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Diastereochemical Diversity of Imidazoline Scaffolds via Substrate Controlled TMSCl Mediated Cycloaddition of Azlactones

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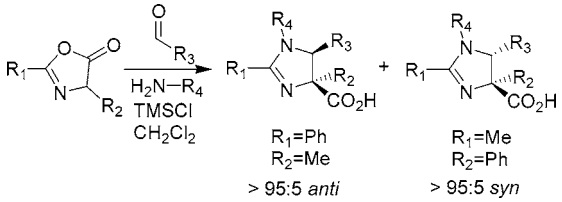
ABSTRACT



We report herein a trimethylsilyl chloride mediated substrate controlled 1,3-dipolar cycloaddition for the diastereoselective synthesis of either *syn*- or *anti*-imidazolines. This method provides scaffolds with four points of diversity and control over two stereocenters.

Small-molecule scaffolds offer a handle to dissect biological pathways, identify targets, and modulate their functions for potential therapeutic use.[1] Diversity-oriented synthesis is a strategy for the construction of libraries with stereochemical, skeletal, and functional group diversity with the aim to create a broad distribution of compounds in chemical space.[2] Control over stereochemical diversity in particular increases the number of relative orientations of potential macromolecule-interacting elements in small molecules.

1,3-Dipolar cycloadditions of *N*-alkylated azlactones (münchnones) with various dipolarophiles provide a general method for the synthesis of aromatic heterocycles such as pyrroles, imidazoles, oxazoles, etc.[3] However, due to the ease of aromatization under standard conditions, the stereochemical information generated in the cycloaddition reaction is lost. Efficient stereoselective syntheses of imidazolines have been very limited with respect to control of diastereochemical diversity and has primarily provided the anti products.[4] As part of our program focused on generating structurally and stereochemically diverse heterocyclic scaffolds, we have reported the use of a Lewis acid mediated generation of münchnones as a mild and stereoselective process to access highly substituted dihydroheterocyclic scaffolds.[5−7]

The stereochemical diversity of these small dihydroheterocyclic scaffolds presents novel territory in terms of both structure and biological activity examplified by the unique

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anticancer properties of *syn*-imidazolines (nutlins)[8] and *anti*-imidazolines (SP-4-84).[9] The *syn*-imidazolines were found to be inhibitors of MDM2, a protein that negatively regulates the activity of the pro-apoptotic transcription factor p53 (Figure 1).[8] The *anti*-imidazoline SP-4-84, on the other hand,

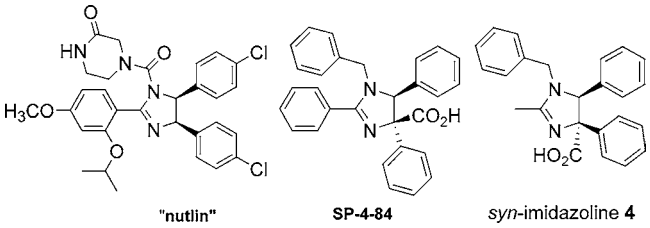
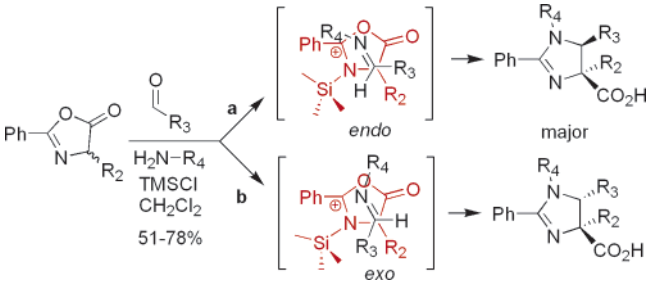


Figure 1. Structure of nutlin (*syn*-imidazoline), SP-4-84, and *anti*-imidazoline (**4**).

was found to be a drastic enhancer of the chemotherapeutic efficacy of anticancer agents and modulator of the *anti*-apoptotic NF-κB signaling pathway.[9] In addition to their diverse biological activities,[10] imidazolines have been utilized as building blocks for biologically interesting scaffolds[11] and recently attracted considerable interest as ligands for asymmetric catalysis.[12]

We previously reported the preparation of *anti*-imidazolines using a trimethylsilyl chloride mediated 1,3-dipolar cycloaddition on the azlactone template in good yields and high diastereoselectivity (Scheme 1).[5,6] In view of a potential

Scheme 1. Proposed Transition States for Diastereoselective Synthesis of *anti*-Imidazolines

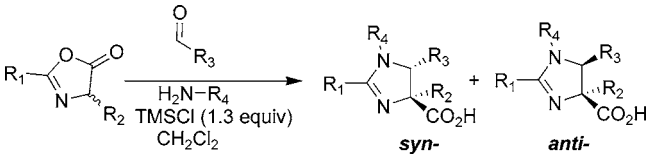


diverse biological response resulting from the stereochemical diversity of these imidazoline scaffolds, we report herein a trimethylsilyl chloride mediated substrate controlled 1,3-dipolar cycloaddition for the diastereoselective formation of *syn*- or *anti*-imidazolines.

In the case of 2-phenylimidazolines, high diastereoselectivity was attributed to A (1,3) strain, in the azlactone dipole, which prevents coplanarity of Ph, TMS, and R_2 groups. To prevent steric interaction between the bulky silyl group of the azlactone and R_3 group of imine, the endo approach of the imine was favored resulting in the anti isomer as the major or sole product (Scheme 1, path a).[6]

However, by reducing the resonance stabilization of the carbocation in the dipole by changing the electronic nature of the R_1 substituent, a significant change in diastereoselectivity was observed (entries 1−4, Table 1). Replacement of

Table 1. Influence of R_1 Group on Diastereoselectivity



entry	R_1	R_2	R_3	R_4	yield	syn:anti
1	Ph	Me	Ph	Bn	75	>5:95
2	Bn	Me	Ph	Bn	76	33:67
3	Me	Me	Ph	Bn	12[a]	50:50
4	Me	Ph	Ph	Bn	72	90:10

[a] The azlactone for entry **2** is volatile resulting in low isolated yields

the phenyl group by a benzyl or a methyl moiety significantly eroded the stereoselectivity (entries 1−3, Table 1). Further, switching the Ph and Me groups at R_1 and R_2 positions favored the formation of *syn*-imidazoline (with respect to R_2 and R_3) as the major product in 90:10 ratio (compare entries 1 and 4, Table 1).

Intrigued by the clear reversal of diastereoselectivity, we investigated the role of the R_1 and R_2 substituents on the azlactone template. The azlactones were prepared from the *N*-acetyl amino acids via an EDCI mediated dehydration process as previously reported.[6,13] The *N*-acyl *p*-methoxy phenylglycine (amino acids for entries 10 and 11, Table 2) was synthesized by employing a modified procedure of Wasserman et al. (see the Supporting Information).[14]

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The cycloaddition reactions were conducted under mild reflux conditions in dichloromethane or THF in the presence of 1.3 equiv of TMSCl. The imidazoline products were isolated by precipitation. *syn*-Imidazolines were reprecipitated from the mixture in modest to good yields and the syn configuration (relative to R_2 and R_3) was confirmed unambiguously by X-ray crystallography (see Figure 2).

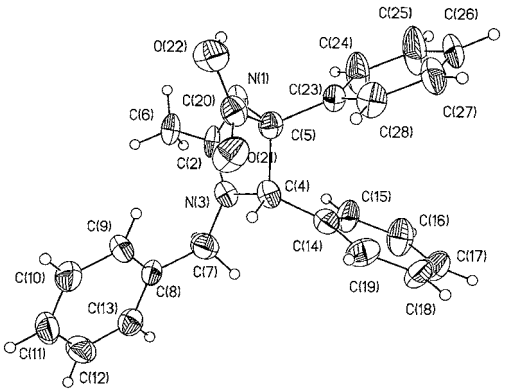


Figure 2. X-ray crystal structure of compound **4**.

To understand the role of the R_2 group in the diastereochemical outcome of the reaction, the R_2 group was varied while R_1 was maintained as methyl or phenyl.

The anti diastereomer was obtained with R_1 as a phenyl group and R_2 an alkyl or aryl group (entries 6, 8, and 9, Table 2). However, when R_1 is methyl and R_2 is methyl, benzyl, or isopropyl (entry 3, Table 1; entries 5 and 7, Table 2) a mixture of diastereomers was obtained. *syn*-Imidazolines were obtained as the major or sole products with the R_2 substituent as an aryl group (entry 4, Table 1; entry 10, Table 2). These results suggest a possible role of π-stacking interactions between neighboring π-donor R_2 and π-acceptor R_3 (the centroid−centroid distance between R_2 and R_3 in **4** was found to be 3.98 Å, corresponding to a van der Waals contact) (Scheme 2).[15]

Table 2. Influence of R_2 Favoring *syn*-Imidazolines

entry	R_1	R_2	R_3	R_4	yield	syn:anti
5	Me	Bn	Ph	Bn	55	75:25
6	Ph	Bn	Ph	Bn	45	>5:95
7	Me	^{i}Pr	Ph	Bn	79	50:50
8	Ph	^{i}Pr	Ph	Bn	71	>5:95
10	Me	p-OMePh	p-NO_2Ph	Bn	66	>95:5
11	Ph	p-OMePh	p-NO_2Ph	Bn	53	>5:95

Some control on the diastereoselectivity was observed based on the electronic nature of the incoming dipolarophile. Electron-donating groups at R_3 resulted in reduced syn-diastereoselectivity (entry 14, Table 3), while electron-withdrawing groups enhanced syn-diastereoselectivity (entry 16, Table 3).

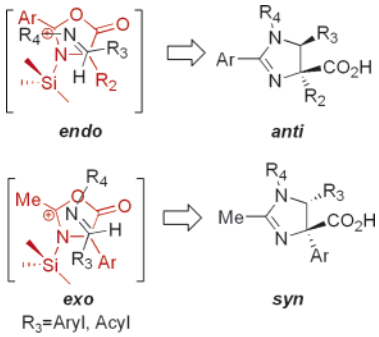
Table 3. Variation of R_3 and R_4

entry	R_1	R_2	R_3	R_4	yield	syn:anti
12	Me	Ph	^{i}Pr	Bn	0[a]	
13	Ph	Me	4-methoxyphenyl	Bn	78	>5:95
14	Me	Ph	4-methoxyphenyl	Bn	60	60:40
15	Ph	Me	4-nitrophenyl	Bn	51	>9:95
16	Me	Ph	4-nitrophenyl	Bn	71	>95:5
17	Ph	Me	−COOEt	Bn	65	>5:95
18	Me	Ph	−COOEt	Bn	32	>95:5
19	Ph	Me	Ph	$-CH_2COOMe$	70	>5:95
20	Me	Ph	Ph	$-CH_2COOMe$	44	>95:5
21	Ph	Me	Ph	4-fluorophenyl	74	>5:95
22	Me	Ph	Ph	4-fluorophenyl	20	>95:5
23	Ph	Me	Ph	n-Bu	5[a]	>95:5
24	Me	Ph	Ph	n-Bu	43	>5:95

[a] Main product is β-lactam

Not surprisingly, when R_1 is phenyl, the nature of R_2, R_3, or R_4 did not compromise the anti-diastereoselectivity (entries 6, 8, 9, and 11, Table 2; entries 13, 15, 17, 19, and 21, Table 3). A bulky group such as isopropyl at the R_3 position did not afford any imidazoline and only yielded β-lactam, presumably via a traditional [2+2] cycloaddition reaction (entry 12, Table 3). Both aryl as well as substituted alkyl groups are tolerated at the R_4 position (entry 4, Table 1; entries 20 and 22, Table 3).

Scheme 2. Proposed Rationale for the Reversal in Diastereoselectivity



The above observations indicate that R_1 controls the branch point of the stereochemical diversity. When R_1 is aryl, the anti diastereomer is exclusively formed via the endo approach. However, when R_1 is alkyl, R_2 needs to be aryl to obtain *syn*-imidazolines with high diastereoselectivity. A possible explanation for this switch in diastereoselectivity

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is the stabilization of the exo approach due to favorable π-stacking interactions between R_2 and R_3 (Scheme 2). In conclusion, we have identified an efficient branch point for enhancing the stereochemical diversity of imidazoline scaffolds by manipulation of the substituents on the general azlactone template. The previously reported high anti diastereoselectivity could be completely reversed favoring the *syn*-imidazolines in synthetically useful yields. The potential biological applications of this class of compounds are currently under investigation and will be reported in the near future.

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Supporting Information Available: The experimental procedures and ^1H and ^{13}C data for all new compounds and X-ray structures for **4**, **5**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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