Chapter 3: Lewis acid promoted construction of chromen-4-one and isoflavone scaffolds via regio- and chemoselective domino Friedel-Crafts acylation/Allan-Robinson reaction

Domino Friedel-Crafts acylation/Allan-Robinson reaction

C-acylation
O-acylation
Aldolization

Ptaeroxylin: $R^1=R^2=\text{Me}$
Karenin: $R^1=\text{CH}_2\text{OH}, R^2=\text{Me}$
Ptaeroxylinol: $R^1=\text{Me}, R^2=\text{CH}_2\text{OH}$

Ipriflavone: $R^1=\text{CH(Me)}_2, R^2=R^3=\text{H}$
Genisteine: $R^1=R^2=R^3=\text{OH}$

Khellin bronchodilating and antispasmodic activity
3.1 Introduction

3.1.1 Friedel-Crafts and Fries acylation and their substituent dependent reversibility

The alkylation or acylation of aromatic compounds catalyzed by aluminum chloride or other Lewis or Brønsted acids is known as the Friedel-Crafts alkylation or acylation respectively. This electrophilic aromatic substitution reaction was an accidental discovery by Charles Friedel and James Crafts in 1877 and now becomes one of the mostly used reaction method in organic synthesis.\(^2\)

![Scheme 3.1. Friedel-Crafts reaction.](image)

Consequently Fries rearrangement is the conversion of a phenolic ester, mediated by Brønsted or Lewis acids such as HF, AlCl\(_3\), BF\(_3\), TiCl\(_4\) or SnCl\(_4\) to an ortho- or a para-hydroxy ketones. Success and the isomeric distribution of this reaction depends upon the reaction conditions, nature of the acyl group and the structure of the phenol derivative.\(^3\)

![Scheme 3.2. Fries rearrangement.](image)

Effect of substituents in Friedel-Crafts acylation reaction or in Fries rearrangement is a major question and several anomalous results can be found in several literatures.\(^4\) In most of the early literatures abnormal results were not well justified as at that time these reactions are thought to be irreversible in nature.\(^5\) Rosenmund and Schnurr first provided experimental evidence in support of the reversibility of the Fries reaction where heating a number of ortho-hydroxy ketones with camphorsulphonic or sulphuric acid or a similar reagent provided the initial esters.\(^6\) Peter Ludwig Reiter examined the effect of substitution towards reversibility of trifluoromethanesulfonic acid (TFMS) catalyzed Fries rearrangement of 3,5-dimethyl substituted phenolic esters.\(^7\) Reveribity of Friedel Crafts acylation via acetyl exchange was
first examined by Peter H. Gore and co-workers. Cullinane et al. made an extensive study on Fries and Friedel Crafts reaction.

### 3.1.2 Allan-Robinson vs Kostanecki-Robinson vs Baker-Venkataraman reaction

When *ortho*-hydroxyaryl ketones 8 reacted with carboxylic acid derivatives 9 (acyl chlorides, anhydrides etc.) under basic conditions, three different outcomes were obtained depending upon the reaction conditions as well as the substrate structure (Scheme 3.3). First of this possible pathways is the Allan-Robinson reaction which is the synthesis of flavones or isoflavones 12 by the condensation of *ortho*-hydroxyaryl ketones 8 with anhydrides of aromatic acids and their sodium or potassium salts. Another mode of reaction is the Kostanechi-Robinson reaction where coumarins 14 are formed by the condensation of *ortho*-hydroxyaryl ketones 8 with aliphatic acid anhydrides under the similar reaction conditions used in Allan-Robinson reaction. Third possible mode of reaction is the base-catalyzed acyl transfer reaction that converts *ortho*-acylated phenol esters 10 to β-diketones 15 and known as Baker-Venkataraman reaction.

**Scheme 3.3.** Possible reaction modes of *ortho*-acylated phenol esters 10 generated from *ortho*-acylated phenols 8.

### 3.1.3 Chromones and isoflavones

Chromones are secondary metabolites widely distributed in the plant kingdom and have attracted interest for a long time either from a biosynthetic and synthetic point of view or because of their interesting biological activities, especially when used in folk medicine. Chromones are often very active as estrogen receptor modulator and thymidine phosphorylase inhibitor. They have also been employed as insecticidal and antifungal
agents possessing high target affinity and specificity. Substituted isoflavones serve as S-nitrosoglutathione reductase (GSNOR) inhibitors\textsuperscript{15a} and shown to have osteogenic activity.\textsuperscript{15b} The above biological properties has stimulated considerable interest toward the synthesis of natural and unnatural analogues of isoflavones.\textsuperscript{16} Fernanda Borges et al. (2014) documented an excellent review on the synthesis and medicinal importance of natural or non-natural chromone derivatives.\textsuperscript{17}

**3.1.4 Review of literatures (Synthesis of chromones)**

![Scheme 3.4](image)

Scheme 3.4. Available methods to fabricate chromone derivatives.

Besides high natural abundance of chromone based molecules, a large number of synthetic procedures are also very literature rich. The most readily used rout to fabricate chromones 12 are from ortho-acylphenols 8 via the classic Claisen condensation or variation of this reaction (Kostanecki-Robinson, Allan-Robinson and Baker-Vekataraman reaction; See Scheme 3.3). 2-Unsubstituted chromones are often synthesized by the reaction of ortho-acylphenols 8 with triethyl ortho formate and a strong mineral acid, like perchloric acid. The reaction propagates via benzopyrylium salts intermediate.\textsuperscript{18} 3-Formyl chromone derivatives can readily be synthesized by the reaction between ortho-acylphenols 8 and a formylating reagent (Vilsmeier-Haack reagent).\textsuperscript{19} Salicylic acid derivatives 16 are also proved to be a useful precursor toward synthesis of chromone derivatives.\textsuperscript{20}

Only a few reports are available for the synthesis of chromones directly from phenols 7. First of this kind of approach is the Simonis reaction where phenol derivatives were condensed with β-ketoesters (e.g., ethyl acetoacetate) in the presence of phosphorus pentoxide (P\textsubscript{2}O\textsubscript{5}) to obtain chromones.\textsuperscript{21} Another approach where phenols were used as the
initial substrate is the Ruhemann reaction which was largely applied to the synthesis of chromone-2-carboxylic acid derivatives.\textsuperscript{22}

Transition metal mediated C–C cross-coupling strategies were also successfully applied to obtain chromones from \textit{ortho}-hydroxyarylalkynylketones \textsuperscript{17}, either used directly or generated \textit{in situ}.\textsuperscript{23}

3.1.5 Statement of the problem

\begin{center}
\textbf{Scheme 3.5.} Comparison between previous approaches and our work.
\end{center}

Among the reported methods for the synthesis of chromones the most common one is the base catalyzed Allan-Robinson reaction of \textit{ortho}-acylphenols and carboxylic acid derivatives\textsuperscript{10} (Scheme 3.5). In fact the most significant route to fabricate chromones is actually a two-step process, first step is the acid mediated Friedel-Crafts acylation of corresponding phenol and the second one is base mediated Allan-Robinson reaction.

In the recent years, complex molecular architectures of natural products have been obtained from structurally simplified building blocks through a series of carefully choreographed synthetic operations. Thus, new domino protocol to construct synthetically and medicinally very important chromone and isoflavone derivatives with pot, step, and atom economy is highly desirable. As a part of our research programme to devise new domino protocols for the synthesis of biologically relevant molecules, here we describe the use of phenols directly for the synthesis of chromones and isoflavones via Lewis acid promoted domino Friedel-Crafts acylation/Allan-Robinson reaction for the first time. Choice of substrates and reaction conditions in this regard is the crucial factor as the Friedel-Crafts acylation reaction is highly sensitive toward substituents.\textsuperscript{4}
3.1.6 Buttressing effect

Effect of ortho-substituent in aromatic ring is a very well-known phenomenon and termed as ortho-effect; origin of which is mainly steric. But substituent on meta-position of aromatic ring has a distinct effect on its reaction profile. This effect is known as buttressing effect, origin of which is not solely the steric or van der Waals interaction and angular deflections, but is the restriction of movement of one functional group in presence of another.\(^{24}\) We have experienced a strong evidence of buttressing effect and reversibility in Fries or Friedel Crafts reaction when acylation of 4-chloro-3,5-xylenol \(7a\) was attempted. Several unsuccessful efforts were made to do the ortho-C-acylation of substrate \(7a\) by different literature known or some modified Fries or Friedel Crafts acylation reaction process.

3.2 Results and discussion

Table 3.1. Attempted Friedel-Crafts acylation of \(7a\).\(^{a}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mmol)</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Product (Yield(^{b}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlCl(_3) (2.5)</td>
<td>none</td>
<td>100</td>
<td>12</td>
<td>(21a) (86)</td>
</tr>
<tr>
<td>2</td>
<td>AlCl(_3) (2.5)</td>
<td>MeNO(_2)</td>
<td>50</td>
<td>18</td>
<td>(21a) (82)</td>
</tr>
<tr>
<td>3</td>
<td>SnCl(_4) (2.5)</td>
<td>MeNO(_2)</td>
<td>50</td>
<td>18</td>
<td>(21a) (82)</td>
</tr>
<tr>
<td>4</td>
<td>TiCl(_4) (2.5)</td>
<td>MeNO(_2)</td>
<td>50</td>
<td>18</td>
<td>(21a) (45)</td>
</tr>
<tr>
<td>5</td>
<td>SnCl(_4) (2.5)</td>
<td>none</td>
<td>100</td>
<td>8</td>
<td>(20ab) (92)</td>
</tr>
<tr>
<td>6</td>
<td>TiCl(_4) (2.5)</td>
<td>none</td>
<td>100</td>
<td>2</td>
<td>(19ab) (96)</td>
</tr>
<tr>
<td>7</td>
<td>TiCl(_4) (2.5)</td>
<td>none</td>
<td>80</td>
<td>6</td>
<td>(19ab) (88)(^{d})</td>
</tr>
<tr>
<td>8</td>
<td>TiCl(_4) (1.5)</td>
<td>none</td>
<td>100</td>
<td>6</td>
<td>(19ab) (65)(^{e})</td>
</tr>
<tr>
<td>9</td>
<td>TiCl(_4) (0.3)</td>
<td>none</td>
<td>100</td>
<td>6</td>
<td>(19ab) (10)(^{f})</td>
</tr>
</tbody>
</table>

\(^{a}\)Reaction conditions: Mixture of \(7a\) (1 mmol) and \(18b\) (10 mmol) with different Lewis acids was heated under argon atmosphere. \(^{b}\)Isolated pure yield in %. \(^{c}\)No reaction. \(^{d}\)10% of \(7a\) was recovered. \(^{e}\)30% of \(7a\) was recovered; \(^{f}\)85% of \(7a\) was recovered.

We started our investigation by taking 4-chloro-3,5-dimethylphenol \(7a\) and propionic acid \(18b\) as the model substrates under different Lewis acid mediated Friedel-Crafts acylation
conditions\textsuperscript{25} (Table 3.1). Initially, a neat mixture of \textit{7}a (1 mmol), \textit{18}b (10 mmol), and anhydrous \textit{AlCl}\textsubscript{3} (2.5 mmol) was heated at 100 °C under argon atmosphere. No reaction took place even after 12 h of heating and the starting phenol \textit{7}a was recovered unconsumed (Table 3.1, entry 1). Next, the above reaction was performed in nitromethane (\textit{CH}\textsubscript{3}NO\textsubscript{2}) at 50 °C for 18 h. Notably, the reaction proceeded smoothly and an unexpected C–C coupled product \textit{21}a was obtained in 86% yield (Table 3.1, entry 2). Neither our expected product \textit{19}ab nor the C–acylated product 4-chloro-3,5-dimethyl-2-propionylphenol \textit{8}ab was formed. Similar result was obtained when \textit{SnCl}\textsubscript{4} or \textit{TiCl}\textsubscript{4} (2.5 mmol) was used as promoter in nitromethane (Table 3.1, entry 3 and 4). Formation of \textit{21}a proceeds via a six-coordinated sigma-type EDA complex of phenolic derivative \textit{7}a with \textit{AlCl}\textsubscript{3} or \textit{SnCl}\textsubscript{4} where nitromethane plays the dual role of solvent and oxidant.\textsuperscript{26} When the above model reaction was carried out with 2.5 mmol of \textit{SnCl}\textsubscript{4} under solvent-free conditions, interestingly, chemoselective O–acylation of \textit{7}a took place instead of C–acylation affording 4-chloro-3,5-dimethylphenyl propionate \textit{20}ab in 92% yield (Table 3.1, entry 5). Having found an optimum reaction conditions for chemoselective O–acylation, we next examined the scope of this reaction by synthesizing some O–acylated derivatives \textit{20} (Table 3.2). This method of \textit{SnCl}\textsubscript{4} mediated O–acylation of phenols having a specific pattern of substitution may be applicable as an alternative to the other existing methods.\textsuperscript{27}

Next, a mixture of \textit{7}a (1 mmol) and \textit{18}b (10 mmol) was treated with 2.5 mmol of \textit{TiCl}\textsubscript{4} under solvent-free inert conditions. The workup of the reaction afforded the expected chromone derivative \textit{19}ab (Figure 3.1) in quantitative yield involving C–acylation, O–acylation, and aldol condensation as key steps (Table 3.1, entry 6). This unique result prompted us to explore the scope of this \textit{TiCl}\textsubscript{4} promoted domino reaction. In this regard, various substituted phenols \textit{7}a–\textit{h} and different \textit{\alpha}-substituted acetic acids \textit{18}a–\textit{h} were selected as counter substrates for the synthesis of chromen-4-ones and isoflavones \textit{19} (Table 3.3).

\begin{table}[h]
\centering
\begin{tabular}{ccc}
\hline
Entry & \textit{7} & \textit{18} & \textit{20} \\
\hline
Entry & \textit{7} & \textit{18} & \textit{20} \\
\hline
\end{tabular}
\caption{\textit{SnCl}\textsubscript{4} mediated O–acylation of substituted phenols \textit{7}a}
\end{table}
Reaction conditions: Mixture of 7 (1 mmol), 18 (10 mmol), and SnCl₄ (2.5 mmol) was heated at 100 °C under argon atmosphere. Isolated pure yield.

Out of a broad range of substituted phenols used, only the phenolic derivatives substituted at both the meta-positions (7a-f) were found to be capable of providing the desired product chromen-4-ones 19. Propionic acid 18b, its higher homologous 18c-f, and substituted phenyl acetic acids 18g-i as reaction partner were also tolerated well affording the desired product 19 in high yields via a domino Friedel-Crafts acylation/Allan-Robinson reaction (Table 3.3).

Table 3.3. Synthesis of chromen-4-ones and isoflavones 19. a

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Reaction</th>
<th>Product</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Cl</td>
<td>Me</td>
<td></td>
<td>EtOH 18b</td>
<td>19ab</td>
<td>(3 h, 96)</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Cl</td>
<td>Me</td>
<td></td>
<td>n-PrOH 18c</td>
<td>19ac</td>
<td>(6 h, 83)</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Cl</td>
<td>Me</td>
<td></td>
<td>EtOH 18d</td>
<td>19ad</td>
<td>(6 h, 91)</td>
</tr>
</tbody>
</table>
A mixture of 1 mmol of 7, excess of 18 (10 mmol) and 2.5 mmol of TiCl₄ was heated at 100 °C under argon. Isolated pure yield in %.

When the substrate 7b was treated with 18b under the similar optimized reaction conditions, surprisingly, only a trace of the desired product 19bb was obtained along with O-acylated product 20bb in 85% yield (Scheme 3.4). This anomalous result could be due to the buttressing effect of large bromine atom flanked by two methyl groups.

Scheme 3.6. Fate of substituted phenol (7b) having bulky para- and both the meta-substituents present.

Next, 7g and 7h (having one or both the meta-substituent absent) were treated separately with excess of 18b in the presence of TiCl₄ under previously optimized reaction conditions mentioned in Table 3.1, entry 6. The workup of the reaction mixture furnished the ortho-acylated products 8gb and 8hb respectively in quantitative yields (Scheme 3.7).

Scheme 3.7. Fate of substituted phenols (7g and 7h) having one or both the meta-substituents absent.

Interestingly, acetic acid 18a along with 7a under the similar reaction conditions gave an inseparable mixture of 6-chloro-2,5,7-trimethyl-4H-chromen-4-one 19aa, 5’-chloro-2’-hydroxy-4’,6’-dimethyl acetonaphthone 8aa, and 3-acetyl-6-chloro-2,5,7-trimethyl-4H-chromen-4-one 22aa (Figure 1) along with unreacted 7a (Scheme 3.8).
Scheme 3.8. Fate of acetic acid 7a in domino Friedel-Crafts acylation/Allan-Robinson reaction.

![Figure 3.1. ORTEP diagrams of 19ab and 22aa.](image_url)

Reversibility of Friedel-Crafts reaction, which is somehow substituent dependent has a key role in the above domino reaction for the formation of chromen-4-ones 19 (Scheme 3.9). Initial C-acylation yielded *ortho*-acylated phenols 8, which are thermodynamically stable due to hydrogen bonding. However, in the case of substrates 7a-f intermediate 8 would become relatively unstable because acyl group suffers steric repulsion by the adjacent methyl group and by its neighbouring substituent –X. Consequently, acyl group tilted from the plane of the aromatic ring resulting redundancy in resonance, thus makes the bond between the acyl group and the aromatic ring quite labile.\(^{24a}\) Hence, 4,6-disubstituted *ortho*-acyl phenol becomes relatively unstable and an equilibrium between C-acylated product 8 and O-acylated product 20 was established (Scheme 3.9). Intermediates 8 and 20 appear to have similar energy and are present side by side in the reaction medium.\(^7\) Next, *in situ* O-acylation of 8 provided intermediate 8′, which is cyclized via aldol condensation to give the desired chromen-4-ones 19. Compound 19 is planar and aromatic in nature hence; steric destabilization is minimized to some extent. As soon as the intermediate 8 is converted to 19, to maintain the equilibrium, 20 is converted to 8 and the reaction moves toward completion.

![Scheme 3.9. Mechanism for the synthesis of chromen-4-ones 19 and 22.](image_url)
As a control experiment and to emphasize our statement about the reversibility between 20 and 8, we performed the reaction of 20ab (1 mmol) with excess of 18b (10 mmol) in the presence of 2.5 mmol of TiCl4 under the optimized reaction conditions. As per our expectation 19ab was formed in 92% yield after 10 hours of heating (Scheme 3.10).

Scheme 3.10. Control experiment to emphasize the hypothesis about the reversibility between 20 and 8.

The destabilizing steric factor is absent in intermediates 8gb and 8hb making them stable due to intramolecular hydrogen bonding. Thus, the equilibrium mentioned earlier is not possible, therefore, substrates 7g and 7h provided the expected single regioisomer of ortho-acylated product 8 (8gb and 8hb, respectively) in quantitative yield (Scheme 3.7). However, in the case of substrate 7b only a trace of the desired domino product 19bb was obtained along with 85% of O-acylated product 3bb. Here, large size of ‘Br’ atom exerts a massive buttressing effect\(^{17}\) that strongly disfavours the formation of ortho-C-acylated intermediate 8bb, hence the equilibrium mentioned earlier entirely moved towards the direction where the steric crowding can be minimized and provided 20bb almost exclusively.

Interestingly, when acetic acid 18a was used as the acylating reagent, desired chromone 19aa was obtained in trace (6%) along with ortho-C-acylated product 8aa in 60% yield (Scheme 3.8). While the substituent –R becomes –H instead of –Me or its sterically higher analogues, destabilization of the C–C bond between the aryl ring and associated acyl group rather decreased, stabilizing the intermediate 8aa to some extent. In this case major part of the intermediate 8’’ is converted to 22’ by acyl exchange (Baker-Venkataraman reaction) which further transformed to 22aa via intermediate 22’’ (Scheme 3.9).

Under the similar reaction conditions SnCl4 might not be able to trigger the condensation steps B and C mentioned in Scheme 3.9, hence only the O-acylated products were obtained. These observations provided insight into the reaction mechanism and substituent dependent reversibility of Friedel-Crafts acylation reaction. Suitable size and coordinating property of TiCl4 facilitates the condensation steps (Step B and C mentioned in
scheme 3.9) and the reaction advanced forward towards formation of highly substituted chromone frameworks 19 and thus making this domino protocol specific to TiCl₄.

To further validate our mechanistic hypothesis, we attempted to synthesize the intermediate 4-chloro-3,5-dimethyl-2-propionylphenol (8ab) via different strategy and further wished to employ it as initial substrate along with 18b to produce 19ab. We succeeded to synthesize 4-halo-2-(1-hydroxypropyl)-3,5-dimethylphenol 24 but failed to oxidize the hydroxyl group of the secondary alcohol 24 to transform it to 8. Several different reported methods of oxidation were performed but none was found to be successful (Scheme 3.11). This observation again supported the presence of strong steric effect and buttressing effect exerted by the methyl and halogen groups present on the phenyl ring of 24, which provided the main obstacle to oxidize the Sp³–C centre of 24 to Sp²–carbonyl carbon of 8 (Scheme 3.11; for details see Section 2.1.3 of Part-1 of Chapter 2).

![Scheme 3.11. Attempted strategy for the synthesis of C-acylated product 8.](image)

3.3 Conclusion

We have designed and developed an operationally simple, highly efficient, and straightforward method for the synthesis of highly functionalized and structurally unique chromone and isoflavone derivatives from phenols for the first time. This one-pot domino protocol involves Lewis-acid promoted Friedel-Crafts acylation/Allan-Robinson reaction creating two C–C and one C–O new bonds in a single operation. We also established the substituent dependent reversibility of Friedel-Crafts acylation through experimental observations. Furthermore, how buttressing effect guided the outcomes of this reaction is thoroughly assessed and supported by appropriate experiments. The scope and diversity of the tolerated substrates in this work is rather broad in comparison with the reported ones. A plausible reaction mechanism was proposed to account for the cascade reaction.
3.4 Experimental section

3.4.1 General experimental details

$^1$H and $^{13}$C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shift ($\delta$) values are given in parts per million (ppm) with reference to tetramethylsilane (TMS) as the internal standard. Coupling constant ($J$) values are given in Hertz (Hz). High resolution mass spectra (HRMS) were recorded by ESI method. Organic solvents were dried by standard methods prior to be used. Commercially obtained reagents were used after further purification when needed. All these reactions were monitored by TLC with silica gel coated plates. Column chromatography was carried out whenever needed, using silica gel of 100/200 mesh. Mixture of hexane/ethyl acetate in appropriate proportion (determined by TLC analysis) was used as eluent.

3.4.2 General procedure for the synthesis of 20

A mixture of 1 mmol of 1, excess of 2 (10 mmol), and 2.5 mmol of SnCl$_4$ was heated at 100 °C under argon atmosphere for the stipulated period of time mentioned in Table 2 of the main manuscript (Completion of the reaction was monitored via TLC analysis). As in some cases boiling point of the initial substrate 2 was less than 100 °C, cold circulatory bath fitted with condenser was used to minimize the evaporation of the concerned substrate. After completion of the reaction, the residue obtained was dissolved in ethyl acetate (100 mL) and washed with 4% aqueous HCl (100 mL×2) followed by water, dilute NaHCO$_3$, and brine. Ethyl acetate was evaporated and crude was purified by column chromatography whenever needed using mixture of EtOAc and hexane in appropriate proportion as eluent to provide pure 3.

3.4.3 Characterization data

4-Chloro-3,5-dimethylphenylpropionate (20ab)

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 6.81 (s, 2H), 2.59 (q, $J = 7.5$ Hz, 2H), 2.35 (s, 6H), 1.27 (t, $J = 7.5$ Hz, 3H); $^{13}$C-NMR (75 MHz, CDCl$_3$) $\delta$ 172.9, 148.3, 137.3, 131.5, 121.3, 27.6, 20.7, 8.9; HRMS (ESI-TOF) of C$_{13}$H$_{11}$ClO$_2$ (m/z) = 235.0504 [M+Na$^+$] (calculated = 235.0502).
4-Chloro-3,5-dimethylphenyl-2-phenylacetate (20ag)

\[ \text{\textsuperscript{1}H-NMR (300 MHz, CDCl}_3) \delta 7.25-7.19 \text{ (m, 5H), 6.67 \text{ (s, 2H), 3.70 (s, 2H), 2.21 (s, 6H));} \text{ \textsuperscript{13}C-NMR (75 MHz, CDCl}_3) \delta 169.8, 148.2, 137.3, 133.2, 131.6, 129.1, 128.6, 127.2, 121.1, 41.2, 20.6; HRMS (ESI-TOF) of C\textsubscript{16}H\textsubscript{15}ClO\textsubscript{2} (m/z) = 275.0838 \text{ [M+H\textsuperscript{+}] (calculated = 275.0839).} \]

4-Bromo-3,5-dimethylphenylpropionate (3bb)

\[ \text{\textsuperscript{1}H-NMR (300 MHz, CDCl}_3) \delta 6.81 \text{ (s, 2H), 2.593 (q, } J = 7.5 \text{ Hz, 2H), 2.38 (s, 6H), 1.27 (t, } J = 7.2 \text{ Hz); \textsuperscript{13}C-NMR (75 MHz, CDCl}_3) \delta 172.8, 149.0, 139.3, 123.9, 121.1, 27.6, 23.8, 8.9; \]

2,3,5-Trimethylphenylpropionate (3eb)

\[ \text{\textsuperscript{1}H-NMR (300 MHz, CDCl}_3) \delta 6.83 \text{ (s, 1H), 6.65 \text{ (s, 1H), 2.62 (q, } J = 7.5 \text{ Hz, 2H), 2.25-2.23 \text{ (m, 6H), 2.00 \text{ (s, 3H), 1.29 (t, } J = 7.5 \text{ Hz, 3H); \textsuperscript{13}C-NMR (75 MHz, CDCl}_3) \delta 172.8, 148.9, 137.9, 135.7, 128.2, 125.2, 119.7, 27.5, 20.6, 19.8, 11.8, 9.1; HRMS (ESI-TOF) of C\textsubscript{12}H\textsubscript{16}O\textsubscript{2} (m/z) = 193.1228 \text{ [M+H\textsuperscript{+}] (calculated = 193.1229).} \]

6-Chloro-2,5,7-trimethyl-4\textit{H}-chromen-4-one (5aa)

\[ \text{\textsuperscript{1}H-NMR (300 MHz, CDCl}_3) \delta 7.15 \text{ (s, 1H), 6.06 \text{ (s, 1H), 2.96 \text{ (s, 3H), 2.47 \text{ (s, 3H), 2.30 \text{ (s, 3H); \textsuperscript{13}C-NMR (75 MHz, CDCl}_3) \delta 179.6, 163.9, 142.0, 138.0, 137.2, 132.3, 117.2, 111.8, 111.7, 21.8, 19.8, 18.0.} \]

6-Chloro-2-ethyl-3,5,7-trimethyl-4\textit{H}-chromen-4-one (5ab)

\[ \text{\textsuperscript{1}H-NMR (300 MHz, CDCl}_3) \delta 7.12 \text{ (s, 1H), 2.97 \text{ (s, 3H), 2.70 (q, } J = 7.65 \text{ Hz, 2H), 2.44 \text{ (s, 3H), 2.00 \text{ (s, 3H), 1.30 (t, } J = 7.65 \text{ Hz, 3H); \textsuperscript{13}C-NMR (75 MHz, CDCl}_3) \delta 179.4, 163.8, 155.2, 141.4, 137.8, 131.7, 119.8, 117.0, 116.6, 25.2, 21.7, 18.0, 11.2, 9.7; CCDC 932483; HRMS (ESI-TOF) of C\textsubscript{14}H\textsubscript{15}ClO\textsubscript{2} (m/z) = 251.0838 \text{ [M+H\textsuperscript{+}] (calculated m/z = 251.0839).} \]
6-Chloro-3-ethyl-5,7-dimethyl-2-propyl-4H-chromen-4-one (5ac)

\[ \text{H-NMR (300 MHz, CDCl}_3 \] \( \delta \) 7.11 (s, 1H), 2.98 (s, 3H), 2.64-2.45 (m, 5H), 1.80-1.72 (m, 2H), 1.29-1.25 (m, 2H), 1.13 (t, \( J = 7.5 \) Hz, 3H), 1.04 (t, \( J = 7.5 \) Hz, 3H); \[ ^{13}\text{C-NMR (75 MHz, CDCl}_3 \] \( \delta \) 178.9, 162.9, 155.2, 141.3, 137.8, 131.7, 123.3, 121.3, 120.3, 117.0, 33.2, 21.7, 20.7, 18.0, 13.8, 13.7; HRMS (ESI-TOF) of C\text{16}H\text{19}ClO\text{2} (m/z) = 279.1152 [M+H\text{+}] (calculated = 279.1154).

6-Chloro-2-heptyl-3-hexyl-5,7-dimethyl-4H-chromen-4-one (5ad)

\[ \text{H-NMR (300 MHz, CDCl}_3 \] \( \delta \) 7.07 (s, 1H), 2.94 (s, 3H), 2.61 (t, \( J = 7.5 \) Hz, 2H), 2.41 (broad, 5H), 1.73-1.63 (m, 2H), 1.27-1.22 (broad, 15H), 0.86 (broad, 7H); \[ ^{13}\text{C-NMR (75 MHz, CDCl}_3 \] \( \delta \) 179.0, 163.3, 155.2, 141.3, 137.8, 131.7, 121.9, 120.2, 116.9, 31.6, 31.4, 29.5, 29.3, 29.2, 28.9, 28.8, 27.3, 24.8, 22.6, 22.5, 21.7, 18.1, 18.0, 14.0; HRMS (ESI-TOF) of C\text{24}H\text{35}ClO\text{2} (m/z) = 391.2401 [M+H\text{+}] (calculated 391.2398).

6-Chloro-5,7-dimethyl-2-nonyl-3-octyl-4H-chromen-4-one (5ae)

\[ \text{H-NMR (300 MHz, CDCl}_3 \] \( \delta \) 7.11 (s, 1H), 2.98 (s, 3H), 2.64 (t, \( J = 7.5 \) Hz, 2H), 2.45 (broad, 5H), 1.71-1.66 (m, 2H), 1.27 (broad, 23H), 0.87-0.85 (broad, 7H); \[ ^{13}\text{C-NMR (75 MHz, CDCl}_3 \] \( \delta \) 179.0, 163.3, 155.2, 141.3, 137.9, 131.7, 122.0, 120.3, 117.0, 31.8, 31.4, 29.9, 29.4, 29.3, 27.3, 24.8, 22.6, 21.7, 18.1, 14.0; HRMS (ESI-TOF) of C\text{28}H\text{43}ClO\text{2} (m/z) = 447.3033 [M+H\text{+}] (calculated 447.3024).

6-Chloro-3-(2-chloroethyl)-2-(3-chloropropyl)-5,7-dimethyl-4H-chromen-4-one (5af)

\[ \text{H-NMR (300 MHz, CDCl}_3 \] \( \delta \) 7.15 (s, 1H), 3.79 (t, \( J = 6.3 \) Hz, 2H), 3.65 (t, \( J = 6.3 \) Hz, 2H), 3.00-2.90 (m, 7H), 2.47 (s, 3H), 2.62-2.21 (m, 2H); \[ ^{13}\text{C-NMR (75 MHz, CDCl}_3 \] \( \delta \) 178.6, 163.4, 155.2, 142.1, 138.0, 132.3, 119.9, 118.4, 117.0, 43.9, 43.3, 29.8, 28.9, 28.6, 21.8, 18.0; HRMS (ESI-TOF) of C\text{16}H\text{17}Cl\text{2}O\text{2} (m/z) = 389.0810 [M+Na\text{+}] (calculated 389.0816).

2-Benzyl-6-chloro-5,7-dimethyl-3-phenyl-4H-chromen-4-one (5ag)

\[ \text{H-NMR (300 MHz, CDCl}_3 \] \( \delta \) 7.46-7.14 (m, 11H), 3.82 (s, 2H), 2.94 (s, 3H), 2.47 (s, 3H); \[ ^{13}\text{C-NMR (75 MHz, CDCl}_3 \] \( \delta \) 155
\[ \delta 178.7, 161.7, 155.2, 142.1, 138.4, 135.9, 133.1, 132.3, 131.0, 130.6, 128.6, 127.0, 124.9, 120.8, 117.3, 38.6, 21.8, 18.2; \text{HRMS (ESI-TOF)} \text{ of } C_{24}H_{19}ClO_2 \text{ (m/z) } = 375.1153 \text{ [M+H\(^+\)]} \text{ (calculated 375.1152).} \\

\text{6-Chloro-2-(4-fluorobenzyl)-3-(4-fluorophenyl)-5,7-dimethyl-4H-chromen-4-one (5ah)} \\
\begin{align*}
1H-NMR & (300 \text{ MHz, CDCl}_3) \delta 7.24-6.93 \text{ (m, 9H), 3.78 (s, 2H), 2.92 (s, 3H), 2.47 (s, 3H); } \text{13C-NMR (75 MHz, CDCl}_3) \delta 178.3, 164.1, 163.5, 161.8, 160.8, 160.2, 155.2, 142.4, 138.4, 132.5, 132.3, 131.5, 130.1, 130.0, 128.7, 123.8, 120.5, 117.2, 115.7, 115.4, 37.4, 21.8, 18.0; \text{HRMS (ESI-TOF)} \text{ of } C_{14}H_{17}ClF_2O_2 \text{ (m/z) } = 411.0964 \text{ [M+H\(^+\)]} \text{ (calculated 411.0958).} \\
\end{align*}

\text{6-Chloro-2-(3,4-dichlorobenzyl)-3-(3,4-dichlorophenyl)-5,7-dimethyl-4H-chromen-4-one (5ai)} \\
\begin{align*}
1H-NMR & (300 \text{ MHz, CDCl}_3) \delta 7.53 \text{ (d, } J = 8.4 \text{ Hz, 1H), 7.35-7.32 \text{ (m, 2H), 7.25-7.18 \text{ (m, 2H), 7.09 (d, } J = 8.1 \text{ Hz, 1H), 6.97 (d, } J = 8.4 \text{ Hz, 1H), 3.77 (s, 2H), 2.92 (s, 3H), 2.49 (s, 3H); } \text{13C-NMR (75 MHz, CDCl}_3) \delta 177.7, 166.8, 160.9, 155.1, 142.9, 138.6, 135.5, 133.1, 132.9, 132.8, 132.6, 132.5, 132.4, 130.7, 130.5, 129.9, 127.9, 123.1, 117.2, 117.2, 37.4, 21.9, 18.1; \text{HRMS (ESI-TOF)} \text{ of } C_{24}H_{15}Cl_2O_2 \text{ (m/z) } = 534.9376 \text{ [M+Na\(^+\)]} \text{ (calculated 534.9383).} \\
\end{align*}

\text{6-Bromo-2-ethyl-3,5,7-trimethyl-4H-chromen-4-one (5bb)} \\
\begin{align*}
1H-NMR & (300 \text{ MHz, CDCl}_3) \delta 7.17 \text{ (s, 1H), 3.05 (s, 3H), 2.71 (q, } J = 7.5 \text{ Hz, 2.51 (s, 3H), 2.01 (s, 3H), 1.26-1.25 \text{ (m, 3H); HRMS (ESI-TOF) of } C_{14}H_{15}BrO_2 \text{ (m/z) } = 294.0237 \text{ [M\(^+\)]} \text{ (calculated 294.0255).} \\
\end{align*}

\text{2-Ethyl-3,5,7-trimethyl-4H-chromen-4-one (5cb)} \\
\begin{align*}
1H-NMR & (300 \text{ MHz, CDCl}_3) \delta 6.98 \text{ (s, 1H), 6.84 (s, 1H), 2.81 (s, 3H), 2.68 (q, } J = 7.5 \text{ Hz, 2H), 2.35 (s, 3H), 1.99 (s, 3H), 1.29 (t, } J = 7.5 \text{ Hz, 3H); } \text{13C-NMR (75 MHz, CDCl}_3) \delta 179.9, 163.8, 157.3, 142.5, 140.1, 128.2, 118.5, 116.2, 115.3, 25.1, 22.5, 21.2, 11.1, 9.3; \text{HRMS (ESI-TOF) of } C_{14}H_{16}O_2 \text{ (m/z) } = 239.1046 \text{ [M+Na\(^+\)]} \text{ (calculated 239.1043).} \\
\end{align*}
2-Ethyl-3,5,6,7-tetramethyl-4H-chromen-4-one (5db)

\[ \text{1H-NMR (300 MHz, CDCl}_3\text{)} \delta 7.01 (s, 1H), 2.84 (s, 3H), 2.68 (q, J = 7.5 Hz, 2H), 2.34 (s, 3H), 2.21 (s, 3H), 2.00 (s, 3H), 1.29 (t, J = 7.5 Hz, 3H); \]

\[ \text{13C-NMR (75 MHz, CDCl}_3\text{)} \delta 180.4, 163.3, 155.3, 141.9, 137.9, 132.1, 118.9, 116.3, 115.7, 25.2, 21.5, 17.1, 15.1, 11.2, 9.7; \]

HRMS (ESI-TOF) of C\textsubscript{15}H\textsubscript{18}O\textsubscript{2}\text{ (m/z) = 253.1193 [M+Na}^+\text{]} (calculated 253.1199).

2-Ethyl-3,5,7,8-tetramethyl-4H-chromen-4-one (5eb)

\[ \text{1H-NMR (300 MHz, CDCl}_3\text{)} \delta 6.86 (s, 1H), 2.78-2.68 (m, 5H), 2.32-2.29 (m, 6H), 2.00 (s, 3H), 1.33 (t, J = 7.5 Hz, 3H); \]

\[ \text{13C-NMR (75 MHz, CDCl}_3\text{)} \delta 180.6, 163.6, 155.3, 140.8, 136.8, 128.7, 122.3 118.8, 115.9, 25.2, 22.5, 20.0, 11.3, 9.4; \]

HRMS (ESI-TOF) of C\textsubscript{15}H\textsubscript{18}O\textsubscript{2}\text{ (m/z) = 231.1381 [M+H}^+\text{]} (calculated 231.1385).

2-Ethyl-3,5,7,8-tetramethyl-4-oxo-4H-chromen-6-yl propionate (5fb)

\[ \text{1H-NMR (300 MHz, CDCl}_3\text{)} \delta 2.73-2.64 (m, 7H), 2.35 (s, 3H), 2.16 (s, 3H), 2.00 (s, 3H), 1.35-1.25 (m, 6H); \]

\[ \text{13C-NMR (75 MHz, CDCl}_3\text{)} \delta 180.5, 172.4, 163.7, 153.1, 144.2, 134.4, 128.2, 123.8, 119.1, 116.0, 27.3, 25.2, 13.8, 13.6, 11.8, 11.2, 9.5, 9.2; \]

HRMS (ESI-TOF) of C\textsubscript{18}H\textsubscript{22}O\textsubscript{2}\text{ (m/z) = 325.1410 [M+Na}^+\text{]} (calculated 325.1410).

5,5'-dichloro-4,4',6,6'-tetramethyl-[1,1'-biphenyl]-2,2'-diol (6a)

\[ \text{1H-NMR (300 MHz, CDCl}_3\text{)} \delta 6.82 (s, 2H), 4.59 (s, 2H), 2.40 (s, 6H), 2.04 (s, 6H); \]

\[ \text{13C-NMR (75 MHz, CDCl}_3\text{)} \delta 151.7, 138.7, 136.6, 127.1, 118.6, 115.6, 21.0, 17.7. \]
$^1$H- and $^{13}$C-NMR of 6-Chloro-2-ethyl-3,5,7-trimethyl-4H-chromen-4-one 5ab
3.5 References


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