**ABSTRACT:** N-Chloroformyl imidazolidinone derivatives of enantiopure amino acids may be deprotonated to give remarkably well-behaved enolates with both nucleophilic and electrophilic character. The enolates undergo diastereoselective C-alkylation with benzylic halides. A Bischler-Napieralski-like cyclization reaction onto the chloroformyl group, induced by either nucleophilic (KI, 2,6-lutidine) or Lewis acid (AlCl₃) catalysis, gives substituted 3,4-dihydroisoquinolone derivatives in enantioenriched form. The reaction sequence constitutes a formal [3+3] route to the 6-membered lactam ring of the dihydroisoquinolones.

The 3,4-dihydroisoquinolone core represents an important structural motif found among a wide variety of natural products (Figure 1). The dihydroisoquinolone skeleton also displays a range of biological activities, including anti-inflammatory, anti-cancer and anti-angiogenic characteristics.

**Figure 1. Natural products containing the dihydroisoquinolone skeleton**

We previously reported that an intramolecular KI-promoted Friedel-Crafts cyclization of N-chloroformylimidazolidinones derived from aromatic amino acids such as L-phenylalanine, provides an efficient synthesis of certain substituted 3,4-dihydroisoquinolones (Scheme 1).

**Scheme 1. Dihydroisoquinolones by cyclization of amino acid-derived N-chloroformylimidazolidinones**

The limitation of this work was the availability of suitable enantiopure amino acids bearing nucleophilic aromatic substituents. We now report a way to circumvent this limitation by exploiting the functionalization of a much wider range of
N-chloroformylimidazolidinones 1 at the α-carbon. In this paper, we show that, remarkably, the enolate of the imidazolidinone 1 can be generated in the presence of the reactive, electrophilic chloroformyl group (Scheme 1). The enolate functions as a formal 1,3-dipole: alkylation of the nucleophilic enolate with benzylzic electrophiles, followed by electrophilic cyclization of the N-chloroformylimidazolidinone 2 provides a dihydroisoquinolone in a formal [3+3] annulation. Introducing the nucleophilic aromatic component of the cyclization after formation of the N-chloroformyl imidazolidinone enables the synthesis of a much wider range of cyclized products, leading to dihydroisoquinolones bearing a variety of functionality on the aryl ring.

The trans-N-chloroformylimidazolidinones 1 were obtained in three simple steps from the commercially available amino acids using our previously reported conditions for the selective formation of the trans diastereoisomer. Treatment of the N-chloroformyl imidazolidinone 1 (R = Me) with KHMDDS and benzyl bromide at −78 °C resulted in clean and stereoselective alkylation of the enolate, with the product 2a formed as a single diastereoisomer. The relative stereochemistry of 2a (and of its diastereoisomer 2u described below) was established by NOE studies (see Supporting Information). As expected, the product is formed by the alkylating agent approaching anti to the bulky tert-butyl group.

Scheme 2 shows the results of alkylating the enolate of 1 with a range of substituted benzyl halides. The enolate of the L-alanine derived N-chloroformylimidazolidinone 1 (R = Me) reacted successfully with benzyl bromides bearing a variety of functional groups and substitution patterns. Electron neutral and electron rich aryl rings were tolerated well, including those substituted with methyl (2b-2d), methoxy (2f), and trifluoromethoxy (2g) groups. Alkylation with halogenated benzyl bromides also proceeded well (giving 2h-2l). Electron deficient rings bearing a trifluoromethyl and a nitrile group (2i and 2m) likewise underwent diastereoselective alkylation, though in slightly diminished yields.

N-Chloroformylimidazolidinones derived from amino acids other than L-alanine also reacted cleanly with benzylzic electrophiles. Alkylated imidazolidinones derived from L-phenylalanine (giving 2n, 2o), L-valine (2p), L-leucine (2q), L-phenylglycine (2r) and L-tryptophan (2s, 2t) were obtained in good yields. Wider reactivity towards alkylating agents was also demonstrated with the L-phenylalanine-derived N-chloroformylimidazolidinones 1 (R = Bu), whose enolate reacted with other electrophiles such as methyl iodide (2u), 3-bromo-2-methylpropene (2v) and 3-bromocyclohexene (2x) in moderate to good yields. This imidazolidinone enolate was unreactive towards more bulky simple (non-alkylating) alkylating agents, but remarkably the carbamoyl chloride function was resistant to hydrogenolysis, so the alkene functions of 2v and 2x could be hydrogenated to give the alkylated products 2w and 2y.

Scheme 2. Scope of diastereoselective alkylation

*Isolated yields shown. N-Chloroformylimidazolidinone (1.0 equiv), THF (0.1 M), KHMDDS (1-1.2 equiv., added dropwise) electrophile (1-1.5 equiv.; the electrophile was added either before or 5 mins after addition of KHMDDS (see SI for further details). Unsaturated product. Saturated product

N-Chloroformylimidazolidinones are potential substrates for Bischler-Napieralski-like ring-closure to form isoquinoline derivatives by intramolecular Friedel-Crafts cyclization. This transformation was explored by subjecting imidazolidinone 2a (in which an unsubstituted benzyl ring lies trans to the tert-butyl group) to nucleophilic catalysis by KI in our previously optimized cyclocarbonylation conditions (Table 1, entry 1: KI, 2,6-lutidine, µW, 150 °C). 12% of the dihydroisoquinolone 3a was isolated after 5 min, increasing to full conversion after 2 h (87% isolated yield, entry 3). With the electron-deficient aryl ring of the para-bromo derivative 2j, the
starting material was completely consumed after 4 h, but only 15% of the isoquinoline product 3j was isolated (entry 5). We therefore turned towards alternative promoters of Friedel-Crafts acylations. After some optimization of the reaction time and temperature (see SI for details), we found that AlCl₃ in 1,2-dichloroethane at 80 °C served as an efficient promoter of the cyclization. Under these optimized conditions, 2j was converted into 3j in excellent yield (entry 5).

Table 1. Optimization of the cyclocarbonylation

<table>
<thead>
<tr>
<th>entry</th>
<th>SM</th>
<th>X</th>
<th>method</th>
<th>time</th>
<th>product</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>H</td>
<td>A</td>
<td>5 min</td>
<td>3a</td>
<td>12%</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>H</td>
<td>A</td>
<td>1 h</td>
<td>3a</td>
<td>83%</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>H</td>
<td>A</td>
<td>2 h</td>
<td>3a</td>
<td>87%</td>
</tr>
<tr>
<td>4</td>
<td>2j</td>
<td>Br</td>
<td>A</td>
<td>4 h</td>
<td>3j</td>
<td>15%</td>
</tr>
<tr>
<td>5</td>
<td>2j</td>
<td>Br</td>
<td>B</td>
<td>16 h</td>
<td>3j</td>
<td>93%</td>
</tr>
<tr>
<td>6</td>
<td>2u</td>
<td>H</td>
<td>A</td>
<td>4 h</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2u</td>
<td>H</td>
<td>B</td>
<td>16 h</td>
<td>4u</td>
<td>83%</td>
</tr>
</tbody>
</table>

*A diastereoisomeric mixture of imidazolidinones lacking the chloroformyl group was recovered.

The other diastereoisomer of 2a, namely 2u, was available from the methylation of the phenylalanine-derived imidazolidinone. In previous work, we found that only aryl substituents trans to the tert-butyl group would undergo clean cyclization onto the chloroformyl group. 2u gave the opportunity to explore whether this was also the case when the α-carbon of the imidazolidinone is fully substituted. Treatment of 2u (where the benzyl group and the tert-butyl group are in a cis relationship) with KI under the standard conditions led to decomposition of the starting material with loss of the chloroformyl group, and gave none of the tricyclic lactam. However, treating cis-imidazolidinone 2u with AlCl₃ under the conditions optimized for 2j promoted successful cyclization, and the tricyclic lactam 4u was obtained in 83% yield. 4u carries the tert-butyl group on the endo face of the bicyclic imidazolidinone, and its relative configuration was confirmed by NOE analysis (see SI). Using these two optimized methods for cyclization, we explored the scope of the cyclocarbonylation reaction with a range of quaternary N-chloroformylimidazolidinones 2 (Scheme 3).

Using the L-alanine derived chloroformylimidazolidinones 2a-2m, good to excellent yields of imidazolidinone-fused dihydroisoquinolones 3a-f were obtained by cyclization of electron-neutral and electron-rich rings bearing different substitution patterns using KI and 2,6-lutidine under the conditions of method A. X-ray crystallography confirmed the structure of 3f.

For comparison, some of these cyclizations were also carried out using the more forcing conditions of method B (AlCl₃ in hot dichloroethane). Yields were generally similar for the cyclization of electron-neutral rings (viz. 93% AlCl₃ vs 87% KI for the para-tolyl derivative 3h). However, for substrates 2h-2m bearing electron-withdrawing groups, AlCl₃ proved to be a far superior reagent for the formation of dihydroisoquinolones 3h-3m. For chloroformylimidazolidinones 2j and 2k bearing an ortho-bromophenyl and para-bromophenyl rings, yields using KI were <35%, whereas with AlCl₃ yields were >85%. The electron deficient ortho-cyano derivative 2m did not cyclize with KI, but gave 58% dihydroisoquinoline 3m with AlCl₃.

Scheme 3. Scope of the cyclocarbonylation

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By method A; ³By method B.

Cyclizations to dihydroisoquinolones were also successful using imidazolidinones derived from other amino acids, such as phenylalanine (giving 3n and 3o), as well as the more hindered branched structures derived from valine (3p), leucine (3q) and phenylglycine (3r).
In the case of the tryptophan-derived \(N\)-chloroformylimidazolidinones 2s and 2t, KI promoted cyclization of the more nucleophilic indole ring, even though this ring is orientated in the less reactive position (see Table 1) \(cis\) to the tert-butyl group. The products of the cyclization of 2s and 2t are thus 4s and 4t, in which the tert-butyl group is located on the \(endo\) face of the bicyclic imidazolidinone. It thus appears that sufficiently reactive, electron rich rings can cyclize from the same face as the tert-butyl group even under the milder KI-promoted conditions.

Other imidazolidinones 2u-2y formed by alkylation of the L-phenylalanine-derived imidazolidinone, and thus bearing benzyl groups \(cis\) to the tert-butyl, did not cyclize with KI. Nonetheless, with AlCl\(_3\), excellent yields were obtained of the \(endo\) products 4u, 4w and 4y.\(^{23}\) The differences in reactivity under the two sets of reaction conditions suggest that different intermediates are generated. We propose that KI leads to a transient carbamoyl iodide,\(^{16,24}\) whereas AlCl\(_3\) promotes formation of an \(N\)-acylium ion, with the carbamoyl iodide being more sensitive to the geometry of imidazolidinone substituents.

The products 3 and 4 of the cyclofunctionalization contain a valuable dihydroisoquinolone core, fused to an imidazolidinone which plays no further role in the synthesis. These imidazolidinones may be hydrolysed to reveal a masked carboxylic acid under acidic conditions. 6M HCl alone was ineffective, but we found that the addition of 20\% TFA to 6M HCl\(^{16,25}\) resulted in clean hydrolysis to the dihydroisoquinolone products in good to excellent yields. Where 3 and 4 are diastereoisomeric (eg 3a and 4a), the hydrolysis provides either enantiomer of the same product (for example 5a), both formed from an L-amino acid precursor.

**Scheme 4. Hydrolysis to give dihydroisoquinolines**

\[\begin{align*}
\text{A}^+ \quad \text{CF}_3\text{COOH} & \quad 6 \text{M HCl (1:4)} & \quad \text{BuMe}_2 \\
\text{O} & \quad \text{N} & \quad \text{R} \\
\text{O} & \quad \text{N} & \quad \text{R} \\
\text{Bu} & \quad \text{Me} & \quad \text{Me}
\end{align*}\]

\[\begin{align*}
3 \text{ or } 4 & \quad \mu \text{W, } 170 \degree \text{C, } 4-8 \text{ h} & \quad 5 \\
\text{A}^+ & \quad \text{O} & \quad \text{C}=\text{O} \\
\text{R} & \quad \text{Me} & \quad \text{Me}
\end{align*}\]

\[\begin{align*}
5a, \ 80\% \text{ from } 3a & \quad \text{ent-}5a, \ 94\% \text{ from } 4a \\
5b, \ 80\% \text{ from } 3b & \quad 5c, \ 62\% \text{ from } 3c \\
5d, \ 68\% \text{ from } 3d & \quad 5e, \ 43\% \text{ from } 3e \\
5f, \ 70\% \text{ from } 3h
\end{align*}\]

"See ref. 16"

Overall, this method is complementary to our previously reported synthesis of dihydroisoquinolines.\(^{16}\) It expands the scope to a range of aromatic substituents by exploiting the remarkably clean nucleophilic reactivity of the \(N\)-chloroformylimidazolidinone enolate. Cyclization of this dipolar reagent by nucleophilic and then electrophilic addition to a benzylic halide provides a carboxylative route to the dihydroisoquinolone ring. Choice of route allows the synthesis of both enantiomers of the product 2-carboxyldihydroisoquinolones 5 starting from naturally occurring L-amino acid precursors.

**Supporting Information**

The supporting information contains full experimental details and spectroscopic characterization of all new compounds. The Supporting Information is available free of charge on the ACS Publications website.

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**REFERENCES**

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(22) CCDC 1895400 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

(23) Imidazolidinones bearing two benzylic substituents at the α-carbon of the imidazolidinone (such as 2n and 2o) did not cyclize cleanly with AlCl3, and instead decomposed to complex mixtures.
