 365.25; Found: 363.0 (M'). Anal. Calcd for C_{19}H_{18}Cl_{2}O_3: C, 62.48; H, 4.97; Cl, 19.41, O, 13.14%; Found: C, 63.24; H, 5.31%.

Ethyl-2-((3,4-dimethylphenyl)(phenyl)methyl)-3-oxobutanoate(27): White solid, Isolated yield: 62%, mp: 94–96 °C. IR (neat): 3063, 3033, 1712 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) (ppm) 7.24–7.33 (m, 4H), 7.15–7.19 (m, 1H), 7.04–7.06 (m, 3H), 4.73 (d, J=12 Hz, 1H), 4.70 (d, J=12 Hz, 1H), 3.96–4.05 (m, 2H), 2.19 (s, 6H), 2.14 (s, 3H), 1.00–1.08 (m, 3H), \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) 201.91, 167.82, 167.76, 141.96, 141.65, 139.01, 138.67, 136.96, 136.64, 135.20, 134.99, 130.02, 129.81, 129.24, 128.8, 128.56, 127.68, 126.81, 126.69, 124.84, 124.76, 65.33, 65.26, 61.38, 50.61, 50.55, 29.95, 29.86, 19.82, 19.27, 13.81, 13.76. MS: m/z Calcd for C_{21}H_{24}O_3: 324.41; Found: 323.2 (M'). Anal. Calcd for C_{21}H_{24}O_3: C, 77.75; H, 7.46; O, 14.80%; Found: C, 78.84; H, 8.18%.

130
3.2.9.1. Spectra

$^1$H NMR (400 MHz, CDCl$_3$) of compound 5

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 5
$^1$H NMR (400 MHz, CDCl$_3$) of compound 8

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 8

132
$^1$H NMR (400 MHz, CDCl$_3$) of compound 9

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 9
$^1$H NMR (400 MHz, CDCl$_3$) of compound 10

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 10
$^1$H NMR (400 MHz, CDCl$_3$) of compound 11

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 11
$^1$H NMR (400 MHz, CDCl$_3$) of compound 13

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 13
$^1$H NMR (400 MHz, CDCl$_3$) of compound 14

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 14
$^1$H NMR (400 MHz, CDCl$_3$) of compound 15

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 15
$^1$H NMR (400 MHz, CDCl₃) of compound 17

$^{13}$C NMR (100 MHz, CDCl₃) of compound 17
$^1$H NMR (400 MHz, CDCl$_3$) of compound 19

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 19
$^1$H NMR (400 MHz, CDCl$_3$) of compound 20

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 20
$^1$H NMR (400 MHz, CDCl$_3$) of compound 21

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 21
$^1$H NMR (400 MHz, CDCl$_3$) of compound 24

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 24
$^{1}H$ NMR (400 MHz, CDCl$_3$) of compound 26

$^{13}C$ NMR (100 MHz, CDCl$_3$) of compound 26
$^{1}H$ NMR (400 MHz, CDCl$_3$) of compound 27

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 27
CHAPTER 3

Study on Lewis acid catalyzed benzylaion reactions

Part-3

TMSOTf–catalyzed benzylaion of 4-hydroxycoumarin
3.3.1. Introduction

Coumarin and its derivatives are very important classes of heterocyclic compounds due to their wide range of biological activities including antibiotic, antimalarial, antifungal, anti-viral, and cytotoxic.\textsuperscript{38-45} In particular, the 4-hydroxycoumarin derivatives (3-alkylated) have evoked a great deal of interest due to their utility as ‘anticoagulant rodenticides as well as antithrombotic agents such as warfarin, brodifacoum, difethialone, bromadiolone, coumatetralone, and flocoumafen\textsuperscript{46} and also as nonpeptide human immuno deficiency virus (HIV) protease inhibitors\textsuperscript{47}(Fig 3.2).

![Chemical structures](image)

Figure 3.2: Examples of bio-active 4-hydroxycoumarin derivatives

The C3-alkylation of 4-hydroxycoumarin (formation of new C-C bond) is undoubtedly one of the most important and challenging reactions in synthetic chemistry due to its pharmaceutical utility as mentioned above and also can be diversified to synthesize 3,4-substitued compounds.\textsuperscript{48-51}
3.3.2. Review of literature

Lin et al. (2009)\textsuperscript{52}: They have reported a highly efficient method for the C-C bond formation via molecular iodine-catalyzed C3-alkylation reaction of 4-hydroxycoumarins with benzylic, benzhydrylic, allylic, and propargyl alcohols at 50 °C in MeNO\textsubscript{2}.

\[
\text{Scheme 3.27}
\]

R\textsuperscript{3} = alkyl, aryl, alkenyl, alkynyl

Narayana et al. (2012)\textsuperscript{53}: Sulfated tin oxide has been found to be an efficient reusable solid superacid catalyst for C3-alkylation of 4-hydroxycoumarins with benzylic alcohol/and corresponding acetates respectively, in acetic acid under reflux conditions with good yield of products.

\[
\text{Scheme 3.28}
\]

Manjumdar et al. (2002)\textsuperscript{54}: They have described the alkylation of 4-hydroxy coumarin using alkyl halide in presence of potassium carbonate in acetone at reflux condition.

\[
\text{Scheme 3.29}
\]
Thirupathi et al. (2010): A mild and efficient Fe(ClO₄)₃.x H₂O-catalyzed direct C-C bond coupling reaction of 4-hydroxycoumarin with secondary benzylic alcohols have been described.

\[
\begin{align*}
\text{Scheme 3.30}
\end{align*}
\]

Reddy et al. (2008): An efficient and operationally simple method for C3-alkylation of 4-hydroxycoumarins has been developed under acidic medium giving good yields of the products. In the method, a reusable Amberlite® IR-120 (H⁺ form) was used as an acid catalyst and secondary benzyl alcohols were used as alkylating agents.

\[
\begin{align*}
\text{Scheme 3.31}
\end{align*}
\]

Kischel et al. (2007): They have synthesized phenprocoumon from alkylation of 4-hydroxycoumarin with 1-phenylpropane-1-ol in presence of iron(III)-chloride catalyst. This compound is an anticoagulant of the warfarin-class that is widely used in thrombosis prophylaxis.

\[
\begin{align*}
\text{Scheme 3.32}
\end{align*}
\]
Hung et al. (2007)\textsuperscript{27}: They have successfully developed an efficient propargylation of 4-hydroxycoumarins with propargylic alcohols in the presence of 5 mol \% Yb(OTf)\textsubscript{3}.

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme334.png}
\end{center}

3.3.3. Objective

In continuation of benzylolation of 1,3-dicarbonyl compounds, we extended the methodology to develop a simple and efficient protocol for benzylolation of 4-hydroxycoumarin using benzylic alcohols as benzylating agents.

3.3.4. Present Work

While various Lewis acids are employed in modern organic synthesis, triflate based reagents still remain prominent as a result of their high Lewis acid strength and ready availability. The strong organic triflate Lewis acid TMSOTf has emerged in recent years as a viable alternative to metal triflates. Owing to its uniqueness and commercial availability, its applications in organic synthesis are growing and have been reviewed.\textsuperscript{18-21} Inspired by the alkylation reactions using metal-triflates as heterogeneous catalysts, we developed a new, mild alkylation of 4-hydroxycoumarin with alcohols, where an organic-triflate that could be used as a homogeneous catalyst that leading to the reduction of the reaction time and practical difficulties of using the heterogeneous catalyst in large-scale experiments.

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme334.png}
\end{center}

Scheme 3.34: Benzylolation of 4-hydroxycoumarin.
3.3.5. Results and discussion

Initially, the reaction of 4-hydroxycoumarin and diphenylmethanol was chosen as the prototype reaction to develop the optimum reaction conditions (Scheme 3.34). It was found that treating of diphenylmethanol (1 equiv) with 4-hydroxycoumarin in the presence of 15 mol % TMSOTf using nitromethane/dioxane (1:1) as solvent at room temperature gave the corresponding 3-alkylated 4-hydroxycoumarin (5a-5j) in 91% yield (Table 3.2).

Table 3.2 TMSOTf catalyzed alkylation of 4-hydroxycoumarin under the optimum conditions.

<table>
<thead>
<tr>
<th>Entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Alcohol</th>
<th>Product</th>
<th>Time (h)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Yield(&lt;sup&gt;c&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Alcohol 1" /></td>
<td>5a</td>
<td>0.5</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Alcohol 2" /></td>
<td>5b</td>
<td>0.5</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Alcohol 3" /></td>
<td>5c</td>
<td>0.5</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Alcohol 4" /></td>
<td>5d</td>
<td>0.5</td>
<td>81&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Alcohol 5" /></td>
<td>5e</td>
<td>0.5</td>
<td>87&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Alcohol 6" /></td>
<td>5f</td>
<td>0.5</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Alcohol 7" /></td>
<td>5g</td>
<td>0.5</td>
<td>60</td>
</tr>
</tbody>
</table>
After optimizing the reaction conditions, we applied the procedure to a series of substituted benzylic alcohols and 4-hydroxycoumarin. As shown in Table 3.2, various diphenylmethanol derivatives were efficiently reacted with 4-hydroxycoumarin and most of them provided the corresponding products in good to excellent yields under the optimized reaction conditions. Whereas, when 1-phenylethanol was used as alkylating agent, the desired products were isolated in slightly poor yields irrespective of the electron-withdrawing (table 3.2, entry 8) or electron-donating (table 3.2, entry 10) groups on the phenyl ring.

3.3.6. Plausible mechanism

The mechanism is explained in section 3.2.6.

3.3.7. Conclusion

In summary we have described a simple, convenient and novel methodology for the direct benzylation of 4-hydroxycoumarins with various benzylic alcohols as benzylating agents, using TMSOTf as catalyst. Operational simplicity and good-to-excellent yields are key features of this protocol.

3.3.8. Experimental section

General experimental procedure for the C3-alkylation of 4-hydroxycoumarins

To a mixture of 4-hydroxycoumarin (1.0 mmol) and secondary benzyl alcohol (1.2 mmol) in a MeNO₂ (10 ml), trimethylsilyl trifluoromethanesulfonate
(0.15 mmol) was added and the reaction mixture was stirred for the given time (see Table 3.2) at room temperature. After completion of the reaction (monitored by TLC), water was added to the reaction mixture and extracted with ethyl acetate, the combined organic phase was dried over anhydrous sodium sulfate and evaporated under vacuum. The residue was purified by silica gel column with hexane/ethyl acetate as eluent to afford the corresponding C3-alkylated 4-hydroxycoumarin.

3.3.9. Characterization of the products

In the present study, we have encountered some new compounds that have not been already reported in the literature (Table -2, 5d, 5e, 5i, 5j) and were confirmed by their IR, LC-MS and $^1$H-, $^{13}$C-, NMR data.

3-((3,4-Dichlorophenyl)(phenyl)methyl)-4-hydroxy-2H-chromen-2-one(5d):
White solid, Isolated yield: 81%, mp: 130–132 °C. IR (neat): 3058, 1661, 1604 cm$^{-1}$. $^1$H NMR (CDCl$_3$): δ (ppm) 11.9 (br s, 1H), 8.05 (d, J=7.6 Hz, 1H), 7.62–7.66 (m, 1H), 7.53–7.55 (d, J=8.4 Hz, 1H), 7.31–7.40 (m, 3H), 7.20–7.28 (m, 6H), 5.86 (s, 1H), $^{13}$C NMR (CDCl$_3$): δ 162.32, 162.22, 152.85, 144.20, 141.24, 132.73, 130.93, 130.86, 130.50, 129.55, 129.07, 128.75, 126.97, 124.34, 124.01, 116.80, 116.63, 107.24, 45.31. MS: m/z Calcd for C$_{24}$H$_{14}$Cl$_2$O$_3$: 396.03; Found: 397.0 (M$^+$). Anal. Calcd for Anal. Calcd for C$_{24}$H$_{14}$Cl$_2$O$_3$: C, 66.52; H, 3.55; Cl, 17.85; O, 12.08%. Found: C, 67.01; H, 3.75%.

3-((3,4-Dimethylphenyl)(phenyl)methyl)-4-hydroxy-2H-chromen-2-one(5e):
White solid, Isolated yield: 87%, mp: 160–161 °C. IR (neat): 3303, 1627, 1618, cm$^{-1}$. $^1$H NMR (CDCl$_3$): δ (ppm) 11.68 (br s, 1H), 8.03 (d, J=8.0 Hz, 1H), 7.59–7.63 (m, 1H), 7.34–7.38 (m, 2H), 7.16–7.28 (m, 5H), 7.02–7.04 (m, 2H), 6.95–6.97 (m, 1H), 5.79 (s, 1H), 2.17 (s, 3H), 2.15 (s, 3H), $^{13}$C NMR (CDCl$_3$): δ 162.29, 161.42, 152.71, 142.73, 139.79, 135.89, 134.17, 132.45, 130.31, 129.54, 129.06,
128.32, 126.64, 126.30, 124.26, 123.88, 116.69, 108.51, 45.72, 20.00, 19.38. MS: m/z Calcd for C_{24}H_{30}O_3: 356.41; Found: 357.2 (M^+). Anal. Calcd for C_{24}H_{20}O_3: C, 80.88; H, 5.66; O, 13.47%. Found: C, 81.76; H, 6.02%.

3-(1-(3-Bromophenyl)ethyl)-4-hydroxy-2H-chromen-2-one(5i): White solid, Isolated yield: 62%, mp: 203–204 °C. IR (neat): 3220.09, 1667.51, 1624.42, cm^{-1}. \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ (ppm) 11.66 (br s, 1H), 8.03 (d, J=7.6 Hz, 1H), 7.59–7.64 (m, 1H), 7.48 (s, 1H), 7.31–7.39 (m, 4H), 7.21–7.25 (m, 1H), 4.57–4.62 (m, 1H), 1.61–1.63 (d, J=7.2 Hz, 3H), \textsuperscript{13}C NMR (CDCl\textsubscript{3}): δ 161.83, 160.74, 152.59, 147.50, 132.38, 130.52, 130.17, 129.02, 126.79, 124.28, 123.92, 121.80, 116.63, 109.31, 33.78, 16.95. MS: m/z Calcd for C_{17}H_{13}BrO_3: 345.19; Found: 343.0 (M^2). Anal. Calcd for C_{17}H_{13}BrO_3: C, 59.12; H, 3.80; Br, 23.15; O, 13.90%. Found: C, 60.22; H, 4.14%.

4-Hydroxy-3-(1-(3-methoxyphenyl)ethyl)-2H-chromen-2-one(5j): Low melting solid, Isolated yield: 50%, IR (neat): 3077, 2961, 1658, 1603, cm^{-1}. \textsuperscript{1}H NMR (CDCl\textsubscript{3}): δ (ppm) 11.50 (br s, 1H), 8.02 (d, J=7.2 Hz, 1H), 7.57–7.61 (m, 1H), 7.32–7.37 (m, 2H), 7.14–7.19 (m, 1H), 6.89–6.91(m, 2H), 6.71–6.75(m, 2H), 4.55–4.58 (m, 1H), 3.71 (s, 3H), 1.62–1.64 (d, J=6.8 Hz, 3H), \textsuperscript{13}C NMR (CDCl\textsubscript{3}): δ 161.86, 160.43, 159.47, 152.53, 146.23, 132.21, 129.27, 124.20, 123.84, 120.14, 119.98, 116.71, 116.55, 113.77, 110.96, 109.87, 55.31, 33.93, 17.17. MS: m/z Calcd for C_{18}H_{16}O_4: 296.1; Found: 297.0 (M^+). Anal. Calcd for C_{18}H_{16}O_4: C, 72.96; H, 5.44; O, 21.60%. Found: C, 73.21; H, 5.89%.
3.3.9.1. Spectra

$^1$H NMR (400 MHz, CDCl$_3$) of compound 5d

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 5d
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5e

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 5e
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5i

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 5i
$^1$H NMR (400 MHz, CDCl$_3$) of compound 5j

$^{13}$C NMR (100 MHz, CDCl$_3$) of compound 5j
LC/MS REPORT

Data File: D:\DATA\2009\AUG09
Vial No.: P1-A-09
Injection Date: 8/24/2009
Injection vol: 5 μL
Sample Name: PH40AC_ACN_PUROSPE

Method info: Column: PUROSPEBRstar rp-18 (4.6X30 mm, 3μm)
Mobile Phase A: 20mM NH4OAc IN 90% H2O, 10% ACN
Mobile Phase B: 20mM NH4OAc IN 100% H2O, 90% ACN
Flow: 2.2ml/min
Time (min.): 0 2 2.5 3
% B: 0 100 100 0

(DAD) C, Sig=210.4 Ref=off(AUG0)

<table>
<thead>
<tr>
<th>Peak</th>
<th>RT (min)</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.093</td>
<td>1.463e+004</td>
<td>99.452</td>
</tr>
<tr>
<td>2</td>
<td>2.186</td>
<td>5.131e+001</td>
<td>0.348</td>
</tr>
</tbody>
</table>

MSD2 YIC, MS File (D:\DATA\2009\AUG09)

MSD2 SPC, time=9.084, 2.200 of D:\DATA\2009\AUG09

Analysed by

Instrument Code: 2008900010045-002
Page 1 of 1
2.4. References


