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

Tracey Pirali,*,† Riccardo Mossetti,† Simona Galli,‡ and Gian Cesare Tron*,†

Dipartimento di Scienze Chimiche, Alimentari, Farmaceutiche e Farmacologiche, Università degli Studi del Piemonte Orientale "A. Avogadro", Via Bovio 6, 28100 Novara, Italy, and Dipartimento di Scienze Chimiche e Ambientali, Università dell'Insubria, Via Lucini 3, 22100 Como, Italy

pirali@pharm.unipmn.it; tron@pharm.unipmn.it

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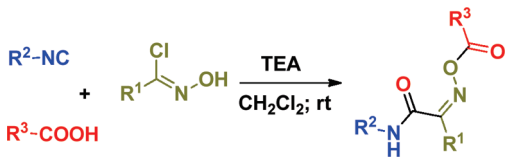
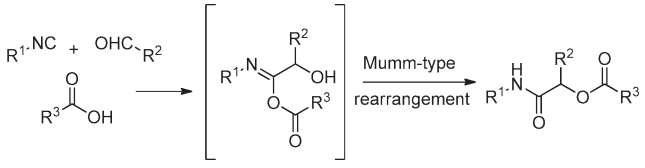
ABSTRACT



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.

Scheme 1. Passerini Reaction



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

† Università degli Studi del Piemonte Orientale "A. Avogadro".
‡ Università dell'Insubria.

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(2) For reviews, see: (a) Akritopoulou-Zanze, I.; Djuric, S. W. *Heterocycles* **2007**, *73*, 125–147. (b) Zhu, J. *Eur. J. Org. Chem.* **2003**, *7*, 1133–1144. (c) Sunderhaus, J. D.; Martin, S. F. *Chem.—Eur. J.* **2009**, *15*, 1300–1308. (d) D'Souza, D. M.; Müller Thomas, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095–1108. (e) Toure, B. B.; Hall, D. G. *Chem. Rev.* **2009**, *109*, 4439–4486. (f) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210.

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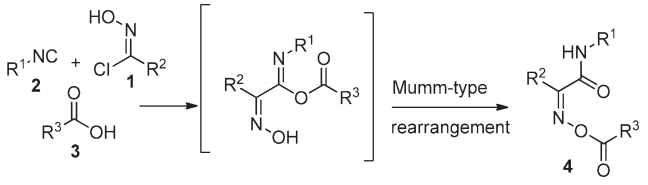
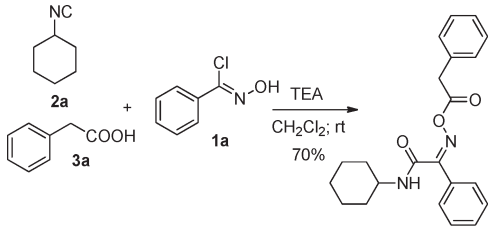
alchools[9] have been reported, while acyl cyanides,[10] epoxides,[11] acylisocyanates,[12] and ketenes[13] emerged as electrophilic partners in the Passerini reaction.[14] In this respect, and in connection with our ongoing projects aiming at the development of multicomponent reactions[15] and their 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 α-adduct,[17] *syn*-chlorooximes could be excellent surrogates for the carbonyl group. Herein, we report a multicomponent reaction among *syn*-chloroximes, isocyanides, and carboxylic acids to afford *syn*-α-oximinoamides with a high level of stereospecificity (Scheme 2).

Scheme 2. Novel Multicomponent Passerini-Type Reaction



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)[21] (Scheme 3).

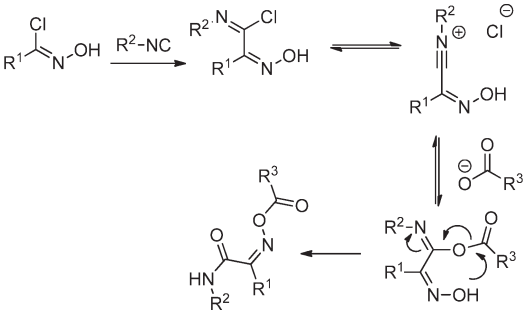
Scheme 3. Three-Component Reaction of Cyclohexylisocyanide **2a**, Phenylacetic Acid **3a**, and Benzylchloroxime **1a**



4a
syn/*anti* 94/6

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 4. Proposed Mechanism for the Three-Component Reaction



Our proposed mechanism for this reaction is depicted in Scheme 4. The *syn*-chlorooxime reacts with the isocyanide, forming the transient α-adduct, which is in equilibrium with its nitrilium form. The nitrilium intermediate is then intercepted by the carboxylate ion. The intermediate so obtained undergoes an irreversible Mumm-type

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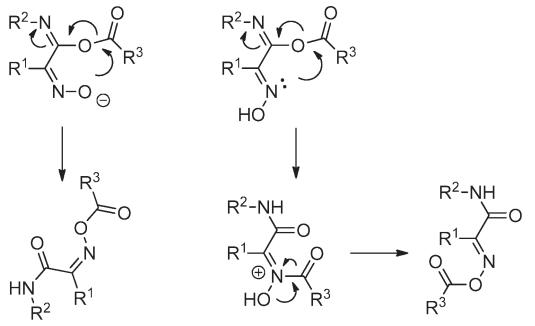
(21) The ratio was established by ^{1}H NMR, by integrating the best resolved peaks.

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]

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



With the *anti* isomer of chloroximes, it is the lone pair of the nitrogen atom which captures the acyl group to give an acylimide[23] and finally the *anti*-oximinoamide (Scheme 5).

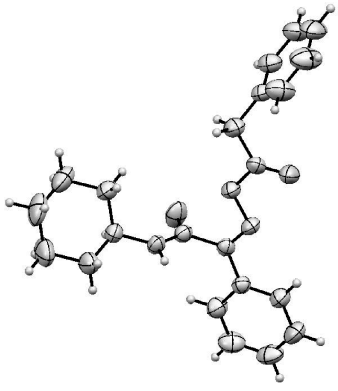


Figure 1. X-ray crystal structure of **4a**.

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 chlorooximes (**1a**–**h**), isocyanides (**2a**–**e**), and carboxylic acids (**3a**–**i**) were chosen (Figure 2).

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

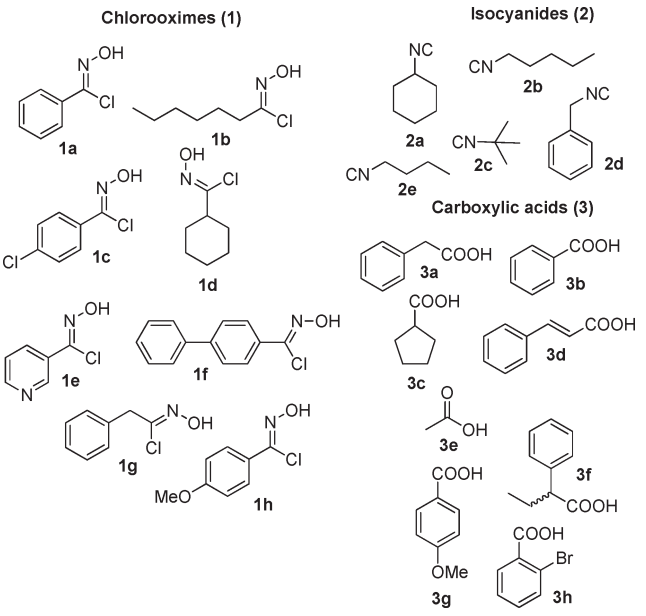

Figure 2. Building blocks.

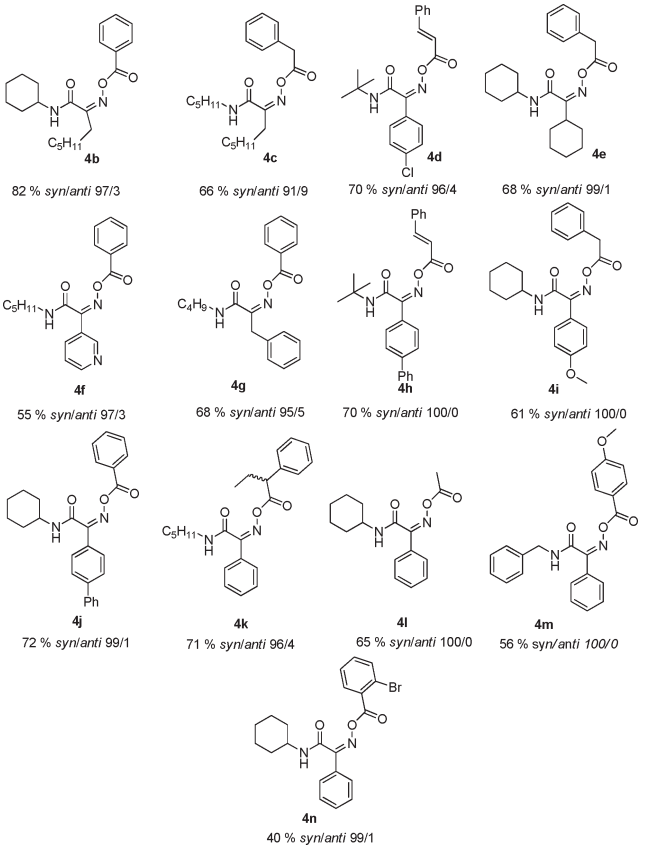

Figure 3. Synthesized α-oximinoamides.

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

depends on the *syn*/*anti* ratio of the starting α-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 α-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 β-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, bastadines, and psammaplin A.[25]

Very recently, α-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*-α-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.

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