Stereospecific Synthesis of syn-α-Oximinoamides by a Three-Component Reaction of Isocyanides, syn-Chlorooximes, and Carboxylic Acids

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ABSTRACT

A stereospecific multicomponent reaction among isocyanides, syn-chlorooximes, and carboxylic acids provides an efficient synthesis of biologically relevant syn-α-oximinoamides.

When three or more starting materials react in the same flask to produce a molecule which contains parts of all the reactants, a multicomponent reaction (MCR) takes place.1 In general, MCRs stand out as a powerful tool for the rapid construction of quite complex molecules, not easily accessible via the classical two-component chemistry.2 Among them, the Passerini reaction (Scheme 1) is the oldest MCR in which isocyanides have been used,3 exploiting their propensity to react with nucleophiles and electrophiles at the same carbon atom. Over the past few decades, this reaction has gained interest as a simple and practical methodology for the synthesis of novel molecular scaffolds. Besides the post-transformation strategy,4 another tactic to expand the scope of this venerable reaction is to use surrogates of the carboxylic or the carbonyl partners.

Successful examples of replacing the carboxylic moiety with water,5 hydrazoic acid,6 o-nitrophenol,7 silanol,8 and

Scheme 1. Passerini Reaction

References and Notes


alcohols\(^9\) have been reported, while acyl cyanides,\(^{10}\) epoxides,\(^{11}\) acylisocyanates,\(^ {12}\) and ketenes\(^{13}\) emerged as electrophilic partners in the Passerini reaction.\(^ {14}\) In this respect, and in connection with our ongoing projects aiming at the development of multicomponent reactions\(^ {15}\) and their applications in medicinal chemistry,\(^ {16}\) we became interested in developing multicomponent processes exploiting novel electrophilic species. We reasoned that, as in principle there are no restrictions on the nature of the electrophile and nucleophile which can react with the isocyanide forming the so-called \(\alpha\)-adduct,\(^ {17}\) syn-chlorooximes could be excellent surrogates for the carbonyl group. Herein, we report a multicomponent reaction among syn-chlorooximes, isocyanides, and carboxylic acids to afford syn-\(\alpha\)-oximinoamides with a high level of stereospecificity (Scheme 2).

### Scheme 2. Novel Multicomponent Passerini-Type Reaction

\[
\begin{align*}
\text{R}^1\text{NC} + \text{R}^2\text{OH} \rightarrow \text{R}^1\text{NCH} = \text{O} - \text{R}^2\text{H} + \text{R}^2\text{COOH}
\end{align*}
\]

To validate our hypothesis, to a solution of cyclohexyl isocyanide (2a) and phenylacetic acid (3a) in dichloromethane as solvent was added 1 equiv of triethylamine to deprotonate the carboxylic acid. After the addition of syn-phenylchlorooxime (1a),\(^ {18,19}\) the reaction was stirred at room temperature for 1 h. To our delight, the desired syn-oximinoamide\(^ {20}\) (4a) was formed in 70% yield, along with a trace of its anti isomer (syn/anti ratio 94.6)\(^ { \text{21}}\) (Scheme 3). The use of a base, to avoid the generation of HCl, was compulsory for the success of this transformation. Indeed, the reaction carried out in the absence of triethylamine gave the desired product in only 21% of yield.

### Scheme 3. Three-Component Reaction of Cyclohexylisocyanide 2a, Phenylacetic Acid 3a, and Benzy1chlorooxime 1a

\[
\begin{align*}
\text{NC} + \text{CH}_2\text{C}_6\text{H}_5\text{COOH} \rightarrow \text{N} = \text{C} - \text{CH}_2\text{C}_6\text{H}_5 + \text{CH}_2\text{C}_6\text{H}_5\text{COOH}
\end{align*}
\]

Our proposed mechanism for this reaction is depicted in Scheme 4. The syn-chlorooxime reacts with the isocyanide, forming the transient \(\alpha\)-adduct, which is in equilibrium with its nitritium form. The nitritium intermediate is then intercepted by the carboxylate ion. The intermediate so obtained undergoes an irreversible Mumm-type...
rearrangement mediated by the syn-oxime driving all the equilibria to the final syn-α-oximinoamide.

Under these buffered conditions (1 equiv of carboxylic acid and 1 equiv of TEA), no generation of nitrile N-oxides and the subsequent formation of the corresponding furoxans from chloroximes were detected, as confirmed in separate experiments, ruling out a direct involvement of nitrile N-oxides in the reaction.22

With the anti isomer of chloroximes, it is the lone pair of the nitrogen atom which captures the acyl group to give an acylimide23 and finally the anti-oximinoamide (Scheme 5).

As shown in Figure 1, the syn stereochemistry for the major stereoisomer of compound 4a was further confirmed by X-ray diffraction analysis.

The scope and limitation of this MCR were next examined. Different chloroximes (1a–h), isocyanides (2a–e), and carboxylic acids (3a–i) were chosen (Figure 2).

(23) Acylimides have been reported. See: Ziegler, E.; Belegratis, K. Monatsh. Chem. 1968, 99, 995–998.

As it is possible to see in Figure 3, this transformation proved to be highly versatile, and the level of stereospecificity

**Scheme 5. Proposed Mechanism for the Formation of the syn and anti Isomers of α-Oximinoamides**

**Figure 1.** X-ray crystal structure of 4a.

**Figure 2.** Building blocks.

**Figure 3.** Synthesized α-oximinoamides.
depends on the syn/anti ratio of the starting \( \alpha \)-chlorooximes. The reaction was tolerant to primary, secondary, and tertiary isocyanides but failed with aromatic isocyanides. Both aliphatic and aromatic carboxylic acids participated well in the reaction. The presence of electron-withdrawing or electron-releasing groups on the benzoic acid did not affect the course of the reaction.

The \( \alpha \)-oximinoamide motif occupies a relevant role in the core of numerous pharmaceuticals and natural products. It can be found in its syn configuration in most of the second- and third-generation cephalosporins, either as such or as the oximino ether (e.g., cefmatilen, cefixime, cefdinir, and cefditoren) and \( \beta \)-lactamase inhibitors (e.g., aztreonam),\(^{24}\) as well as in some natural products such as the antibacterial nocardicin A. The anti form is displayed in marine natural products such as verongamine, bastardines, and psammaplin A.\(^{25}\)

Very recently, \( \alpha \)-oximinoamides have been reported as an effective zinc chelating moiety in a series of potent HDAC inhibitors.\(^{26}\)

In conclusion, we have successfully developed a MCR where chlorooximes are involved to produce syn-\( \alpha \)-oximinoamides in a stereospecific manner. The reaction is effective across a range of structures in each component, producing diverse oximinoamides in a single step.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds synthesized. This material is available free of charge via the Internet at http://pubs.acs.org.