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Azomethine ylide mediated inversion of configuration of quaternary imidazoline carbon: converting *trans*- to its *cis*-imidazolines

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Abstract

An efficient synthetic methodology of converting *trans*-4,5-diaryl-2-imidazolines to the corresponding *cis*-4,5-diaryl-2-imidazolines has been developed. This methodology features mild reaction conditions and a simple one-pot two-step procedure.

Keywords

Cancer treatment; Azomethine ylide; Imidazoline; Oxazolone

The stereochemistry of small molecules is often key to their biological function. Stereoisomers of the same scaffolds can even elicit opposite biological responses, as exemplified by the 4,5-diaryl-2-imidazolines. *Cis*-4,5-diaryl-2-imidazolines (Nutlins) disrupt the binding the E3-ligase MDM2 to the pro-apoptotic transcription factor p53, resulting in activating apoptotic pathways in cancer cells,(1) whereas the corresponding *trans*-4,5-diaryl-2-imidazolines have been found to inhibit the anti-apoptotic transcription factor NF-κB, thus inhibiting anti-apoptotic pathways (Scheme 1).(2,3)

Imidazolines not only show diverse biological activities,(4,5) but also are important building blocks in synthetic organic chemistry,(6–9) including their role as ligands for asymmetric catalysis. (10–14) Based on the important biological and chemical potential of both *cis*- and *trans*- imidazolines, an efficient synthetic methodology to realize the transformation between the two stereoisomers is described herein.

Previously, we reported a multicomponent diastereoselective synthesis of *trans*-imidazolines using oxazolone **1**, which react readily with imines via a chlorotrimethylsilane-mediated azomethine ylide intermediate (Scheme 2).(15–17) The resulting zwitterion **2** contains a reactive carboxylic acid, which following mild thermal decarboxylation, readily reacts with aldehydes to yield the *cis*-imidazoline **3**. We report herein the formation of highly substituted *cis*-imidazolines, by converting *trans*-4,5-diaryl-2-imidazolines (**2**) to the corresponding *cis*-4,5-diaryl-2-imidazolines (**3**).

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Supplementary data

Supplementary data (detailed experimental procedures and full spectroscopic characterization data for all new compounds and X-ray crystal structures for **4**, **9**, **11**, **20**, **21**) associated with this article can be found in the online version, at doi.

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Imidazolines **4–8** were prepared from the corresponding amino acids using Schotten-Baumann reaction, as previously described.⁽¹⁸⁾ We hypothesized that a successful transformation between the *cis* and *trans* 4,5-diaryl-2-imidazolines could be accomplished by trapping the reactive azomethine ylide intermediate with an appropriate electrophile, such as an aldehyde, following a mild decarboxylation of **2**. To test this hypothesis, *trans*-4,5-diaryl-2-imidazolines containing various substitutions α - to the carboxylate (imidazolines **4–8**) were refluxed in THF in the presence of benzaldehyde for two hours (Table 1). The intermediate alcohol **3** can be isolated as a 1:1 mixture of diastereomers (Scheme 2) and was oxidized with IBX during work-up to afford the new ketone-substituted imidazoline derivatives **9–11** as single diastereomers (Table 1). Of the α -substituents tested, both electron rich and poor aryl groups rendered the products efficiently. However, alkyl substituents did not provide the desired products, likely due to a decrease in the resonance stabilized azomethine ylide intermediate **14** (Scheme 3), but rendered mainly in recovery of starting material and imidazole.

The relative stereochemistry of the imidazoline scaffold was established on the basis of X-ray crystallography (Figure 1). To explain the stereochemical outcome, we envision benzaldehyde to approach the azomethine ylide intermediate **14** from the opposite direction of the 5-position aryl group (Scheme 3) in order to minimize the steric hindrance, which results in the observed stereochemistry.

To further explore the scope of this method, imidazoline **5** has been reacted with a variety of aldehydes. To our satisfaction, moderate to excellent yields of the *cis*-4,5-diaryl-2-imidazolines were obtained in all cases (Table 2). Aromatic (entry 1–4), heteroaromatic (entry 5) and aliphatic (entry 6–7) aldehydes all successfully undergo this conversion. The steric hindrance appears to play a role in this transformation as the relatively hindered aldehyde, isobutyraldehyde (entry 7), was incorporated in the product in only moderate yield.

In conclusion, we have taken advantage of the decarboxylation of imidazolines to generate the reactive azomethine ylide *in situ* to facilitate the transformation from *trans*-4,5-diaryl-2-imidazolines into their *cis* isomers. An overall inversion of the stereochemistry of a quaternary substituted carbon is created in this process. This interconversion from *trans*- to *cis*- imidazolines allows efficient access to both classes of biologically important scaffolds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
X-ray crystal structure of compound **9**.

Cis-4,5-diaryl-2-imidazoline

Trans-4,5-diaryl-2-imidazoline

Scheme 1.

Biological responses to *cis*- and *trans*- 4,5-diaryl-2-imidazolines.

Scheme 2.

Conversion of *trans*-4,5-diaryl-2-imidazolines to the corresponding *cis*-4,5-diaryl-2-imidazolines

Scheme 3.

Transformation of *trans*-4,5-diaryl-2-imidazolines to its *cis* isomer.

Variation of Starting Imidazoline.

^a Isolated yield.

Table 2

Variation of Aldehyde.

Entry	Compound	Aldehyde	R	Yield (%) ^a
1	17			86
2	18			45
3	19			72
4	20			58
5	21			90
6	22			69
7	23			32

^aIsolated yield.