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Highly Diastereoselective Multicomponent Synthesis of Unsymmetrical Imidazolines

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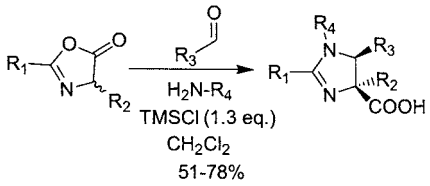
ABSTRACT

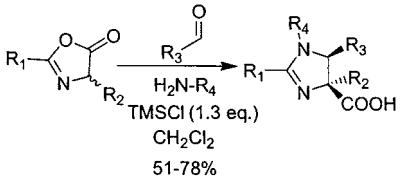


We report here a highly diastereoselective multicomponent synthesis of imidazolines. These low molecular weight scaffolds contain a four-point diversity applicable to alkyl, aryl, acyl, and hetereocyclic substitutions.

The development of small molecular weight scaffolds containing a high degree of diversity has become a leading focus in modern drug discovery.[1−5] As part of our program to develop small molecule libraries containing antiinflammatory activity, we developed a highly diastereoselective multicomponent one-pot synthesis of substituted imidazolines. These low molecular weight scaffolds contain a four-point diversity applicable to alkyl, aryl, acyl, and heterocyclic substitutions.

1,3-Dipolar cycloaddition reactions utilizing N-methylated mesoionic oxazolones (or munchnones) provide a general route for the syntheses of pyrroles and imidazoles.[6−8] Surprisingly, the utilization of oxazolones (or azlactones) has not yet resulted in an efficient entry into a stereoselective highly diverse class of imidazoline scaffolds. Because of their interesting synthetic and pharmacological properties,[9−15] we examined the synthesis of imidazolines via the reaction of oxazolones with a variety of imines in the presence of Lewis acids. After screening a small number of Lewis acids, we found that TMSCl promotes the reaction of oxazolones and imines to afford the imidazoline scaffold in very good yields as single diastereomers (Scheme 1).

Scheme 1. Multicomponent One-Pot Synthesis of Imidazolines



The oxazolones were prepared from different *N*-acyl-α-amino acids by EDCI-mediated dehydration to provide the pure oxazolones in high yields.[16−18] The cycloaddition

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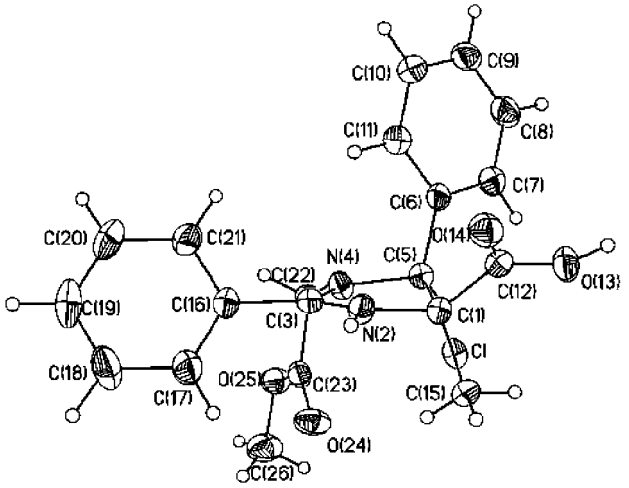
reactions proceeded well with a wide variety of imines at slightly elevated temperatures (40 °C) to provide the highly substituted imidazolines in very good yields. Only the trans diastereomers (with respect to R_2 and R_3) of the imidazolines were observed as determined by NOE experiments and X-ray crystallography (Figure 1).



Compound 7

Figure 1. X-ray crystal structure of compound **7**. HCl salt.

This diastereoselective multicomponent one-pot synthesis provides a wide range of aryl, acyl, alkyl, and heterocyclic-substituted imidazolines in very good yields (Figure 2). Some limitation of the cycloaddition reaction was noticed with respect to the R_4 moiety. Increasing the steric environment, for example, by using 1-phenyl ethylamine, resulted in no product formation (Figure 2, compound **6**). In addition, only compound **5** was isolated as a mixture of diastereomers (68% yield, 3:1 trans:cis, with respect to R_2:R_3), whereas all other compounds were isolated as single diastereomers.

While the complete mechanistic details of this process are still under investigation, the reaction does not seem to proceed via a ring-opened nitrilium ion intermediate as anticipated (Scheme 2, pathway a).[14] The possibility of a Michael-type addition via the formation of the nitrilium ion was investigated by first preparing the silyl enol ether with TMSCl (1.0 equiv) and TEA (1.0 equiv) followed by the addition of the imine and an additional 1 equiv of TMSCl.

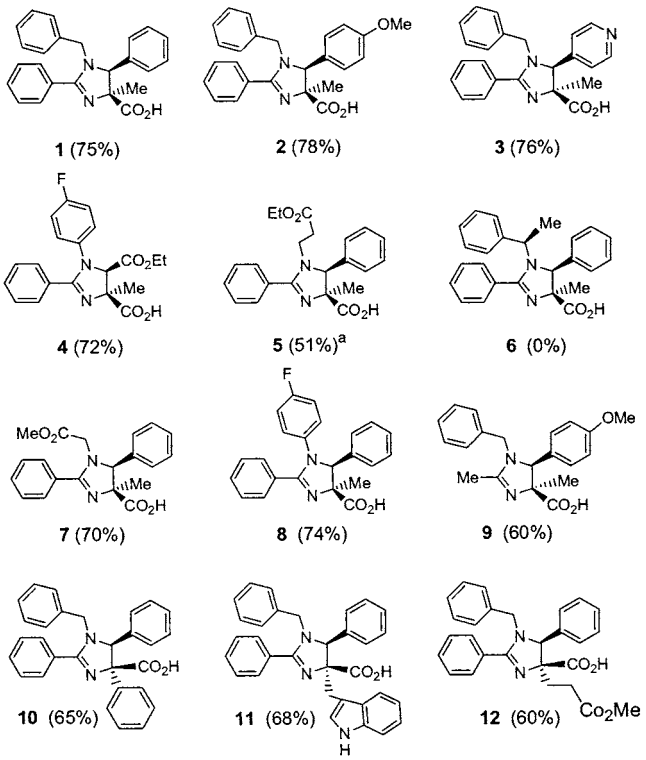
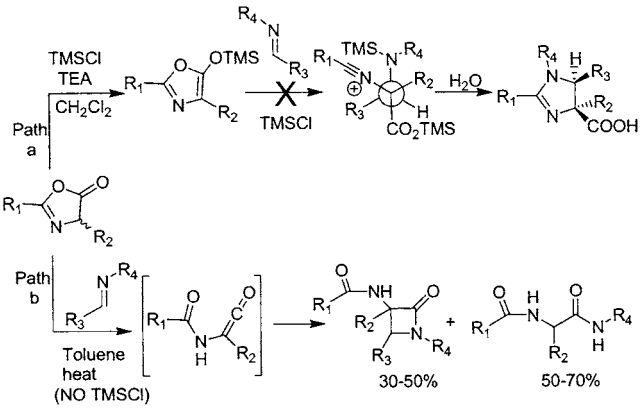


Figure 2. Structures of imidazolines **1**−**12** (% yield is listed in Figure 2). Yield of compound **5** was based on the isolated trans product.

This resulted merely in isolation of starting materials. Excess of triethylamine also halted the reaction suggesting that acidic conditions were required. However, Lewis acids such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ or protic acids such as camphor sulfonic acid and methyl sulfonic acid did not promote product formation. The absence of trimethylsilyl chloride resulted in the formation of β-lactams and *N*-acyl amino acid amides presumably via the corresponding ketene intermediate (Scheme 2, path b).[19,20]

O-Silation with TMSOTf also did not result in any product formation. This indicates the requirement of a nucleophilic

Scheme 2. Proposed Mechanisms of Oxazolone Reactions



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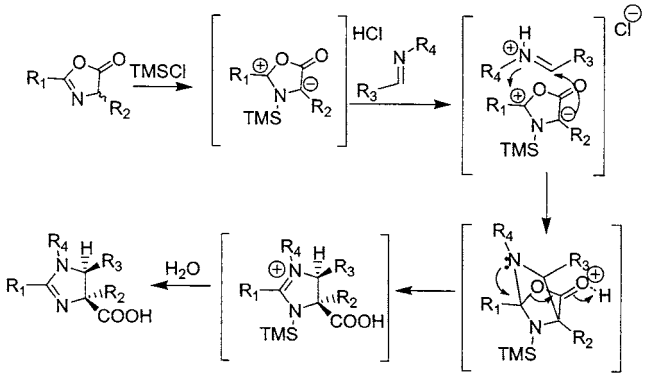
counterion to establish an equilibrium between O-silation and N-silation of the azlactone (Scheme 3). In light of these

Scheme 3. Proposed Mechanism of 1,3-Dipolar Cycloaddition



findings, we propose that the reaction proceeds via a 1,3-dipolar cycloaddition. Steric repulsion of the R_3 group during the cycloaddition might explain the diastereoselectivity obtained in this reaction (Scheme 3).

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Other silyl chlorides such as triphenyl silyl chloride and triethyl silyl chloride also provided the product as a single diastereomer, in notably longer reaction times and lower yields (compound **1**, 45 and 70%, respectively). In support of the proposed mechanism shown in Scheme 3, we found that 1 equiv of acetyl chloride provided the formation of the imidazoline, in somewhat lower yields (compound **1**, 55%).

In conclusion, we have identified an efficient diastereoselective synthesis of imidazoline scaffolds with a high degree of diversity. The potential clinical applications and antiinflammatory activity of this new class of compounds will be reported soon.

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Supporting Information Available: Experimental procedures and IR, ^{1}H and ^{13}C NMR, and HRMS data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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