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N-Chloroformylimidazolidinone Enolates as 1,3-Dipolar Reagents for the Stereoselective Synthesis of 3,4-Dihydroisoquinolones

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Supporting Information Placeholder

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 (AlCl_3) 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-dihydroisoquinoline^{1–7} core represents an important structural motif found among a wide variety of natural products (Figure 1).^{8–11} The dihydroisoquinoline skeleton also displays a range of biological activities,^{12,13} including anti-inflammatory,¹⁰ anti-cancer¹⁴ and anti-angiogenic¹⁵ characteristics.

Figure 1. Natural products containing the dihydroisoquinoline 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).¹⁶

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 benzylic 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.^{16–18} Treatment of the *N*-chloroformyl imidazolidinone **1** (R = Me) with KHMDS 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 benzylic 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 = Bn), 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-allylic) 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^a

^aIsolated yields shown. *N*-Chloroformylimidazolidinone (1.0 equiv), THF (0.1 M), KHMDS (1–1.2 equiv., added dropwise) electrophile (1–1.5 equiv.); the electrophile was added either before or 5 mins after addition of KHMDS (see SI for further details). ^bUnsaturated product. ^cSaturated product

N-Chloroformylimidazolidinones are potential substrates¹⁶ for Bischler-Napieralski-like ring-closure^{19–21} 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 isoquinolone 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 AlCl_3 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

entry	SM	X	method	time	product	yield
1	2a	H	A	5 min	3a	12%
2	2a	H	A	1 h	3a	83%
3	2a	H	A	2 h	3a	87%
4	2j	Br	A	4 h	3j	15%
5	2j	Br	B	16 h	3j	93%
6	2u	H	A	4 h	^a	--
7	2u	H	B	16 h	4u	83%

^aA 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 AlCl_3 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 crystallography²² confirmed the structure of **3f**.

For comparison, some of these cyclizations were also carried out using the more forcing conditions of method B (AlCl_3 in

hot dichloroethane). Yields were generally similar for the cyclization of electron-neutral rings (*viz.* 93% AlCl_3 vs 87% KI for the *para*-tolyl derivative **3b**). However, for substrates **2h-2m** bearing electron-withdrawing groups, AlCl_3 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 AlCl_3 yields were >85%. The electron deficient *ortho*-cyano derivative **2m** did not cyclize with KI, but gave 58% dihydroisoquinolone **3m** with AlCl_3 .

Scheme 3. Scope of the cyclocarbonylation

^aBy method A; ^bBy 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 AlCl₃, 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 AlCl₃ 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 **4u**), 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 dihydroisoquinolones

^aSee ref. 16

Overall, this method is complementary to our previously reported synthesis of dihydroisoquinolones.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 dipole

lar reagent by nucleophilic and then electrophilic addition to a benzylic halide provides a carbonylative route to the dihydroisoquinolone ring. Choice of route allows the synthesis of both enantiomers of the product 2-carboxydihydroisoquinolones **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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