
Peer reviewed version

Link to published version (if available): 10.1021/acs.orglett.8b03551

Link to publication record in Explore Bristol Research

PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via ACS at https://pubs.acs.org/doi/10.1021/acs.orglett.8b03551. Please refer to any applicable terms of use of the publisher.

**University of Bristol - Explore Bristol Research**

**General rights**

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: http://www.bristol.ac.uk/pure/about/ebr-terms
Substituted dihydroisoquinolinones by iodide-promoted cyclocarbonylation of aromatic α-amino acids

Mostafa M. Amer, Ana C. Carrasco, Daniel J. Leonard, John W. Ward and Jonathan Clayden

School of Chemistry, University of Bristol, Cantock’s Close, Bristol BS8 1TS, UK; School of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK

Supporting Information Placeholder

ABSTRACT: Imidazolidinone derivatives of a range of aromatic α-amino acids, on treatment with phosgene and potassium iodide, undergo a mild Bischler-Napieralski-style cyclocarbonylation reaction that generates a tricyclic lactam by insertion of a C=O group between amino acid nitrogen and the ortho position of the aryl substituent. Regio- and diastereoselective functionalization of the lactam generates a library of substituted dihydroisoquinolinones and their congeners in enantiorenciched form.

The dihydroisoquinoline ring system is found in some key biologically active compounds, not least among them the Amaryllidaceae alkaloids such as narciclasine and pancratistatin. Dihydroisoquinolines have also been identified as key scaffolds for fragment-based drug discovery. Among synthetic approaches to this ring system, reactions in which an aromatic amine precursor is cyclised with addition of one or two carbon atoms are the most common approaches. For example, aromatic amides or hydroxamic acids give dihydroisoquinolines by metal catalysed C-H activation with alkynes or alkynes or palladium catalysed cyclocarbonylation of amines. Alternatively, Bischler-Napieralski-style cyclisation can give dihydroisoquinolines by activation of N-carbamoyl derivatives of secondary homobenzylic amines using highly electrophilic reagents such as triflic anhydride, or Lewis-acid promoted cyclisation of carbamoyl chlorides.

In this paper we report a practical and operationally simple carbonylative cyclisation that converts aromatic amino acids into substituted dihydroisoquinolinones and their analogues in an efficient, versatile and stereoselective manner, without the need for powerful activating agents or Lewis acids. The reaction involves the activation of an easily formed, stable carbamoyl chloride derivative using iodide, and gives rise to architecturally varied motifs that can readily be derivatised stereoselectively to yield families of enantiomerically-enriched cyclic amino acid derivatives.

The cyclofunctionalisation at the core of the method is outlined in Scheme 1. The method entails the formation of the N-chloroformyl derivative B of a trans imidazolidinone, followed by its cyclisation by intramolecular Friedel-Crafts acylation to yield the lactam C. This lactam may be readily elaborated by further alkylation and ring-cleavage reactions to provide a diverse range of products very efficiently from simple amino acid precursors A.

Scheme 1. Cyclocarbonylation of aromatic amino acids.

We first noted the Bischler-Napieralski-like cyclisation of B to C as a side reaction that occurs when using the unusually unreactive carbamoyl chloride B as an electrophile. Given the limitations of classical Bischler-Napieralski conditions when applied to amino acids, this reaction appeared to offer a very appealing way to make cyclic amino acid derivatives under mild conditions. Preliminary studies indicated that a cyclisation product was formed only from the trans diastereoisomer of B, so we first set out to optimise a practical method for the trans-selective synthesis of N-chloroformylimidazolidinones B.
N-Chloroformyldimidazolinones may be formed non-diastereoselectively by treatment of pivalidimine derivatives of amino acids with phosgene in the presence of base. In order to develop a method for the diastereoselective synthesis of trans imidazolinones, the cyclisation of Phe-derived pivalidimine 1a was investigated (Scheme 2). Simply stirring the imine 1a with phosgene at room temperature gave good selectivity for the trans diastereoisomer, but generally with low yields, probably as a result of precipitation of an intermediate hydrochloride salt. Improved yields were obtained in THF, and addition of pyridine 30 min after the start of the reaction returned the chromatographically stable trans N-chloroformyldimidazolinide 2a in excellent yield (Scheme 2). Triphosgene also gave good trans diastereoselectivity but lower yields than phosgene.

Scheme 2. Diastereoselective formation of trans N-chloroformyl imidazolidinones.

\[
\begin{array}{cccc}
\text{N} & \text{O} & \text{O} & \text{N}\\
\text{Me} & \text{Me} & \text{Me} & \text{Me}\\n\text{Cl} & \text{Cl} & \text{Cl} & \text{Cl}\\n\text{R} & \text{R} & \text{R} & \text{R}\\
\text{COCl} & \text{COCl} & \text{NaHMDS} & \text{NaNHMDS}\\
\text{base} & \text{solvent} & \text{MeCN} & \text{MeCN}\\
\text{MeCN} & \text{THF} & \text{pyridine} & \text{pyridine}\\
\text{MeCN} & \text{MeCN} & \text{MeCN} & \text{MeCN}\\
\text{(15\% in tol., 2.5 equiv)} & \text{H} & \text{H} & \text{H}\\
\text{(15\% in tol., 2.5 equiv)} & \text{H} & \text{H} & \text{H}\\
\text{2a} & \text{2a} & \text{2a} & \text{2a}\\
\end{array}
\]

\[\text{Scheme 2. Diastereoselective formation of trans N-chloroformyl imidazolidinones.}\]

\[\frac{[a]}{[b]}\text{Diastereoisomeric ratio by NMR of crude reaction mixture; \[\frac{[c]}{[d]}\text{Yield of mixture determined by NMR using internal standard; \[e]\text{Isolated yield of major diastereoisomer; \[f]\text{Added 30 min after start of reaction.}\]

Using these optimal reaction conditions, a broad series of N-chloroformyldimidazolidinones 2a-m (see Supporting Information) were made from their corresponding amino acid pivalidimine precursors 1 with excellent trans diastereoselectivity. The trans carbamoyl chlorides were remarkably stable, and each of 2a-2m could be purified by chromatography on silica without difficulty. They were also rather unreactive as electrophiles, and their reaction with neutral nucleophiles necessitated the use of KI16 to increase their electrophilicity. During the KI-promoted reaction of 2a with an aniline, we identified a cyclic by-product, which became the sole product when 2a was heated with potassium iodide alone. This product, the benzo-fused lactam 3a (Table 1) is evidently formed by an intramolecular Friedel-Crafts acylation that amounts to a Bischler-Napieralski cyclisation of 2 to 3. The reaction was optimised with 2a and its electronically varied derivatives 2b-d, as shown in Table 1.

Table 1. Optimisation of the cyclocarbonylation

<table>
<thead>
<tr>
<th>entry</th>
<th>SM</th>
<th>time</th>
<th>solvent</th>
<th>t/°C</th>
<th>product, yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>2 h</td>
<td>tol</td>
<td>170</td>
<td>3a, 90</td>
</tr>
<tr>
<td>2</td>
<td>2b</td>
<td>2 h</td>
<td>tol</td>
<td>170</td>
<td>3b, 97</td>
</tr>
<tr>
<td>3</td>
<td>2b</td>
<td>10 s</td>
<td>CH₃CN</td>
<td>150</td>
<td>3b, 100 (91:9)</td>
</tr>
<tr>
<td>4</td>
<td>2c</td>
<td>2 h</td>
<td>tol</td>
<td>170</td>
<td>3c, 48 (71:29)</td>
</tr>
<tr>
<td>5</td>
<td>2c</td>
<td>1 h</td>
<td>CH₃CN</td>
<td>150</td>
<td>3c, 96 (76:24)</td>
</tr>
</tbody>
</table>

\[\frac{[a]}{[b]}\text{Isolated with minor 2,3-dimethoxy substituted regiosomer 3b. Ratio determined by ¹H NMR; \[c]\text{SM recovered in 49% yield; \[d]\text{Isolated with a minor 2-fluoro substituted regiosomer 3c. Ratio determined by ¹H NMR. \[e]\text{Using 2.0 equiv lutidine.}\]

Treatment of trans phenylalanine-derived carbamoyl chloride 2a under activating conditions of KI (1.1 equiv) and 2,6-lutidine (2.0 equiv) in dry toluene under microwave irradiation at 170 °C for 2 h provided the cyclised product 3a in 90% yield (entry 1). The more electron-rich DOPA derivative 2b gave a yield of 97% of 3b under these conditions (entry 2), but also turned out to be highly reactive in acetonitrile, cyclising quantitatively within 10 seconds of reaching 150 °C (entry 3). Under these conditions, a small amount of the 2,3-disubstituted regiosomer 3b was also formed by attack on the ring ortho, rather than para, to the 3-MeO substituent.

When the 3-fluorophenylalanine derivative 2c was heated with the same reagents in toluene, the reaction did not go to completion even after 2 h (entry 4). This reaction produced 34% of the regiosomer 3c formed by cyclisation para to the 3-F substituent, alongside 14% of the ortho regiosomer 3c′ and 49% recovered starting material. Changing the solvent to acetonitrile accelerated the reaction, but still gave poor regioselectivity (entry 5). Improved selectivity was ensured by lowering the temperature: at 120 °C the two regioisomers were formed in 89% and in 5% yield after 30 min (entry 6). Shortening the reaction time also appeared to improve regioselectivity, suggesting equilibration between the regioisomers: at 150 °C, only 2% of the minor regioisomer was formed, and the major product was isolated in 90% yield (entry 7).

Cyclisation of the 4-nitrophenylalanine derivative 2d was unsuccessful in toluene (starting material recovered) or acetonitrile (6% product and many by-products) even after prolonged reaction time and elevated temperature (entries 8, 9). Changing the solvent to DMF did however allow a 30% yield of the product 3i to be isolated from other by-products (entry 10). As is usual for Friedel-Crafts substitutions, the reaction is evidently heavily dependent on the electronic effects of the substituents on the aryl ring, and is accelerated by a polar solvent. Nonetheless, it is remarkable that the acylation is successful with a fluoro or nitro substituted ring using a carbamoyl chloride electrophile in the absence of a Lewis acid.

The optimal conditions identified for the cyclisation of 2 were applied to a range of aromatic, heteroaromatic and unsaturated amino acid derivatives shown in Scheme 3. Cyclisations on up to 10 g scale were successful not only with the phenylalanine derivatives 2a-2d, but also with the tyrosine derivative 2e, and with 1- and 2-naphthylalanine derivatives 2f and 2g, each of which cyclised in >90% yield. The retained relative stereochemistry of product 3b, and therefore presumably other products as well, was confirmed by X-ray crystal structure (Scheme 3b). Other ring sizes (5-membered
in 3h; 7-membered in 3i) formed after more extended reaction times, albeit in lower yield. An aliphatic Friedel-Crafts cyclisation of the allylglycine derivative 2j gave dihydropryridone 3j, and the nucleophilic furan and thiophene heterocycles of 2k-m gave 3k-m by attack at either the 2- or 3-position. The indole-containing product 3n was also formed, but without isolation of the N-chloroformylimidazolidinone 2n: the reactivity of the indole precursor 1n is such that attempted formation of 2n by the method of Scheme 3 led directly to the cyclised product 3n, even without heating or KI.

We presume that KI promotes formation of a transient carbamoyl iodide and thence maybe a carbamoyl cation, with lutidine neutralising the acid formed during the acylation (Scheme 3b). The reaction of 2b to give 3b was followed by in situ infra-red spectroscopy (Scheme 3d). Over a period of 4 hours at 70 °C, direct conversion of 2b to 3b was noted, with no detectable intermediate. Any carbamoyl iodide intermediate must react faster than it forms.

Scheme 3. (a) Cyclisation of a range of N-chloroformylimidazolidinones; (b) X-ray crystal structure of 3a; (c) Proposed mechanism for the cyclisation; (d) in-situ infra-red trace for the cyclisation of 2b.

1a) < 1 g scale at 0.15 M; [b] 10 g scale at 1 M; [c] for 10 s; [d] 2-5 g scale at 0.5-1 M; [e] with 2.0 equiv lutidine, for 3 h; [f] H2, Pd/C, EtOH, 18 h; [g] On 1 g scale at 0.15 M; [h] Formed directly from 1n.

Imidazolidinones are valuable intermediates in the synthesis of quaternary amino acids by alkylation of their enolate derivatives. The enantiopure products of the cyclisation contain an imidazolidine motif amenable to diastereoselective alkylation, directed by the tert-butyl substituent. 3a was thus alkylated by treatment with base followed by an electrophile (Scheme 4).

Scheme 4. Regioselective alkylations of 3.
the imidazolidinone carbonyl group, to give 4a (from MeI) and 4b (from EtI) with full diastereoselectivity.22 X-ray crystallography17 (Scheme 4) and NOE experiments confirmed the relative stereochemistry of the products 4a and 4b, which are consistent with both retentive quench of the coordinated anion 3-Li and with alkylation anti to the tert-butyl group. Quenching with benzyl bromide similarly gave the β-alkylated product 4c, but as a 70:30 mixture of diastereoisomers.23 Formation of an extended ‘arylogous’ enolate 3-Li at the β position is possible, but it seems unlikely that the β proton is thermodynamically more acidic than the α; plausibly, benzyl β-lithiation is directed by coordination to the amide carbonyl group,24 and is favoured over removal of the encumbered proton at the ring junction cis to the tert-butyl group.25

Enolate formation was evident in the synthesis of the valuable spirocycle 4d, which was formed in 86% by treating 3a first with 1,3-dibromopropane and then with two portions each of 2 equiv of LDA at –78 °C (X-ray crystal structure;17 Scheme 4). We expected a weaker base, or one with a less coordinating counterion, to be more selective for enolisation of the amide. 3a was therefore treated instead with KHMDS at 0 °C for 30 min, and the anion, this time red, quenched with D₂O (Scheme 4). 3a-D was returned with 67% incorporation of D at the α-position (by NMR analysis of the crude mixture). By treating the substrate with KHMDS (1.5 eq) at 0 °C for 3 h in THF (0.1 M) followed by methyl iodide (5 eq), the α-methylated product 5a was formed as a single diastereoisomer in 96% yield (Scheme 4). A similar result (91%) was obtained with LiHMDS. Excellent yields of single diastereoisomers of 5b and 5c were likewise obtained with allyl bromide and benzyl bromide. Alkylation of 3e, b, l, n likewise gave excellent yields of diastereoisomerically pure products 5d-5j. The stereochemistry of 5e was confirmed by X-ray crystallography (Scheme 4).

A second alkylation of the products 5 was possible by treatment with LDA at –78 °C for 30 min, followed by a second electrophile. The products 6a-c were formed as single diastereoisomers for which NOE studies of (6a) and X-ray crystallography17 (of 6c) confirmed that the new alkyl group lies anti to both the first-introduced alkyl group and the tert-butyl group. Double alkylation can be achieved in a one-pot reaction by first forming an enolate with KHMDS and secondly with LDA. By this method (method D) yields of 6a-c were higher than the stepwise alkylation procedure.

**Scheme 5. Hydrolysis of imidazolidinones**
The products 4-6 contain an imidazolidinone motif which is prone to acid-catalysed hydrolysis. As shown in Scheme 5 valuable carboxyisouquinolone products 7 and 8 are formed by microwave irradiation in a mixture of hydrochloric and trifluoroacetic acid.28

In summary, mild carboxylative cyclisation of aromatic amino acids may be achieved by intramolecular Friedel-Crafts acylation of trans-N-chloroformylimidazolidinones, promoted simply by potassium iodide. The product lactams may be further functionalized by regio- and diastereoselective alkylation, and the imidazolidinones may be hydrolysed to reveal enantiopure heterocyclic carboxylic acids of potential value in drug discovery programmes.[4]

Supporting Information
Full experimental details and NMR spectra of all new compounds.

Acknowledgements
This work was supported by the Presidential Leadership Programme of Egypt, the European Research Council (AdG ROCOCO), the EPSRC, and the EU Erasmus Programme.

References
(17) X-ray crystallographic data has been deposited with the CCDC: 3a 1871270; 4a 1871271; 4b 1871272; 4d 1871273; 5e 1872160; 6c 1872068.
(20) Acyl iodides have been detected by 13C NMR (ref 16), but mixing 2d with Kl showed no evidence of a new species by either 13C NMR or IR.
(22) These reactions required rigorous degassing to avoid oxidative formation of isoquinolones. In addition, small amounts of α,β-doubly alkylated products were formed.