Chapter 3

Three Component Condensation Reactions of Isoquinoline and Dimethyl acetylenedicarboxylate with N-Tosylimines and Aldehydes

3.1 Introduction

Organic synthesis has reached a high degree of sophistication, thus allowing the synthesis of complex molecules, natural and unnatural, divergently rather than convergently or sequentially in many steps according to their complexity. An "ideal synthesis" should lead to the desired product in as few steps as possible, in good overall yield and by using environmentally compatible reagents. In this respect, multicomponent reactions provide a powerful tool for the one-pot synthesis of diverse and complex organic molecules on the one hand, and small and 'drug like' heterocycles on the other hand. In the following section a brief introduction to multicomponent reactions is provided.

3.1.1 Multicomponent Reactions (MCRs)

Reactions in which more than two starting materials react to form a product, in such a way that most of the atoms of the starting materials are retained in the product are called multicomponent reactions (MCRs). These are efficient reactions where atom economy is maintained. These reactions by virtue of their convergence, productivity, facile execution and generally high yields of products, are especially attractive from the vantage point of combinatorial chemistry.
In contrast to the conventional two component reactions, MCRs are variable. Many of the classical MCRs are name reactions; Strecker synthesis\(^2\), Mannich reaction\(^3\), Biginelli reaction\(^4\) and Hantzsch pyridine synthesis\(^5\) are examples of well-known MCRs that have been known for nearly a centuary. A large and important class of MCRs are the isocyanide based multicomponent reactions (IMCRs).\(^6\) The following sections will give a brief account of IMCRs. Passerini reaction (P-3CR) and Ugi reaction (U-4CR) are the two major IMCRs.

**Passerini Reaction (P-3CR)**

The classical reaction between carboxylic acids, oxo compounds and C-isocyanides, described by Passerini in 1921, provided an efficient and direct access to \(\alpha\)-acyloxy carboxamides in one step. A typical example of Passerini reaction is given below (Scheme 3.1).

![Scheme 3.1](image)

The Passerini reaction is accelerated in aprotic solvents, indicating a non-ionic mechanism. A plausible mechanistic rationale for the reaction is given in Scheme 3.2.

![Scheme 3.2](image)

An interesting variation of Passerini reaction with \(\alpha\)-chloroketone 5, isocyanide 6 and carboxylic acid 7, resulted in the synthesis of 3-acyloxy-2-azetidinones (Scheme 3.3).\(^8\)
Ugi Reaction (U-4CR)

In 1959, Ugi et al. described an important four-component condensation, the U-4CRs. The characteristic feature of the Ugi reaction is the α-addition of an iminium ion and the anion of a suitable acid to an isocyanide, followed by a spontaneous rearrangement of the α-adduct into a stable α-amino carboxamide derivative (Scheme 3.4).

\[
\text{R}_1\text{-CHO} + \text{R}_2\text{-NH}_2 + \text{R}_3\text{-CO}_2\text{H} + \text{R}_4\text{-NC} \rightarrow \text{R}_1\text{-CON}_2\text{H} + \text{R}_2\text{CON}\text{H}_2 + \text{R}_3\text{-CO}_2\text{H} + \text{R}_4\text{-CON}\text{H}_2
\]

Scheme 3.4

The mechanism for the formation of stable α-amino carboxamide derivatives can be outlined as follows (Scheme 3.5).

This reaction was found to be general and applicable to the synthesis of a variety of organic compounds depending on the selection of each component. Any known type of C-isocyanide can be used as the isocyanide component and the only restriction for the acid component is that it must be able to rearrange...
irreversibly from the intermediate $\alpha$-adduct of the isocyanide to deliver a stable product. Except for sterically hindered diaryl ketones, most aldehydes and ketones can generally be used as carbonyl components. Ammonia, primary amines and secondary amines as well as hydrazine derivatives can be used as amine component. The U-4CR and related reactions can produce more different classes of chemical products than any other type of known reaction and are highly useful for the synthesis of peptide and $\beta$-lactam derivatives.\(^\text{10}\)

An interesting application of U-4CR is the one step formation of the $\beta$-lactam 12 from $\beta$-aminoacid 9, oxo compound 10 and isocyanide 11 (Scheme 3.6).\(^\text{11}\)

1,4-Dihydropyridines such as 21 were first synthesized more than a hundred years ago in a four component reaction by Hinsch et al. from ammonia, formaldehyde and butane-2,3-dione. Recently this dihydropyridine synthesis has been applied to the synthesis of Motuporin\(^\text{12}\), a very important calcium channel blocker in cardiovascular therapy.

**Scheme 3.6**

MCRs with isocyanides are often used in the total synthesis of natural products. A typical example of this application is furnished in the total synthesis of protein phosphatase (PP) inhibitor Motuporin 13 (Scheme 3.7).\(^\text{12}\)

**Scheme 3.7**
3.1.2 Heterocyclic Synthesis Using Multicomponent Reactions

The first important application of MCRs in natural product synthesis dates back to 1917, when Robinson synthesised the alkaloid tropinone 17 from succinic aldehyde 14, methylamine 15 and dimethyl acetonedicarboxylate 16 (Scheme 3.8).\[^{13}\]

![Scheme 3.8](image)

1,4-Dihydropyridines such as 21 were first synthesized more than a hundred years ago in a four component reaction by Hantzsch et al. from ammonia 20, aldehyde 18 and acetoacetic ester 19 (Scheme 3.9).\[^{4}\] Recently this dihydropyridine synthesis has been applied to the synthesis of Nifedipin®, a very important calcium channel blocker for cardiovascular therapy.\[^{14}\]

![Scheme 3.9](image)

Another important MCR is the Bucherer-Bergs hydantoin synthesis, an extension of Strecker's $\alpha$-aminoacid synthesis, by the introduction of CO$_2$ as the fourth component (Scheme 3.10).\[^{15}\]

![Scheme 3.10](image)
In 1967 Huisgen et al. described an efficient three component condensation based on 1,4-dipolar cycloaddition reaction. They have shown that the reaction of isoquinoline, DMAD and various dipolarophiles leads to the synthesis of condensed isoquinoline derivatives (Scheme 3.11).  

\[
\text{\begin{align*}
\text{Isoquinoline} + \text{DMAD} + \text{Dipolarophile} & \rightarrow \text{Condensed Isoquinoline Derivative} \\
\text{Scheme 3.11}
\end{align*}}
\]

3.2 Background to the Present Work

In the context of the general interest in heterocyclic constructions via dipolar cycloaddition reactions, investigations carried out in our laboratory have shown that the 1,3-dipolar species generated by the reaction of cyclohexyl isocyanide and DMAD can be trapped with dipolarophiles such as aldehydes and \(N\)-tosylamines, resulting in the facile synthesis of aminofurans and aminopyrroles respectively (Scheme 3.12).  

\[
\text{\begin{align*}
\text{Scheme 3.12}
\end{align*}}
\]
Related investigations in our laboratory have also shown that dipolar species generated by the addition of dimethoxy carbene to DMAD can be trapped with aldehydes, leading to the formation of dihydrofurans in high yields (Scheme 3.13).\(^\text{18}\)

Impressed by the reactivity of the 1,4-dipole generated from pyridine and DMAD towards dipolarophiles (see Chapter 2), it was considered worthwhile to explore the reactivity of 1,4-dipole generated from isoquinoline and DMAD towards various dipolarophiles. The results of our investigations constitute the subject matter of this chapter.

### 3.3 Results and Discussion

#### 3.3.1 Reaction of Isoquinoline and DMAD with N-tosylimines

The N-tosylimines selected for our study are shown in Figure 3.1
Figure 3.1

Our studies were set to motion by dissolving isoquinoline, DMAD and N-tosylimine 25, in dry DME and stirring the solution at room temperature for 3 h under argon atmosphere. An exceedingly facile reaction occurred with stereoselective formation of novel 2H-pyrimido[2,1-a]isoquinoline derivatives 34a and 34b in 93% yield in the ratio 6:1 (Scheme 3.14).19

The structure of the products 34a and 34b were elucidated by spectroscopic methods. The diastereomeric ratio was determined from $^1$H NMR and the major diastereomer 34a was separated by crystallisation. In the IR spectrum, the sharp bands at 1748 and 1703 cm$^{-1}$ were assigned to the two ester carbonyls. In the $^1$H NMR spectrum, the signals due to methoxy groups were observed at $\delta$ 3.63 and 3.85 as two singlets, while the ring junction proton was observed as a singlet at $\delta$ 6.13. The other benzylic proton was observed as a
singlet at $\delta$ 5.90, while the two olefinic protons were discernible as doublets at $\delta$ 5.89 and 5.64 respectively. In the $^{13}$C NMR spectrum, the two ester carbonyl signals were observed at $\delta$ 164.99 and 162.91, while the two methoxy carbons were seen resonating at $\delta$ 52.98 and 51.88. Finally, the structure and stereochemistry of the major diastereomer 34a was established unambiguously by single crystal X-ray analysis (Figure 3.2).

![Figure 3.2 X-ray Crystal structure of 34a](image)

![Figure 3.3 $^1$H NMR of 34a](image)
Mechanistically the reaction may be rationalized to involve the initial addition of isoquinoline to DMAD to form the 1,4-dipole 24, which adds to carbon-nitrogen double bond of the N-tosylimine, resulting in the [4+2] adduct (Scheme 3.15).

Figure 3.4 $^{13}$C NMR of 34a

In all the cases, the compounds were completely characterised and their structure established by spectroscopic methods. The pyrimido-isoquinolines 35-37, showed characteristic carbomethoxy carbonyl broad at 10.1 and $^{13}$C NMR spectra. All the other spectroscopic data were also in agreement with the assigned structure.
Similar reactivity was observed with other aromatic $N$-tosylimines with electron withdrawing groups such as $N$-tosyl-2-chlorobenzaldimine 26, $N$-tosyl-3-nitrobenzaldimine 27, $N$-tosyl-3,4-dichlorobenzaldimine 28, which underwent facile reaction with isoquinoline and DMAD yielding the corresponding 2H-pyrimido[2,1-$a$]isoquinoline derivatives as mixture of diastereomers with good selectivity and in high yields (Table 3.1).

**Table 3.1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>$N$-tosylimine</th>
<th>Product $^a$</th>
<th>Ratio $^b$</th>
<th>Yield(%)$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><img src="https://example.com/image1" alt="Image" /></td>
<td><img src="https://example.com/image2" alt="Image" /></td>
<td>10:1</td>
<td>92</td>
</tr>
<tr>
<td>2.</td>
<td><img src="https://example.com/image3" alt="Image" /></td>
<td><img src="https://example.com/image4" alt="Image" /></td>
<td>10:1</td>
<td>73</td>
</tr>
<tr>
<td>3.</td>
<td><img src="https://example.com/image5" alt="Image" /></td>
<td><img src="https://example.com/image6" alt="Image" /></td>
<td>5:1</td>
<td>60</td>
</tr>
</tbody>
</table>

Reaction conditions: dry DME, Ar, rt, 3 h, $a =$ structure of major isomer shown, $b =$ ratio determined by $^1$H NMR, $^*$ = isolated yield

In all the cases, the compounds were completely characterised and their structure established by spectroscopic methods. The pyrimido-isoquinolines 35-37, showed characteristic carbomethoxy carbonyls both in the IR and $^{13}$C NMR spectra. All the other spectroscopic data were also in good agreement with the assigned structure.

Analogous reaction was observed with other $N$-tosylimines 29-33 derived from electron donating aldehydes, furnishing the pyrimido-isoquinoline adducts
38-42 in moderate yields with good diastereoselectivity (Table 3.2).

Table 3.2

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-tosylimine</th>
<th>Product</th>
<th>Ratio</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>NTs</td>
<td><img src="image1.png" alt="Image" /></td>
<td>6:1</td>
<td>43</td>
</tr>
<tr>
<td>2.</td>
<td>CH3</td>
<td><img src="image2.png" alt="Image" /></td>
<td>6:1</td>
<td>35</td>
</tr>
<tr>
<td>3.</td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td>5:1</td>
<td>56</td>
</tr>
<tr>
<td>4.</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>5:1</td>
<td>45</td>
</tr>
<tr>
<td>5.</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td>5:1</td>
<td>50</td>
</tr>
</tbody>
</table>

Reaction conditions: dry DME, Ar, RT, 3 h, a = major isomer was shown, b = determined by $^1$H NMR, * = isolated yield.

In all cases, the compounds were completely characterised and their structure established by spectroscopic methods. The $^1$H and $^{13}$C NMR spectra of compounds are similar to those of 34a, which exhibited characteristic signals with expected chemical shifts.
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The structure of the product 48 was elucidated using spectroscopic techniques. The diastereomeric ratio was determined by $^1$H NMR. The major diastereomer of 48 showed the following characteristic spectral data. In the IR spectrum, the sharp bands at 1748 and 1708 cm$^{-1}$ were assigned to the two ester carbonyls. In the $^1$H NMR spectrum, the signals due to methoxy groups were observed at δ 4.02 and 3.63 as two singlets, while the ring junction proton was observed as a singlet at δ 5.85. The other benzylic proton was observed as a singlet at δ 5.78, while the two olefinic protons were discernible as doublets at δ 6.27 and 5.70. In the $^{13}$C NMR spectrum, the two ester carbonyls were observed at δ 164.63 and 163.44.

A mechanistic rationale similar to that involved in the reaction of $N$-tosylimines may be invoked in this case also. Thus the initial formation of 1,4-dipole 24 followed by its addition to carbonyl group of aldehyde can deliver the cycloadduct (Scheme 3.17).

![Scheme 3.17](image)

Analogous reaction was observed with other aromatic aldehydes with electron withdrawing groups such as 4-trifluoromethylbenzaldehyde 44, 4-chloro benzaldehyde 45, 2-nitrobenzaldehyde 46 and 3,4-dichlorobenzaldehyde 47, affording an inseparable diastereomeric mixture of [1,3]oxazino[2,3-a] isoquinoline derivatives in good yields (Table 3.3).
Table 3.3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Ratio (^b)</th>
<th>Yield(%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>CHO</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>6:1</td>
<td>75</td>
</tr>
<tr>
<td>2.</td>
<td>CF₃CHO</td>
<td><img src="image2.png" alt="Structure" /></td>
<td>6:1</td>
<td>42</td>
</tr>
<tr>
<td>3.</td>
<td>NO₂CHO</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>1.7:1</td>
<td>76</td>
</tr>
<tr>
<td>4.</td>
<td>ClCHO</td>
<td><img src="image4.png" alt="Structure" /></td>
<td>5.5:1</td>
<td>72</td>
</tr>
</tbody>
</table>

Reaction conditions: dry DME, Ar, RT, 3 h, \( b \) = determined by \(^1\)H NMR, \( * \) = isolated yield.

In all the cases, the compounds were characterised and their structure established by spectroscopic methods. The \([1,3]\)oxazino[2,3-a]isoquinoline derivatives 49-52, showed characteristic carbomethoxy carbonyls both in the IR and \(^{13}\)C NMR spectra. All the other spectroscopic data were also in good agreement with the assigned structure.
3.4 Conclusion

In conclusion, we have found that the one pot reaction of isoquinoline and DMAD with N-tosylimines leads to an efficient diastereoselective synthesis of 2H-pyrimido[2,1-a]isoquinoline derivatives. Similarly aldehydes, as dipolarophiles, afforded novel [1,3]oxazino[2,3-a]isoquinoline derivatives. It may be mentioned that both 2H-pyrimido[2,1-a]isoquinoline and [1,3]oxazino[2,3-a]isoquinoline derivatives manifest a number of important and therapeutically useful biological activities\(^{20}\). It is conceivable that the novel three component reaction described herein will be applicable to the synthesis of a variety of heterocycles.

3.5 Experimental Details

General information about the experiments is given in Section 2.13 (Chapter 2).

**Dimethyl-1,11b-dihydro-1-[(4-methyl phenyl)sulfonyl]-2-[(4-trifluoromethylphenyl)]-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 34a**

To a mixture of N-tosyl-4-trifluoromethylbenzaldimine 25 (173 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of 34a and 34b (232 mg, 93%). The major diastereomer 34a was separated by crystallisation from CH\(_2\)Cl\(_2\)-hexane mixture as a pale yellow crystalline solid.

Mp: 150-152 °C.

**IR (KBr) \(\nu_{max}\):** 2955, 1748, 1703, 1600, 1573, 1420, 1330, 1230, 1162, 1128, 1080 cm\(^{-1}\).

\(^1\)H NMR: \(\delta\ 7.66\ (d, J = 8.17\ Hz, 2H),\ 7.51\ (d, J = 9.32\ Hz, 2H),\ 7.47\ (d, J = 7.89\ Hz, 4H),\ 7.29-7.16\ (m, 4H),\ 6.66\ (d, J = 4.89\ Hz, 1H),\ 6.38-6.25\ (m, 2H),\ 4.68\ (d, J = 14.80\ Hz, 2H),\ 3.53\ (d, J = 14.80\ Hz, 2H),\ 3.21\ (d, J = 9.32\ Hz, 4H),\ 2.47\ (s, 1H),\ 2.30\ (s, 3H),\ 2.16\ (s, 3H),\ 1.90\ (s, 3H),\ 1.71\ (s, 3H),\ 1.58\ (s, 3H),\ 1.45\ (s, 3H),\ 1.18\ (s, 3H),\ 1.08\ (s, 3H),\ 0.96\ (s, 3H)\ cm\(^{-1}\).
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$\text{CF}_3$

78 Hz, 4H), 7.29-7.16 (m, 3H), 7.03-6.95 (m, 2H), 6.66 (d, $J = 7.68$ Hz, 1H), 6.13 (s, 1H), 5.90 (s, 1H), 5.89 (d, $J = 8.10$ Hz, 1H), 5.64 (d, $J = 7.84$ Hz, 1H), 3.85 (s, 3H), 3.63 (s, 3H), 2.39 (s, 3 H).

$^{13}$C NMR: $\delta$ 164.99, 162.91, 145.61, 144.65, 143.89, 136.95, 129.76, 129.64, 129.57, 129.33, 129.05, 127.90, 127.87, 127.40, 126.77, 126.54, 125.66, 125.61, 125.41, 125.04, 124.30, 104.84, 102.46, 67.18, 57.84, 52.98, 51.88, 21.52.

Anal. Calcd. for C$_{30}$H$_{25}$F$_3$N$_2$O$_6$S: C, 60.19; H, 4.21; N, 4.68; S, 5.36; Found C, 59.90; H, 4.07; N, 4.91; S, 5.40.

\textbf{Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-[(2-chlorophenyl)-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 36}

To a mixture of N-tosyl-2-chorobenzaldimine 26 (155 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (274 mg, 92%). The major diastereomer 36 was separated by crystallisation from CH$_2$Cl$_2$-hexane mixture as a pale yellow crystalline solid.

\textbf{Mp: 122-124 °C.}

\textbf{IR (KBr) $\nu_{max}$: 2948, 2362, 1742, 1708, 1593, 1566, 1425, 1337, 1276, 1236, 1108 cm$^{-1}$.}

$^1$H NMR: $\delta$ 7.47, (d, $J = 7.89$ Hz, 1H), 7.38-7.25 (m, 5H), 7.07-6.93 (m, 4H), 6.64-6.57 (m, 2H), 6.30 (d, $J = 7.71$ Hz, 1H), 6.22 (s, 1H), 6.13 (d, $J = 7.86$ Hz, 1H), 5.61 (d, $J = 7.88$ Hz, 1H), 3.96 (s,
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3H), 3.59 (s, 3H), 2.34 (s, 3H).

$^{13}$C NMR: $\delta$ 164.82, 163.81, 144.45, 143.10, 139.02, 137.98, 133.67, 132.27, 130.67, 130.59, 129.57, 128.84, 128.78, 128.29, 128.08, 127.76, 126.62, 126.17, 125.22, 125.13, 124.30, 104.24, 102.96, 66.38, 55.71, 53.31, 51.96, 21.53.

Anal. Calcd. for C$_{29}$H$_{25}$ClN$_2$O$_6$S: C, 61.64; H, 4.46; N, 4.96; S, 5.68; Found C, 61.32; H, 4.56; N, 4.75; S, 5.64.

Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-[(3-nitrophenyl)]-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 37

To a mixture of N-tosyl-3-nitrobenzaldehyde 27 (160 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (220 mg, 73 %). The major diastereomer 37 was separated by crystallisation from CH$_2$Cl$_2$-hexane mixture as a pale yellow crystalline solid.

Mp: 160-162 °C.

IR (KBr) $\nu_{\text{max}}$: 2955, 1748, 1708, 1593, 1573, 1533, 1430, 1351, 1236, 1162 cm$^{-1}$.

$^1$H NMR: $\delta$ 8.18 (d, $J = 8.12$ Hz, 1H), 8.11 (s, 1H), 7.77 (d, $J = 6.18$ Hz, 2H), 7.60 (t, $J = 7.92$ Hz, 1H), 7.51 (d, $J = 8.24$ Hz, 2H), 7.26-7.16 (m, 2H), 7.03 (d, $J = 7.44$ Hz, 1H), 6.95 (t, $J = 7.55$ Hz, 1H), 6.60 (d, $J = 7.71$ Hz, 1H), 5.95 (d, $J = 7.82$ Hz, 1H), 5.87 (s, 1H), 5.68 (d, $J = 7.86$ Hz, 1H), 3.87 (s, 3H), 3.63 (s, 3H), 2.43
(s, 3H).

$^{13}$C NMR: $\delta$ 164.80, 162.87, 148.49, 144.22, 143.84, 136.50, 134.58, 129.64, 129.52, 129.48, 129.10, 127.79, 127.71, 127.48, 127.31, 126.78, 126.37, 125.51, 124.77, 124.11, 123.25, 122.97, 105.10, 101.46, 67.15, 57.45, 53.19, 52.07, 21.51.

Anal. Calcd. for C$_{29}$H$_{25}$N$_{3}$O$_{8}$S: C, 60.51; H, 4.38; N, 7.30; S, 5.57; Found C, 60.23; H, 4.05; N, 7.25; S, 5.41.

**Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-[(3,4-dichlorophenyl)]-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 38**

To a mixture of $N$-tosyl-3,4-dichlorobenzaldehyde 28 (173 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (190 mg, 60%). The major diastereomer 38 was separated by crystallisation from CH$_2$Cl$_2$-hexane mixture as a pale yellow crystalline solid.

Mp: 159-161 °C.

IR (KBr) $\nu_{\text{max}}$: 2955, 1742, 1694, 1600, 1499, 1425, 1360, 1236, 1169 cm$^{-1}$.

$^1$H NMR: $\delta$ 7.51-7.42 (m, 4H), 7.34-7.10 (m, 4H), 7.02 (d, $J = 8.01$ Hz, 2H), 6.71 (d, $J = 7.62$ Hz, 1H), 6.01 (s, 1H), 5.91 (s, 1H), 5.87 (d, $J = 7.82$ Hz, 1H), 5.65 (d, $J = 7.84$ Hz, 1H), 3.84 (s, 3H), 3.63 (s, 3H), 2.44 (s, 3H).
Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-phenyl-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 39

To a mixture of N-tosyl-benzaldimine 29 (137 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (121 mg, 43%). The major diastereomer 39 was separated by crystallisation from CH$_2$Cl$_2$-hexane mixture as a pale yellow crystalline solid.

**Physical data**: Mp: 150-152 °C.

**IR (KBr) $\nu_{\text{max}}$**: 2955, 1742, 1694, 1600, 1499, 1357, 1236, 1007 cm$^{-1}$.

**$^1$H NMR**: $\delta$ 7.52 (d, $J = 8.26$ Hz, 2H), 7.39-7.25 (m, 5H), 7.20-7.14 (m, 3H), 7.01-6.92 (m, 2H), 6.67 (d, $J = 7.69$ Hz, 1H), 6.10 (s, 1H), 5.99 (s, 1H), 5.88 (d, $J = 7.84$ Hz, 1H), 3.84 (s, 3H), 3.57 (s, 3H), 2.42 (s, 3H).

**$^{13}$C NMR**: $\delta$ 165.26, 163.16, 144.02, 143.58, 141.60, 129.53, 129.15, 128.78, 128.59, 128.54, 128.17, 127.87, 127.77, 127.36, 126.51, 125.22,
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125.16, 124.38, 105.75, 103.11, 66.66, 58.12, 52.98, 51.86, 21.53.

Anal. Calcd. for C$_{29}$H$_{26}$N$_2$O$_6$S: C, 65.65; H, 4.94; N, 5.28; S, 6.04; Found C, 65.52; H, 5.13; N, 5.46; S, 6.17.

**Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-[(4-methylphenyl)]-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 40**

To a mixture of N-tosyl-4-methylbenzaldimine 30 (144 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (105 mg, 35%). The major diastereomer 40 was separated by crystallisation from CH$_2$Cl$_2$-hexane mixture as a pale yellow crystalline solid.

Mp: 175-177 °C.

**IR (KBr) $\nu_{\text{max}}$:** 2948, 2362, 1742, 1701, 1593, 1431, 1337, 1280, 1229, 1162, 1000 cm$^{-1}$.

$^1$H NMR $\delta$ 7.52 (d, $J = 8.22$ Hz, 2H), 7.25-7.13 (m, 7H), 6.98-6.89 (m, 2H), 6.68 (d, $J = 7.69$ Hz, 1H), 6.06 (s, 1H), 5.99 (s, 1H), 5.88 (d, $J = 7.81$ Hz, 1H), 5.61 (d, $J = 7.83$ Hz, 1H), 3.84 (s, 3H), 3.61 (s, 3H), 2.42 (s, 3H), 2.35 (s, 3H).

$^{13}$C NMR: $\delta$ 165.42, 163.30, 143.91, 138.76, 137.63, 137.23, 136.96, 129.66, 129.38, 129.23, 128.84, 128.62, 127.98, 127.93, 126.58, 125.47, 125.23, 124.59, 120.05, 104.33, 66.70, 58.12, 52.99, 51.89, 21.61, 21.16.
Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-pipernyl-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 41

To a mixture of N-tosyl-3-[1,3]dioxolobenzaldimine 31 (160 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (170 mg, 56%). The major diastereomer 41 was separated by crystallisation from CH₂Cl₂-hexane mixture as a pale yellow crystalline solid.

\[ \text{Mp: 170-172 °C.} \]

\[ \text{IR (KBr) } \nu_{\text{max}}: 2955, 1748, 1705, 1600, 1573, 1485, 1445, 1351, 1236, 1169, 1040 \text{ cm}^{-1}. \]

\[ \text{H NMR } \delta 7.51 \text{ (d, } J = 8.25 \text{ Hz, } 2H), 7.19-7.15 \text{ (m, } 3H), 7.00 \text{ (dd, } J = 2.35, 7.68 \text{ Hz, } 2H), 6.93 \text{ (s, } 1H), 6.79-6.72 \text{ (m, } 3H), 6.03-5.98 \text{ (m, } 4H), 5.86 \text{ (d, } J = 7.81 \text{ Hz, } 1H), 5.62 \text{ (d, } J = 7.84 \text{ Hz, } 1H), 3.83 \text{ (s, } 3H), 3.62 \text{ (s, } 3H), 2.41 \text{ (s, } 3H). \]

\[ \text{C NMR: } \delta 165.31, 163.21, 148.16, 147.52, 143.91, 143.71, 136.85, 135.81, 129.65, 129.58, 128.89, 127.95, 127.84, 126.65, 126.53, 125.36, 125.29, 124.45, 122.70, 108.86, 107.98, 104.50, 103.20, 101.32, 66.47, 57.96, 53.07, 52.00, 21.64. \]

Anal. Cald. for C₃₀H₂₆N₂O₈S: C, 62.71; H, 4.56; N, 4.88; S, 5.58; Found C, 62.53; H, 4.58; N, 4.67; S, 5.61.
**Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-furyl-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 42**

To a mixture of N-tosyl-1-furfuraldimine 32 (132 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (125 mg, 45%). The major diastereomer 42 was separated by crystallisation from CH$_2$Cl$_2$-hexane mixture as a pale yellow crystalline solid.

**Mp:** 147-149 °C.

**IR (KBr) $\nu_{\text{max}}$:** 2955, 1748, 1708, 1593, 1573, 1357, 1263, 1236, 1162, 1020 cm$^{-1}$.

**$^1$H NMR** $\delta$ 7.80 (d, $J = 8.27$ Hz, 2H), 7.46 (s, 1H), 7.40 (d, $J = 8.26$ Hz, 2H), 7.29 (d, $J = 8.10$ Hz, 1H), 7.13 (t, $J = 8.12$ Hz, 1H), 7.01 (d, $J = 7.30$ Hz, 1H), 6.77 (t, $J = 7.51$ Hz, 2H), 6.55 (d, $J = 7.68$ Hz, 1H), 6.34 (s, 1H), 6.24-6.18 (m, 1H), 6.04 (d, $J = 7.80$ Hz, 1H), 5.67 (d, $J = 7.83$ Hz, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 2.41 (s, 3H).

**$^{13}$C NMR:** $\delta$ 165.00, 163.31, 153.95, 143.79, 143.03, 137.99, 131.34, 130.28, 129.96, 129.52, 128.77, 127.87, 127.47, 126.41, 125.36, 124.52, 124.17, 110.50, 110.23, 104.59, 102.91, 68.40, 66.89, 53.16, 51.91, 21.51.

Anal. Calcd. for C$_{27}$H$_{24}$N$_2$O$_7$S: C, 62.30; H, 4.65; N, 5.38; S, 6.16; Found C, 62.15; H, 4.42; N, 5.17; S, 5.96.
Dimethyl-2-(3-nitrophenyl)-2H,11bH-[1,3]oxazino[2,3-a]isoquinoline-3,4-dicarboxylate 49

To a mixture of 3-nitro benzaldehyde 43 (80 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (215 mg, 96%, 2:1). The spectral data for the major diastereomer is given below.

IR (KBr) $\nu_{max}$: 2955, 1748, 1708, 1600, 1573, 1539, 1357, 1236 cm$^{-1}$.

$^1$H NMR: $\delta$ 8.34 (s, 1H), 8.23 (d, $J = 8.15$ Hz, 1H), 7.77 (d, $J = 7.69$ Hz, 1H), 7.61 (t, $J = 7.90$ Hz, 1H), 7.23 (d, $J = 7.60$ Hz, 1H), 7.15 (t, $J = 7.55$ Hz, 1H), 7.03-6.95 (m, 2H), 6.27 (d, $J = 7.78$ Hz, 1H), 5.85 (s, 1H), 5.78 (s, 1H), 5.70 (d, $J = 7.80$ Hz, 1H), 4.02 (s, 3H), 3.63 (s, 3H).

$^{13}$C NMR: $\delta$ 164.63, 163.44, 148.52, 143.21, 141.95, 134.89, 133.91, 129.65, 129.44, 127.16, 126.70, 126.20, 125.03, 123.68, 123.22, 108.69, 105.03, 102.48, 82.97, 72.60, 53.34, 51.80.

Dimethyl-2-(4-trifluoromethylphenyl)-2H,11bH-[1,3]oxazino[2,3-a]isoquinoline-3,4-dicarboxylate 50

To a mixture of 4-trifluoromethyl benzaldehyde 44 (92 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an
inseparable mixture of diastereomers (175 mg, 75%, 6:1). The spectral data for the major diastereomer is given below.

\[ \text{IR (KBr) } \nu_{\text{max}}: 2955, 1743, 1703, 1600, 1431, 1330, 1243, 1128 \text{ cm}^{-1}. \]

\[ \text{H NMR: } \delta 7.69 (d, J = 8.16 \text{ Hz}, 2\text{H}), 7.57 (d, J = 8.13 \text{ Hz}, 2\text{H}), 7.23 (t, J = 6.67 \text{ Hz}, 1\text{H}), 7.13 (t, J = 6.92 \text{ Hz}, 1\text{H}), 7.02-6.95 (m, 2\text{H}), 6.26 (d, J = 7.77 \text{ Hz}, 1\text{H}), 5.84 (s, 1\text{H}), 5.75 (s, 1\text{H}), 5.68 (d, J = 7.79 \text{ Hz}, 1\text{H}), 4.01 (s, 3\text{H}), 3.62 (s, 3\text{H}). \]

\[ \text{C NMR: } \delta 164.96, 163.73, 143.73, 141.80, 129.81, 129.62, 129.45, 128.60, 127.79, 127.15, 126.91, 126.49, 125.60, 125.04, 123.68, 109.64, 104.89, 103.31, 83.03, 73.00, 53.41, 51.84. \]

**Dimethyl-2-(4-chlorophenyl)-2H,11bH-[1,3]oxazino[2,3-d]isoquinoline-3,4-dicarboxylate 51**

To a mixture of 4-chlorobenzaldehyde 45 (74 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (92 mg, 42%). The spectral data for the major diastereomer is given below.

\[ \text{IR (KBr) } \nu_{\text{max}}: 2955, 1742, 1708, 1600, 1438, 1249, 1101 \text{ cm}^{-1}. \]

\[ \text{H NMR: } \delta 7.40-7.35 (m, 3\text{H}), 7.25-7.18 (m, 2\text{H}), 7.11 (t, J = 7.47 \text{ Hz}, 1\text{H}), 6.97 (t, J = 7.30 \text{ Hz}, 2\text{H}), 6.25 (d, J = 7.77 \text{ Hz}, 1\text{H}), 5.84 (s, 1\text{H}), 5.67-5.64 (m, 2\text{H}), 3.99 (s, 3\text{H}), 3.60 (s, 3\text{H}). \]
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**13C NMR:** δ 164.98, 163.73, 143.43, 139.66, 134.36, 130.39, 129.78, 129.51, 129.29, 128.73, 127.73, 127.00, 126.90, 126.57, 124.91, 123.70, 104.63, 103.78, 82.96, 72.92, 53.30, 51.72.

**Dimethyl-2-(2-nitrophenyl)-2H,11bH-[1,3]oxazino[2,3-a]isoquinoline-3,4-dicarboxylate 51**

To a mixture of 2-nitro benzaldehyde 46 (80 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (170 mg, 76%, 1:7:1). The spectral data for the major diastereomer is given below.

**IR (KBr)** ν max: 2955, 1748, 1715, 1607, 1526, 1438, 1357, 1236 cm⁻¹.

**¹H NMR:** δ 7.91 (d, J = 7.84 Hz, 1H), 7.68-7.45 (m, 3H), 7.29-7.13 (m, 2H), 6.91 (dd, J = 7.42, 17.18 Hz, 1H), 6.57 (s, 1H), 6.26-6.21 (m, 2H), 5.72 (s, 1H), 5.59 (d, J = 7.80 Hz, 1H), 4.00 (s, 3H), 3.65 (s, 3H).

**13C NMR:** δ 164.46, 163.28, 148.64, 143.90, 142.37, 133.98, 131.63, 129.39, 129.14, 128.48, 127.65, 127.17, 126.53, 124.94, 123.68, 123.08, 105.00, 101.26, 82.99, 71.87, 53.17, 51.62.

**Dimethyl-2-(3,4-dichlorophenyl)-2H,11bH-[1,3]oxazino[2,3-a]isoquinoline-3,4-dicarboxylate 53**

To a mixture of 3,4-dichloro benzaldehyde 47 (92 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h.
The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (170 mg, 72%, 5.5:1). The spectral data for the major diastereomer is given below.

**IR (KBr)** $\nu_{\text{max}}$: 2955, 1735, 1701, 1593, 1465, 1236, 1142 cm$^{-1}$.

**$^1$H NMR**: δ 7.53-7.48 (m, 2H), 7.29-7.20 (m, 2H), 7.14 (t, $J = 7.45$ Hz, 1H), 6.99 (t, $J = 6.48$ Hz, 2H), 6.25 (d, $J = 7.77$ Hz, 1H), 5.85 (s, 1H), 5.69-5.64 (m, 2H), 4.00 (s, 3H), 3.62 (s, 3H).

**$^{13}$C NMR**: δ 164.80, 163.60, 143.82, 141.43, 133.07, 132.85, 130.57, 129.46, 128.30, 127.44, 126.97, 126.51, 125.06, 123.65, 121.91, 108.83, 104.99, 103.01, 78.08, 72.56, 53.38, 51.85.

### 3.6 References


