Section 2C: Arginine catalyzed aldol addition of methyl vinyl ketone to isatins: rapid access to 3-alkyl-3-hydroxyindolin-2-ones
**Section 2C: Arginine catalyzed aldol addition of methyl vinyl ketone to isatins: rapid access to 3-alkyl-3-hydroxyindolin-2-ones**

**2C.1: Introduction**

Methyl vinyl ketone, the simplest among the enones, has historically proved challenging to aldolise. The aldol reaction, without doubt, is one of the most useful carbon-carbon bond forming reactions and β-hydroxyketones derived from methyl vinyl ketone can be particularly interesting as a building block. However, despite tremendous synthetic potential, base instability of methyl vinyl ketone and its aldol adducts has proved a major impediment to the development of general protocols; hence, few reports are available on its aldol reaction, direct or otherwise which are discussed in the previous section also.\(^1\) Trost’s elegant asymmetric Zn-aldol reaction of methyl vinyl ketone with aliphatic aldehydes is noteworthy for a direct aldolisation protocol (Scheme 1). It was observed by the authors that the product profile was time dependent and formation of the dehydrated by-product was observed upon running the reaction for a longer time. However, the reaction was highly enantioselective giving the aldol adducts in 90-95% enantiomeric purity.\(^1\) This has been the most efficient and elegant of the approaches towards the synthesis of these aldols till date.

**Scheme 1:** Reaction of aliphatic aldehydes with methyl vinyl ketone using Zn dinuclear catalyst

Another method reported by Denmark and co-workers involved the use of a preformed trichlorosilylenolate for a Mukaiyama-type aldol addition (Scheme 2). Pertinently, the also mentioned the instability of the aldol derived from methyl vinyl

**Scheme 2:** Aldol additions of trichlorosilylenolate of methyl vinyl ketone to benzaldehyde

![Scheme 1](image1.png)

![Scheme 2](image2.png)
ketone in their report, as the product formed polymerized upon purification. The instability of this product precluded the further use of enolate of methyl vinyl ketone for subsequent studies in their work.\textsuperscript{1b}

Additionally, an enantioselective version catalyzed by Cu- and Ni-sparteine complexes has been reported under Et\textsubscript{3}N-promoted double catalytic activation (DCA) conditions. For direct aldol adducts derived from 4-nitrobenzaldehyde, the authors reported a strong preference for the (R)-isomer with 79\% enantioselectivity with catalyst 10. Whereas the reaction catalyzed by 11 showed a preference for the (S)-isomer with 56\% ee in DMF (76\% ee in MeOH) (Scheme 3).\textsuperscript{1c}

![Scheme 3: Direct aldol reactions of aromatic benzaldehydes with methyl vinyl ketone under DCA conditions](image)

The other significant report on aldolisation of methyl vinyl ketone constitutes the use of lanthanide (III) promoted addition, where the reaction of methyl vinyl ketone with benzaldehyde in presence of lithium diisopropylamine at -78 °C was reported to deliver low yields of aldols (Scheme 4).\textsuperscript{1d}

![Scheme 4: LnCl\textsubscript{3} mediated aldolisation of methyl vinyl ketone and aromatic aldehydes](image)

The above methods are the only significant reports on a general aldolisation protocol for methyl vinyl ketone. On a parallel note, apart from methyl vinyl ketone, other enones have been used extensively for the aldol reaction with different electron acceptors to form various biologically important \(\beta\)-hydroxyketones. In particular, the aldol reaction of isatins with ketones or enolisable aldehydes leads to the formation of 3-alkyl-3-hydroxyindolin-2-ones, which are important biologically active natural products and medicinal compounds (Figure 1).\textsuperscript{2,3} Several elegant methods have been
Figure 1: Some of the biologically active natural products which can be synthesized by 3-alkyl-3-hydroxyindolin-2-ones employed to effect this transformation; including enamine mediated asymmetric protocols, over the last decade or so.\(^4\) One of the methods, reported by Liu & Xie recently, involved an arginine catalyzed aldol addition of several aromatic enones to isatins to obtain the corresponding adducts in very good yields;\(^5\)(Scheme 5).

Scheme 5: L-Arginine catalyzed aldol addition of aromatic enones to isatins

The use of enones as donors adds another dimension to the reaction in terms of generating further structural complexity.\(^5\) For eg., the groups of Tanaka and Wang demonstrated an enantioselective hetero-Diels-Alder reaction of several enones with isatin to obtain novel bioactive spirooxindole tetrahydropyrans,\(^5a-c\) while Beccalli \textit{etal} utilized isatin-enone adducts for the construction of carbazole alkaloids and spiro systems.\(^5f\) Substantial efforts have also been made recently on modifying isatin-enone adducts for the synthesis of biologically active compounds.\(^5g,h\) Despite the obvious potential, the use of the “difficult” methyl vinyl ketone as a donor in this reaction has not been reported, to our knowledge. The isatin-methyl vinyl ketone adduct arouses interest as it opens up further synthetic avenues (Figure 2) that might not be possible to envisage on the substituted enone adducts.
From an organocatalysis perspective, an additional factor to be considered when discussing the challenges of aldolising methyl vinyl ketone pertains to the generation of the desired enamine. Within the ever expanding realm of organocatalysis, enones are popular substrates for reactions involving the LUMO-lowered iminium species, e.g., Diels-Alder and Michael addition reactions, and methyl vinyl ketone is no exception. Its highly receptive olefinic moiety has also been utilized proficiently in organocatalytic Baylis-Hillman chemistry. However, enamine formation has been that much more difficult to realize. Pertinently, a recent report by Zhao and co-workers elegantly showed that an organocatalytic enolate mediated aldol reaction could be a viable alternative when enamine generation is difficult, especially with an activated acceptor such as isatin; their report on the quinidine thiourea catalyzed enantioselective synthesis of isatin aldols elucidates the success of this approach. On a parallel note, a vital aspect in the blossoming of organocatalysis over the past decade has been its green quotient, reflected in the considerable recent research attention towards more sustainable organocatalytic protocols. Reactions in water evidently present a huge attraction and, along with solvent-free reactions, provide the most straightforward approach to address the toxic organic solvent problem, a big contributor to the sheer magnitude of waste in chemical manufacture.

As we were interested in the development of environment friendly protocols for effecting important transformations, we wished to explore the challenge of aldolisation of methyl vinyl ketone, in light of the preceding literature reports. This section thus deals with the first use of methyl vinyl ketone in an aldol reaction with isatins; the reaction, mediated by arginine, proceeded rapidly in aqueous medium to afford 3-oxobutenyl-3-hydroxyindolin-2-ones in excellent yields. Our efforts also resulted in the
Section 2C

generation of interesting molecular entities via functionalization of adducts by characteristic carbon-carbon bond forming reactions.

2C.2: Results and discussion

In our twin endeavours towards harnessing the synthetic potential of methyl vinyl ketone and developing aqueous based methods for the synthesis of 3-alkyl-3-hydroxyindolin-2-ones, we attempted an arginine mediated reaction of N-methyl isatin (9a) with methyl vinyl ketone (2a) in water; to our delight the reaction proceeded swiftly and cleanly at room temperature to deliver the corresponding aldol adduct. The exciting features of the reaction – efficient aldolisation of methyl vinyl ketone in particular – stimulated a full-fledged study. In optimizing the reaction (Table 1) we chose to focus on faster reactions, since it involved a sensitive ketone and the relatively

Table 1: Optimization of the Arginine mediated aldol reaction of N-methylisatin with methyl vinyl ketone

<table>
<thead>
<tr>
<th>Entry</th>
<th>2a(equiv.)</th>
<th>Arginine(equiv.)</th>
<th>H2O(µL)</th>
<th>Time(min)</th>
<th>10a / Yield(%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>5</td>
<td>0.5</td>
<td>-</td>
<td>15</td>
<td>N.R. c</td>
</tr>
<tr>
<td>2.</td>
<td>5</td>
<td>0.5</td>
<td>100</td>
<td>15</td>
<td>52</td>
</tr>
<tr>
<td>3.</td>
<td>5</td>
<td>0.5</td>
<td>250</td>
<td>15</td>
<td>81</td>
</tr>
<tr>
<td>4.</td>
<td>5</td>
<td>0.5</td>
<td>350</td>
<td>15</td>
<td>96</td>
</tr>
<tr>
<td>5.</td>
<td>5</td>
<td>0.5</td>
<td>500</td>
<td>15</td>
<td>86</td>
</tr>
<tr>
<td>6.</td>
<td>3</td>
<td>0.5</td>
<td>350</td>
<td>15</td>
<td>72</td>
</tr>
<tr>
<td>7.</td>
<td>1.5</td>
<td>0.5</td>
<td>350</td>
<td>15</td>
<td>51</td>
</tr>
<tr>
<td>8.</td>
<td>5</td>
<td>0.3</td>
<td>350</td>
<td>15</td>
<td>41</td>
</tr>
<tr>
<td>9.</td>
<td>5</td>
<td>0.1</td>
<td>350</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>10.</td>
<td>5</td>
<td>0.1</td>
<td>350</td>
<td>150</td>
<td>94</td>
</tr>
</tbody>
</table>

a All reactions were carried out on 0.5 mmol of isatin 9a; b Refers to isolated yields
inexpensive arginine. An initial reaction attempted in the absence of water did not show any conversion, presumably since the arginine remained out of solution (entry 1). The use of water as solvent gave instant results and with gradual increase in water the yield increased. An optimum value of 350 µL of water for 0.5 mmol of 9a was arrived after studying various amounts (entries 2-5). It is worth mentioning that the reaction performed reasonably well within the same short time frame using reduced ketone stoichiometries too (entries 6 & 7). With reduced catalyst loading, an expected drop in yield occurred in 15 min reactions (entries 8 & 9). Nonetheless, we were pleased to obtain 94% of the aldol with just 10 mol% catalyst in 2.5 h, reflecting the admirable efficiency of the protocol (entry 10).

We then explored the scope of the reaction using substituted isatins (Table 2). With N-methyl isatins bearing different substituents, such as – chloro, bromo, nitro - at the 4/5 position, the corresponding aldol adducts of methyl vinyl ketone were obtained in excellent yields (entries 1-4). N-benzyl isatin also proved to be a good substrate, resulting in a swift conversion to 93% of the aldol within short span of time (entry 5), though reactions proceeded with slow rate and a drop in yield was observed when substituted N-benzyl isatins were used (entries 6 & 7). Three reactions each were also carried out with N-allyl and N-propargyl isatins, where the former resulted in excellent yields of the corresponding aldols (entries 8-10), whereas, slightly lower conversions were obtained with the latter (entries 11-13). It was also pleasing to note that the protocol exhibited good scalability – a gram scale reaction using the optimized conditions proceeded quite smoothly to deliver the desired aldol adduct in 90% yield in quick time (entry 14).

Interestingly, when the reaction was carried out with isatin where the nitrogen was free, the second molecule of 2a accompanied the desired aldol adduct in an aza-Michael addition to a certain extent resulting in a different product 11 (Scheme 6). This product had two molecules of methyl vinyl ketone, one as a nucleophile which attack the isatin’s carbonyl carbon forming the aldol adduct, whereas the other molecule acted as an electrophile to which the isatin nitrogen attacks in an aza-Michael manner. Here both the molecules are incorporated onto the isatin scaffold simultaneously under the same conditions; disappointingly though, the mixture of this product and the N-unsubstituted aldol adduct 10o proved inseparable in our hands.

The use of methylvinyl ketone also presents an opportunity for a cascade cyclisation to generate a spirooxindole system, as previously demonstrated with other
Table 2. Aldol addition of methyl vinyl ketone to various isatins

<table>
<thead>
<tr>
<th>Entry</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;, R&lt;sub&gt;2&lt;/sub&gt;, R&lt;sub&gt;3&lt;/sub&gt; / 9</th>
<th>Time(min)</th>
<th>10 / Yield(%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Me, H, Cl / b</td>
<td>15</td>
<td>b / 95</td>
</tr>
<tr>
<td>2.</td>
<td>Me, H, Br / c</td>
<td>60</td>
<td>c / 90</td>
</tr>
<tr>
<td>3.</td>
<td>Me, H, NO&lt;sub&gt;2&lt;/sub&gt; / d</td>
<td>60</td>
<td>d / 91</td>
</tr>
<tr>
<td>4.</td>
<td>Me, Br, H / e</td>
<td>180</td>
<td>e / 94</td>
</tr>
<tr>
<td>5.</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;, H, H / f</td>
<td>40</td>
<td>f / 93</td>
</tr>
<tr>
<td>6.</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;, H, Cl / g</td>
<td>180</td>
<td>g / 59</td>
</tr>
<tr>
<td>7.</td>
<td>PhCH&lt;sub&gt;2&lt;/sub&gt;, Br, H / h</td>
<td>180</td>
<td>h / 65</td>
</tr>
<tr>
<td>8.</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;=CHCH&lt;sub&gt;2&lt;/sub&gt;, H, H / i</td>
<td>60</td>
<td>i / 93</td>
</tr>
<tr>
<td>9.</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;=CHCH&lt;sub&gt;2&lt;/sub&gt;, H, Br / j</td>
<td>90</td>
<td>j / 95</td>
</tr>
<tr>
<td>10.</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;=CHCH&lt;sub&gt;2&lt;/sub&gt;, Br, H / k</td>
<td>240</td>
<td>k / 90</td>
</tr>
<tr>
<td>11.</td>
<td>CH=CCH&lt;sub&gt;2&lt;/sub&gt;, H, H / l</td>
<td>60</td>
<td>l / 80</td>
</tr>
<tr>
<td>12.</td>
<td>CH=CCH&lt;sub&gt;2&lt;/sub&gt;, H, NO&lt;sub&gt;2&lt;/sub&gt; / m</td>
<td>180</td>
<td>m / 76</td>
</tr>
<tr>
<td>13.</td>
<td>CH=CCH&lt;sub&gt;2&lt;/sub&gt;, Br, H / n</td>
<td>180</td>
<td>n / 67</td>
</tr>
<tr>
<td>14.</td>
<td>Me, H, H / a</td>
<td>30</td>
<td>a / 90</td>
</tr>
</tbody>
</table>

<sup>a</sup> Refers to isolated yields; <sup>b</sup> Reaction was carried out on 6.5 mmol of 9a.

Scheme 6: Reaction of isatin with methyl vinyl ketone

enones.<sup>5a-c</sup> Indeed, a prolonged reaction of 2a with 9a was carried out over 24 h under the standard conditions resulted in the formation of the
spirooxindoletetrahydropyranone 12 in a reasonable yield (Scheme 7).\textsuperscript{8} The absence of 12 in the initial stages of the reaction until the starting isatin had been completely converted to the aldol alludes to a step-wise process rather than a concerted one. Bioactivity studies of this compound may be worth carrying out, based on Tanaka’s interesting findings for similar compounds in their report.\textsuperscript{5b}

Scheme 7: Synthesis of a spirooxindoletetrahydropyranone system by a cascade cyclisation

The utility of the present protocol was demonstrated with other ketone donors as well (Table 3). The acetone-isatin adduct is a particularly significant one, as it forms a part of biologically active compounds such as ConvolutamydineA.\textsuperscript{3d} The present protocol gave excellent yields of the acetone aldols in very swift reactions (entries 1,3-5). The use of acetophenones as donors is also known to lead to important isatin adducts such as the one discovered recently as a lead compound for treating Ewing’s

Table 3: Arginine mediated aldol addition of ketones to isatins

<table>
<thead>
<tr>
<th>Entry</th>
<th>R\textsubscript{1}, R\textsubscript{2} / 1</th>
<th>R\textsubscript{3} / 2</th>
<th>Time (min)</th>
<th>3 / Yield(%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Me, H / a</td>
<td>Me / b</td>
<td>10</td>
<td>3p / 96</td>
</tr>
<tr>
<td>2.</td>
<td>Me, H / a</td>
<td>Ph / c</td>
<td>120</td>
<td>3q / 90</td>
</tr>
<tr>
<td>3.</td>
<td>PhCH\textsubscript{2}, H / f</td>
<td>Me / b</td>
<td>30</td>
<td>3r / 94</td>
</tr>
<tr>
<td>4.</td>
<td>H, H / o</td>
<td>Me / b</td>
<td>15</td>
<td>3s / 96</td>
</tr>
<tr>
<td>5.</td>
<td>H, Br / p</td>
<td>Me / b</td>
<td>15</td>
<td>3t / 89</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Refers to isolated yields.
sarcoma.\textsuperscript{11} Again, the present conditions operated smoothly in delivering the adduct in 90% yield albeit in a slightly longer duration (entry 2).

Turning to the mechanism, Xie & Liu had proposed an enamine pathway for their arginine catalyzed addition of enones to isatins.\textsuperscript{5d} They reasoned that the zwitter ionic form of arginine – protonated at the guanidine owing to its high side chain basicity (pKa = 12.8) – rendered the \( \alpha \)-amino group free for enamine formation. We wish to propose an alternative non-covalent mechanism involving an enolate intermediate (Scheme 8), similar to the mechanism proposed by Zhao for the quinidinethiourea mediated aldol reaction.\textsuperscript{4a} They showed that an organocatalytic enolate mediated aldol reaction could be a viable alternative when enamine generation is difficult, especially with an activated acceptor such as isatin; their report on the quinidine thiourea catalysed enantioselective synthesis of isatinaldols elucidates the success of this approach.\textsuperscript{9a} On similar lines, an alternative non-covalent mechanism involving the formation of an enolate species, may be invoked for the present reaction.

Enamine formation from methyl vinyl ketone has generally proved difficult. A second factor is the important role of a free \(-\text{COOH}\) group in accelerating enamine formation; if the high side chain basicity of arginine were to keep the \(-\text{COOH}\) group immobilized as a carboxylate, a less effective enamine formation would ensue. The enolate pathway is also corroborated by the lack of stereocontrol in arginine catalyzed aldol additions,\textsuperscript{9} including the present reaction and Xie’s report, a trait that is remarkably overturned with the use of a Bronsted acid additive to protonate the guanidine moiety.\textsuperscript{10} At last, we

\begin{center}
\textbf{Scheme 8}: Proposed enolate pathway for the arginine mediated aldol addition of methyl vinyl ketone to 1a
\end{center}
wish to emphasize that the proposed mechanism is merely speculative at this stage and the enolate mediated pathway has been suggested just as an alternative based on literature reports pertinent to the use of arginine discussed above. A more detailed study would definitely be required with respect to several important aspects, e.g. the role of water, to fully comprehend the reaction and establish the pathway.

2C.3 Conclusions

In summary, we have carried out a highly efficient arginine mediated aldol addition of methyl vinyl ketone to isatins in water to generate the corresponding 3-substituted-3-hydroxyindolin-2-ones; to our knowledge, this is the first report of the aldolisation of methyl vinyl ketone with isatins. The rapid reaction times and aqueous conditions combined with the scalability of the reaction impart green features to the protocol. The reaction was successfully applied to various substituted isatins and also extended to other ketones to obtain the corresponding adducts in quick times and very good yields. A prolonged reaction with methyl vinyl ketone also delivered the interesting spirooxindoletetrahydropyranone system via a cascade cyclisation (formal hetero-Diels-Alder) process. Lastly, an enolate mediated pathway has been proposed for the reaction, which might be more plausible since it involves the highly basic arginine. As a future prospective, further functionlizations of aldol adduct by the Baylis-Hillman, Diels-Alder and Michael addition reactions can also came to fruition, These exciting features ought to attract significant future research attention toward the reaction, potentially in the domain of natural product synthesis.

2C.4: Experimental Section

General procedure for the aldol reaction:

Methyl vinyl ketone (2a, 2.5 mmol) and H$_2$O (350 µL) were added to arginine (0.25 mmol) in a 5-mL vial and stirred for 5 min at room temperature. The isatin derivative (9, 0.5 mmol) was then added and the reaction mixture was stirred at room temperature for the time mentioned in Tables 2 & 3 for the respective adducts. Direct column chromatographic purification of the reaction mixture over silica gel (EtOAc-petroleum ether, 1:2) afforded the pure adducts.

3-Hydroxy-1-methyl-3-(2-oxobut-3-en-1-yl)indolin-2-one (10a):
Yield: 111 mg (96%); white solid; M.P.: 136 ºC; IR (neat): 3291, 2923, 1697, 1672, 1614, 1089, 954, 755 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.39 (d, J = 7.5 Hz, 1H), 7.35 (dt, J = 7.5 & 1 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.35 (dd, J = 17.5& 10.5 Hz, 2H), 6.24 (d, J = 17.5 Hz, 1H), 5.91 (d, J = 10.5 Hz, 1H), 4.44 (bs, 1H), 3.42 (d, J = 17.0 Hz, 1H), 3.24 (s, 3H), 3.14 (d, J = 17.0 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz): δ: 198.77, 176.12, 143.59, 136.42, 130.04, 130.01, 129.78, 124.00, 123.12, 108.60, 74.35, 45.15, 26.33; HRMS (ESI): m/z [M + Na] calcd. for C₁₃H₁₁NO₃: 254.0792; found: 254.0793.

5-Chloro-3-hydroxy-1-methyl-3-(2-oxobut-3-en-1-yl)indolin-2-one (10b):

Yield: 126 mg (95%); cream colored solid; M.P.: 113 ºC; IR (neat): 3335, 2923, 2853, 1709, 1680, 1609, 1488, 1347, 1103, 1066, 965, 813 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.38 (d, J = 2.0 Hz, 1H), 7.32 (dd, J = 8.3& 2.0 Hz, 1H), 6.80 (d, J = 8.3 Hz, 1H), 6.34 (dd, J = 17.0& 10.3 Hz, 1H), 6.25 (d, J = 17.0 Hz, 1H), 5.96 (d, J = 17.0 Hz, 1H), 4.47 (bs, 1H), 3.44 (d, J = 17.4 Hz, 1H), 3.23 (s, 3H), 3.15 (d, J = 17.4 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 198.77, 176.12, 143.59, 136.42, 130.04, 130.01, 129.78, 124.00, 123.12, 108.60, 74.35, 45.15, 26.33; HRMS (ESI): m/z [M + Na] calcd. for C₁₃H₁₁ClNO₃: 288.0403; found: 288.0409

5-Bromo-3-hydroxy-1-methyl-3-(2-oxobut-3-en-1-yl)indolin-2-one (10c):

Yield: 140 mg (90%); orange solid; M.P.: 132 ºC; IR (neat): 3343, 2923, 2850, 1709, 1679, 1605, 1486, 1345, 1101, 1064, 964, 813 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.50 (d, J = 1.9 Hz, 1H), 7.46 (dd, J = 8.3& 1.9 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 6.32
(dd, J = 17.7& 10.3 Hz, 1H), 6.24 (d, J = 17.0 Hz, 1H), 5.93 (d, J = 10.3 Hz, 1H), 4.54 (bs, 1H), 3.44 (d, J = 17.5 Hz, 1H), 3.22 (s, 3H), 3.19 (d, J = 17.5 Hz, 1H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 198.17, 175.81, 142.78, 136.14, 132.78, 131.76, 130.27, 127.31, 115.76, 110.10, 74.10, 45.42, 26.45; HRMS (ESI): \(m/z\) [M + H] calcd. for C\(_{13}\)H\(_{12}\)BrNO\(_3\): 310.0073; found: 310.0083.

3-Hydroxy-1-methyl-5-nitro-3-(2-oxobut-3-en-1-yl)indolin-2-one (10d):

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{O}_2\text{N} & \quad \text{OH} \\
\text{N} & \quad \text{Me}
\end{align*}
\]

Yield: 126 mg (91%); orange solid; M.P.: 150 ºC; IR (neat): 3339, 2922, 2852, 1714, 1680, 1610, 1517, 1492, 1325, 1292, 1105, 1068, 967 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 8.33 (d, J = 8.6 Hz, 1H), 8.26 (s, 1H), 6.97 (d, J = 8.6 Hz, 1H), 6.24-6.34 (m, 2H), 5.96 (d, J = 9.6 Hz, 1H), 4.30 (bs, 1H), 3.56 (d, J = 17.5 Hz, 1H), 3.30 (d, J = 17.5 Hz, 1H), 3.22 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 197.58, 176.58, 149.59, 143.70, 135.79, 130.65, 130.52, 127.15, 119.83, 108.30, 73.45, 45.74, 26.80; HRMS (ESI): \(m/z\) [M + H] calcd. for C\(_{13}\)H\(_{12}\)N\(_2\)O\(_5\): 277.0819; found: 277.0806.

4-Bromo-3-hydroxy-1-methyl-3-(2-oxobut-3-en-1-yl)indolin-2-one (10e):

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{O} & \quad \text{OH} \\
\text{N} & \quad \text{Me}
\end{align*}
\]

Yield: 146 mg (94%); cream colored solid; M.P.: 139 ºC; IR (neat): 3218, 2922, 2852, 1705, 1680, 1600, 1453, 1345, 1111, 1084, 991, 780 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.19 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 7.4 Hz, 1H), 6.80(d, J = 7.5 Hz, 1H), 6.10-6.30 (m, 2H), 5.80-5.95 (m, 1H), 4.03 (d, J = 17.1 Hz, 1H), 3.70 (bs, 1H), 3.46 (d, J = 17.1 Hz, 1H), 3.22 (s, 3H); \(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 197.20, 176.58, 149.59, 143.70, 135.79, 130.65, 130.52, 127.15, 119.83, 108.30, 73.45, 45.74, 26.80; HRMS (ESI): \(m/z\) [M + Na] calcd. for C\(_{13}\)H\(_{12}\)BrN\(_2\)O\(_3\): 331.9898; found: 331.9900.

1-Benzyl-3-hydroxy-3-(2-oxobut-3-en-1-yl)indolin-2-one(10f):
Yield: 143 mg (93%); white solid; M.P.: 150 °C; IR (neat): 3306, 1683, 1615, 1493, 1467, 1391, 1351 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.43-7.28 (m, 6H), 7.22 (dt, J = 7.5 & 1 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 7.5 Hz, 1H), 6.35 (dd, J = 17.6 & 10.4 Hz, 1H), 6.25 (d, J = 17.5 Hz, 1H), 5.92 (d, J = 10.5 Hz, 1H), 4.99 (d, J = 15.7 Hz, 1H), 4.94 (d, J = 15.7 Hz, 1H), 4.51 (bs, 1H), 3.50 (d, J = 17.0 Hz, 1H), 3.23 (d, J = 17.0 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 198.57, 176.42, 142.79, 136.41, 135.43, 130.12, 129.96, 129.75, 128.84, 127.71, 127.30, 123.95, 123.17, 109.73, 74.36, 45.27, 43.95; HRMS (ESI): m/z [M+ Na] calcd. for C₁₉H₁₇NO₃: 330.1105; found: 330.1107.

1-Benzyl-5-chloro-3-hydroxy-3-(2-oxobut-3-en-1-yl)indolin-2-one (10g):

Yield: 101 mg (59%); orange semi solid; IR (neat): 3365, 2920, 2850, 1706, 1611, 1485, 1435, 1344, 1169, 1069, 812 cm⁻¹; ¹H NMR (CDCl₃, 500 MHz): δ 7.41-7.29 (m, 6H), 7.17 (d, J = 7.5 Hz, 1H), 6.63 (d, J = 8.3 Hz, 1H), 6.33 (dd, J = 17.6 & 10.2 Hz, 1H), 6.26 (d, J = 17.5 Hz, 1H), 5.93 (d, J = 10.1 Hz, 1H), 4.97 (d, J = 15.8 Hz, 1H), 4.87 (d, J = 15.78 Hz, 1H), 4.68 (bs, 1H), 3.53 (d, J = 17.3 Hz, 1H), 3.30 (d, J = 17.3 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz): δ 197.83, 176.42, 142.79, 136.41, 135.43, 130.12, 129.96, 129.75, 128.84, 127.71, 127.30, 123.95, 123.17, 109.73, 74.36, 45.27, 43.95; HRMS (ESI): m/z [M + H] calcd. for C₁₉H₁₆ClNO₃: 342.0891; found: 342.0898.

1-Benzyl-4-bromo-3-hydroxy-3-(2-oxobut-3-en-1-yl)indolin-2-one (10h):
Yield: 125 mg (65%); light yellow solid; M.P.: 131 ºC; IR (neat): 3360, 2920, 2850, 1710, 1602, 1453, 1347, 1077, 818 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.33-7.43 (m, 4H), 7.22-7.32 (m, 1H), 7.13 (d, \(J = 8.1\) Hz, 1H), 7.06 (t, \(J = 8.1\) Hz, 1H), 6.65 (d, \(J = 7.7\) Hz, 1H), 6.26-6.33 (m, 2H), 6.26 (d, \(J = 17.5\) Hz, 1H), 4.99 (d, \(J = 15.9\) Hz, 1H), 4.92 (d, \(J = 15.9\) Hz, 1H), 4.14 (d, \(J = 17.1\) Hz, 1H), 3.75 (bs, 1H), 3.55 (d, \(J = 17.1\) Hz, 1H); \(^1^3\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 197.12, 176.20, 145.52, 136.04, 135.01, 131.27, 129.72, 128.87, 127.75, 127.26, 127.21, 127.04, 119.01, 108.88, 75.40, 44.22, 44.15; HRMS (ESI): \(m/z\) [M+ H\(^+\)] calcd. for C\(_{19}\)H\(_{16}\)BrNO\(_3\): 386.0386; found: 386.0385.

1-Allyl-3-hydroxy-3-(2-oxobut-3-en-1-yl)indolin-2-one (10i):

Yield: 120 mg (93%); cream colored solid; M.P.: 103 ºC; IR (neat): 3358, 1679, 1613, 1466, 1365, 1181, 975, 777 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.40 (d, \(J = 7.5\) Hz, 1H), 7.31 (t, \(J = 7.7\) Hz, 1H), 7.07 (t, \(J = 7.5\) Hz, 1H), 6.87 (d, \(J = 10.4\) Hz, 1H), 6.35 (dd, \(J = 17.5\) & 10.4 Hz, 1H), 6.24 (d, \(J = 17.6\) Hz, 1H), 5.94 (d, \(J = 7.5\) Hz, 1H), 5.84-5.94 (m, 1H), 5.34 (d, \(J = 17.2\) Hz, 1H), 5.27 (d, \(J = 10.3\) Hz, 1H), 4.43 (dd, \(J = 16.2\) & 5.0 Hz, 1H), 4.31 (dd, \(J = 16.2\) & 5.0 Hz, 1H), 4.26 (bs, 1H), 3.45 (d, \(J = 17.1\) Hz, 1H), 3.17 (d, \(J = 17.1\) Hz, 1H); \(^1^3\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 198.53, 175.85, 142.86, 136.44, 131.08, 130.04, 129.94, 129.72, 124.01, 123.07, 117.89, 109.55, 74.26, 45.27, 42.49; HRMS (ESI): \(m/z\) [M+ Na\(^+\)] calcd. for C\(_{15}\)H\(_{15}\)NO\(_3\): 280.0944; found: 280.0938.

1-Allyl-5-bromo-3-hydroxy-3-(2-oxobut-3-en-1-yl)indolin-2-one (10j):

Yield: 160 mg (95%); cream colored solid; M.P.: 125 ºC; IR (neat): 3262, 1697, 1672, 1609, 1483, 1360, 1178, 1060, 968, 821 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.50 (s, 1H), 7.43 (d, \(J = 8.2\) Hz, 1H), 6.75 (d, \(J = 8.3\) Hz, 1H), 6.32 (dd, \(J = 17.6\), 10.1 Hz, 1H), 6.24 (d, \(J = 17.5\) Hz, 1H), 5.94 (d, \(J = 10.1\) Hz, 1H), 5.82-5.92 (m, 1H), 5.33 (d, \(J = 17.1\) Hz, 1H), 5.27 (d, \(J = 10.3\) Hz, 1H), 4.35-4.48 (m, 2H), 4.27 (dd, \(J = 16.4\) & 5.3
Hz, 1H), 3.47 (d, $J = 17.4$ Hz, 1H), 3.22 (dd, $J = 17.4$, 2.2 Hz, 1H); $^{13}$C NMR (CDCl₃, 125 MHz): $\delta$ 197.93, 175.57, 142.03, 136.15, 132.69, 131.75, 130.69, 130.22, 127.29, 118.10, 115.73, 111.10, 74.00, 45.52, 42.57; HRMS (ESI): $m/z$ [M + H] calcd. for C₁₅H₁₄BrNO₃: 336.0230; found: 336.0234.

1-Allyl-4-bromo-3-hydroxy-3-(2-oxobut-3-en-1-yl)indolin-2-one (10k):

Yield: 151 mg (90%); orange solid; M.P.: 139 ºC; IR (neat): 3337, 1702, 1673, 1604, 1451, 1337, 993, 764 cm⁻¹; $^1$H NMR (CDCl₃, 500 MHz): $\delta$ 7.10 - 7.30 (m, 2H), 6.75-6.90 (m, 1H), 6.15-6.35 (m, 2H), 5.80-6.00 (m, 2H), 5.40 (d, $J = 17.2$ Hz, 1H), 5.28 (d, $J = 10.4$ Hz, 1H), 4.40-4.55 (m, 1H), 4.22-4.38 (m, 1H), 4.14 (d, $J = 17.2$ Hz, 1H), 3.77 (bs, 1H), 3.49 (d, $J = 17.2$ Hz, 1H); $^{13}$C NMR (CDCl₃, 125 MHz): $\delta$ 197.01, 175.84, 145.60, 135.99, 131.24, 130.74, 129.70, 127.25, 126.94, 118.98, 118.05, 108.70, 75.23, 44.37, 42.66; HRMS (ESI): $m/z$ [M+ Na] calcd. for C₁₅H₁₃BrNO₃: 336.0230; found: 336.0234.

3-Hydroxy-3-(2-oxobut-3-en-1-yl)-1-(prop-2-yn-1-yl)indolin-2-one (10l):

Yield: 102 mg (80%); yellow semi solid; IR (neat): 3395, 3278, 1711, 1612, 1489, 1467, 1353, 1176, 753 cm⁻¹; $^1$H NMR (CDCl₃, 500 MHz): $\delta$ 7.30-7.45 (m, 2H), 7.02-7.15 (m, 2H), 6.30 (dd, $J = 17.6$ & 10.3 Hz, 1H), 6.21 (d, $J = 10.3$ Hz, 1H), 5.89 (d, $J = 10.3$ Hz, 1H), 4.40-4.60 (m, 3H), 3.43 (d, $J = 17.1$ Hz, 1H), 3.18 (d, $J = 17.1$ Hz, 1H), 2.28 (t, $J = 2.4$ Hz, 1H); $^{13}$C NMR (CDCl₃, 125 MHz): $\delta$ 198.33, 175.36, 141.77, 136.30, 130.08, 129.99, 129.63, 124.02, 123.46, 109.66, 76.60, 74.25, 72.70, 45.38, 29.47; HRMS (ESI): $m/z$ [M+ Na] calcd. for C₁₅H₁₃NO₃: 278.0788; found: 278.0787.

3-Hydroxy-5-nitro-3-(2-oxobut-3-en-1-yl)-1-(prop-2-yn-1-yl)indolin-2-one (10m):
Yield: 114 mg (76%); orange solid; M.P.: 124 ºC; IR (neat): 3254, 2927, 1713, 1670, 1613, 1518, 1488, 1332, 1173, 1075, 970 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 8.33 (d, \(J = 8.5\) Hz, 1H), 8.25 (s, 1H), 7.21 (d, \(J = 8.5\) Hz, 1H), 6.20-6.38 (m, 2H), 5.90-6.02 (m, 1H), 4.52-4.70 (m, 2H), 4.50 (bs, 1H), 3.60 (d, \(J = 17.6\) Hz, 1H), 3.38 (d, \(J = 17.6\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 197.40, 175.63, 147.70, 143.96, 135.70, 130.81, 130.54, 126.98, 119.85, 109.57, 75.49, 73.73, 73.47, 45.87, 29.99; HRMS (ESI): \(m/z\) [M+H] calcd. for C\(_{15}\)H\(_{12}\)N\(_2\)O\(_5\): 301.0819; found: 301.0801.

4-Bromo-3-hydroxy-3-(2-oxobut-3-en-1-yl)-1-(prop-2-yn-1-yl)indolin-2-one (10n):

Yield: 112 mg (67%); yellow solid; M.P.: 150 ºC; IR (neat): 3377, 3288, 1712, 1666, 1605, 1451, 1373, 1206, 1173, 1079, 983 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 71.16-7.26 (m, 2H), 7.04 (d, \(J = 7.4\) Hz, 1H), 6.25 (d, \(J = 3.2\) Hz, 1H), 6.24 (s, 1H), 5.89 (dd, \(J = 7.3\) & 4 Hz, 1H), 4.57 (dd, \(J = 17.8\) & 2.5 Hz, 1H), 4.46 (dd, \(J = 17.8\) & 2.5 Hz, 1H), 4.04 (d, \(J = 17.1\) Hz, 1H), 3.60 (bs, 1H), 3.47 (d, \(J = 17.1\) Hz, 1H), 2.29 (t, \(J = 2.4\) Hz, 1H); \(^13\)C NMR (CDCl\(_3\), 125 MHz): \(\delta\) 197.40, 174.84, 143.96, 135.97, 131.43, 129.88, 127.40, 126.98, 119.07, 108.79, 76.15, 75.34, 72.93, 43.97, 29.60; HRMS (ESI): \(m/z\) [M+H] calcd. for C\(_{13}\)H\(_{12}\)BrNO\(_3\): 334.0073; found: 334.0082.

3-Hydroxy-1-methyl-3-(2-oxopropyl)indolin-2-one (10p):

Yield: 105 mg (96%); \(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta\) 7.39 (d, \(J = 7.4\) Hz, 1H), 7.35 (dt, \(J = 7.8, 1.2\) Hz, 1H), 7.09 (t, \(J = 7.5\) Hz, 1H), 6.86 (d, \(J = 7.5\) Hz, 1H), 4.48 (bs, 1H), 3.23 (s, 3H), 3.20 (d (1 peak hidden), \(J = 17\) Hz, 1H), 2.97 (d, \(J = 17.0\) Hz, 1H), 1.27 (s, 3H).
2.19 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 207.65, 176.13, 143.55, 130.05, 129.74, 123.87, 123.16, 108.62, 74.23, 48.72, 31.43, 26.31.

3-Hydroxy-1-methyl-3-(2-oxo-2-phenylethyl)indolin-2-one (10q):$^{19}$

![Structure](image)

Yield: 127 mg (90%); $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.91 (d, $J = 7.4$ Hz, 2H), 7.59 (d, $J = 7.7$ Hz, 1H), 7.47 (d, $J = 7.9$ Hz, 1H), 7.39 (d, $J = 7.4$ Hz, 2H), 7.35 (t, $J = 7.7$ Hz, 1H), 7.06 (t, $J = 7.3$ Hz, 1H), 6.89 (d, $J = 7.5$ Hz, 1H), 4.55 (s, 1H), 3.84 (d, $J = 17.5$ Hz, 1H), 3.54 (d, $J = 17.5$ Hz, 1H), 3.26 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 198.47, 176.20, 143.71, 136.40, 133.84, 130.06, 129.99, 128.72, 128.18, 124.05, 123.10, 108.59, 74.53, 44.48, 26.37.

1-Benzyl-3-hydroxy-3-(2-oxopropyl)indolin-2-one (10r):$^{20}$

![Structure](image)

Yield: 139 mg (94%); $^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 7.35-7.40 (m, 5H), 7.26-7.33 (m, 1H), 7.23 (t, $J = 7.5$ Hz, 1H), 7.05 (t, $J = 7.3$ Hz, 1H), 6.73 (d, $J = 7.8$ Hz, 1H), 4.98 (d, $J = 15.8$ Hz, 1H), 4.87 (d, $J = 15.8$ Hz, 1H), 4.46 (s, 1H), 3.29 (d, $J = 17.0$ Hz, 1H), 3.07 (d, $J = 17.3$ Hz, 1H), 2.20 (s, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta$ 207.27, 176.41, 142.76, 135.41, 129.94, 129.76, 128.84, 127.70, 127.27, 123.87, 123.17, 109.74, 74.21, 48.96, 43.93, 31.35.

3-Hydroxy-3-(2-oxopropyl)indolin-2-one (10s):$^{4a}$

![Structure](image)

Yield: 98 mg (96%); $^1$H NMR (DMSO, 500 MHz): $\delta$ 10.21 (s, 1H), 7.25 (d, $J = 7.3$ Hz, 1H), 7.18 (t, $J = 7.6$ Hz, 1H), 6.91 (t, $J = 7.5$ Hz, 1H), 6.78 (d, $J = 7.7$ Hz, 1H), 5.98 (s, 1H), 3.28 (d, $J = 16.5$ Hz, 1H), 3.00 (d, $J = 16.5$ Hz, 1H), 2.01 (s, 3H); $^{13}$C NMR
(DMSO, 125 MHz): \( \delta \) 205.61, 178.61, 142.98, 131.97, 129.44, 124.15, 121.69, 109.89, 73.12, 50.73, 31.03.

**5-Bromo-3-hydroxy-3-(2-oxopropyl)indolin-2-one (10t):**

![Structural formula of 5-bromo-3-hydroxy-3-(2-oxopropyl)indolin-2-one (10t)]

Yield: 126 mg (89%); \( ^1 \)H NMR (DMSO, 500 MHz): \( \delta \) 10.36 (s, 1H), 7.43, (s, 1H), 7.36 (d, \( J = 8.2 \) Hz, 1H), 6.76 (d, \( J = 8.2 \) Hz, 1H), 6.10 (s, 1H), 3.35-3.50 (peak merged with DMSO, 1H), 3.08 (d, \( J = 17.4 \) Hz, 1H), 2.02 (s, 3H); \( ^{13} \)C NMR (DMSO, 125 MHz): \( \delta \) 205.77, 178.21, 142.45, 134.61, 132.00, 127.12, 113.39, 111.85, 73.06, 50.41, 30.77.

**1-Methyl-5',6'-dihydrospiro[indoline-3,2'-pyran]-2,4'(3'H)-dione (12):**

![Structural formula of 1-methyl-5',6'-dihydrospiro[indoline-3,2'-pyran]-2,4'(3'H)-dione (12)]

Synthesized from the arginine mediated reaction of \( \text{1a} \) with \( \text{2a} \) following the general procedure and allowing the reaction to run for 24 h.

Yield: 67 mg (58%); white semisolid; IR (neat): 2924, 1706, 1614, 1462, 1418, 1372, 1170, 1080, 996 cm\(^{-1}\); \( ^1 \)H NMR (CDCl\(_3\), 500 MHz): \( \delta \) 7.40 (t, \( J = 7.8 \) Hz, 1H), 7.36 (d, \( J = 7.3 \) Hz, 1H), 7.13 (t, \( J = 7.5 \) Hz, 1H), 6.87 (d, \( J = 7.8 \) Hz, 1H), 4.70-4.83 (m, 1H), 4.20-4.32 (m, 1H), 3.20 (s, 3H), 2.62-2.85 (m, 4H); \( ^{13} \)C NMR (CDCl\(_3\), 125 MHz): \( \delta \) 203.96, 173.89, 143.30, 130.60, 128.07, 124.20, 123.30, 108.83, 78.23, 62.36, 45.98, 41.22, 26.10; HRMS (ESI): \( m/z \) [M+ Na]+ calcd. For C\(_{13}\)H\(_{13}\)NO\(_3\): 254.0792; found: 254.0792.

**2C5: References:**


Section 2C

2C.6: $^1$H and $^{13}$C NMR spectra of selected aldol adducts