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A modular approach to the synthesis of 1,4,5-substituted-2-aminoimidazoles

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ABSTRACT

Diversified 1,4,5-substituted-2-aminoimidazoles were rapidly assembled via sequential N–H insertion and Grignard addition to α-diazoesters. Lead compounds were identified as antibiotics against Gram-positive bacteria with an MIC value as low as 2 μg/mL.

Multidrug resistant bacteria continue to be a growing threat to the biomedical community.[1] For example, it is estimated that 70% of nosocomial infections in the United States are resistant to at least one antibiotic.[2] The ability of bacteria to develop resistance to every antibiotic introduced into the clinic[3] clearly underpins the necessity to develop novel antibiotics and approaches to control pathogenic bacterial behavior.

A plethora of small molecules containing a core 2-aminoimidazole (2-AI) heterocycle have emerged over the past few decades[4a–c] with activities ranging from biofilm inhibition to tubulin-binding agents.[4d,e] Our own interest in the biological activity of the 2-AI framework was inspired by bromoageliferin/oroidin and an initial report that bromoageliferin possessed anti-biofilm activity.[5] Given the paucity of small molecules reported with antibiofilm activity, our group has explored the structure–activity relationship (SAR) of a variety of 2-AI and 2-aminobenzimidazole scaffolds in the context of both antibiofilm and antibiotic activity.[6] We have noted that as one transitions from simple 4-substituted-2-aminoimidazoles to 2-aminoimidazole scaffolds that contain higher substitution patterns, the biological activity typically transitions from non-toxic modulators of biofilm formation to molecules that become microbicidal (Fig. 1). This was recently highlighted in studying the biological activity of both 4,5-substituted and 1,5-substituted-2-aminoimidazoles.[7] Given this trend, we posited that transitioning to 1,4,5-substituted-2-aminoimidazoles would deliver a class of compounds that had augmented microbicidal activity.

Recently, Van der Eycken and co-workers have presented an elegant route to the synthesis of trisubstituted-2-AIs via an intramolecular silver catalyzed heterocyclization.[8] Parallel to this approach, we have developed a facile approach to highly diversified 1,4,5-substituted-2-AIs via N–H insertion followed by Grignard addition to α-diazoesters. For our purposes, this approach was preferable due to its modular nature in which we could rapidly assemble diverse 2-AIs for preliminary biological screening. Using this approach, we have accessed a pilot library and demonstrated antibiotic activity against *Acinetobacter baumannii* (*A. baumannii*), *Escherichia coli* (*E. coli*), methicillin sensitive *Staphylococcus aureus* (MSSA), and methicillin resistant *S. aureus* (MRSA).

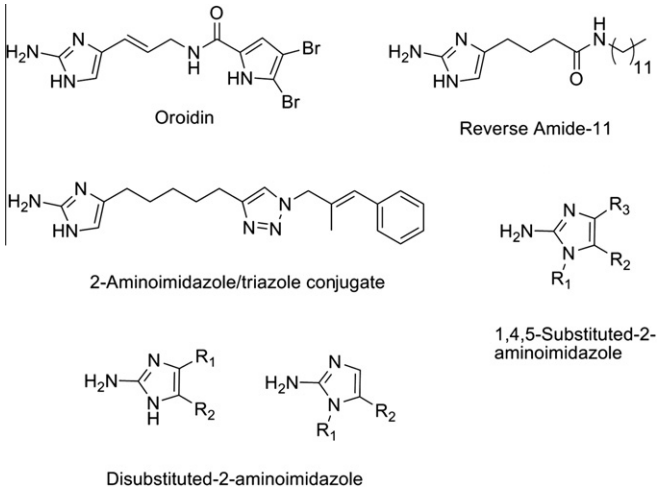

Figure 1. Oroidin derived 2-aminoimidazole scaffolds.

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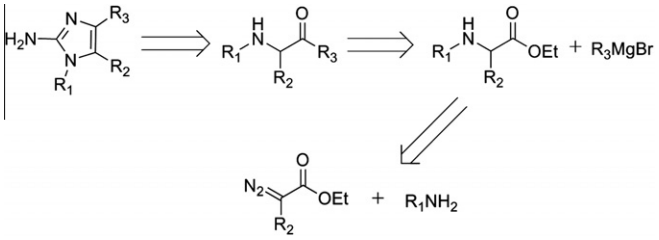
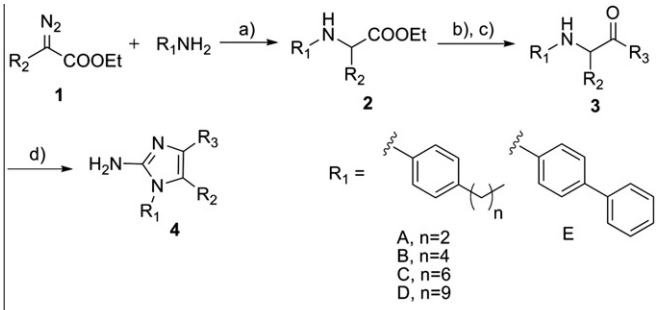


Figure 2. Retrosynthesis of 1,4,5-substituted-2-AI.



Entry	R_1	R_2	**2**, yield (%)	R_3	**3**, yield (%)	**4**, yield (%)
a	Ph	Ph	**2a**, 93	Me	**3a**, 90	**4a**, 71
b	Ph	Ph		*n*-Hexyl	**3b**, 52	**4b**, 66
c	Ph	Ph		Ph	**3c**, 91	**4c**, 72
d	C	Ph	**2b**, 92	Me	**3d**, 63	**4d**, 79
e	C	Ph		*n*-Hexyl	**3e**, 42	**4e**, 15
f	C	Ph		Ph	**3f**, 69	**4f**, 41
g	D	Ph	**2c**, 99	Me	**3g**, 96	**4g**, 30
h	D	Ph		*n*-Hexyl	**3h**, 53	**4h**, 17
i	D	Ph		Ph	**3i**, 72	**4i**, 14
j	E	Ph	**2d**, 99	*n*-Hexyl	**3j**, 68	**4j**, 41
k	E	Ph		Ph	**3k**, 92	**4k**, 20
l	Ph	*p*-Tol	**2e**, 89	*n*-Hexyl	**3l**, 56	**4l**, 52
m	Ph	*p*-Tol		Ph	**3m**, 66	**4m**, 82
n	A	Ph	**2f**, 96	Me	**3n**, 81	**4n**, 87
o	B	Ph	**2g**, 98	Me	**3o**, 57	**4o**, 58

Scheme 1. Synthesis of 1,4,5-substituted-2-AIs. Reaction conditions: (a) [Ru(*p*-cymene)Cl_2]$_2$ (1 mol %), DCM, rt, 2 h; (b) *N*,*O*-dimethylhydroxylamine hydrochloride, *i*-PrMgCl, THF, −20 °C, 1 h; (c) R_3MgBr, THF, −20–0 °C, 1 h; (d) NH_2CN, EtOH/H_2O, pH 4.3, 95 °C, 3 h.

From a synthetic standpoint, we envisioned that the desired 1,4,5-substituted-2-aminoimidazole could be assembled from cyclization of an N-substituted α-amino ketone with cyanamide. In turn, the corresponding α-amino ketone could be readily prepared from an N–H insertion between an appropriate diazoester and a commercially available amine followed by conversion to the Weinreb amide and Grignard addition (Fig. 2).

Our application of this synthetic approach is outlined in Scheme 1. We initiated our work by screening of conditions for the N–H insertion reaction. Ruthenium complexes have been extensively studied recently for N–H insertion[9] and, after tests for several conditions, [$RuCl_2$(*p*-cymene)]$_2$ in DCM was determined to be the most effective conditions. Ethyl diazoarylacetate **1** was then reacted with a variety of anilines to afford the desired *N*-aryl-α-amino ester **2** in 89–99% yield. With **2** in hand, the key Weinreb intermediate was delivered by treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and isopropylmagnesium chloride in 79–93% yield. Subsequent addition with various readily available Grignard reagents allowed installation of diversified substituents on **3** with yields from 42–92%. Finally, cyclization with cyanamide at pH 4.3 delivered the target 1,4,5-substituted-2-AIs **4** in 14–87% yield.

Table 1
Antibiotic activity screening of the pilot library[a]

Compound	*A. baumannii*	*E. coli*	MSSA	MRSA[b]
4a	128	256	256	256
4b	>256	>256	16	8
4c	>256	>256	>256	>256
4d	64	>256	4	2
4e	>256	>256	>256	128
4f	>256	>256	>256	>256
4g	>256	>256	32	4
4h	>256	>256	>256	>256
4i	>256	>256	>256	>256
4j	>256	>256	4	4
4k	>256	>256	>256	>256
4l	>256	>256	8	4
4m	>256	>256	>256	>256
4n	64	64	32	32
4o	16	>256	8	4

[a] MIC values were determined in μg/mL.
[b] ATCC number is BAA 44 for tested MRSA.

Table 2
Biological screening of lead compounds against different MRSA strains[a]

MRSA[b]	**4d**	**4o**	MRSA	**4d**	**4o**
BAA 1770	8	8	BAA 44	2	4
BAA 1556	4	8	33591	8	8
BAA 811	2	8	700789	4	8
BAA 1685	4	8	43300	2	8
BAA 1753	4	8			

[a] MIC values were determined in μg/mL.
[b] MRSA strains were identified by ATCC number.

With the pilot library in hand, we first screened for its antibiotic activity against both Gram-positive and Gram-negative bacteria strains that include MRSA, MSSA, *A. baumannii*, and *E. coli*. The microdilution protocol[10] was used to quantify activity and the minimum inhibitory concentration (MIC) values were determined (summarized in Table 1). We observed from this screen that this class of small molecules was microbicidal primarily against Gram-positive strains. Compounds **4d**,**n,** and **o** were determined to be our lead compounds with MIC values (μg/mL) of 2, 4, 64, >256; 32, 32, 64, 64, and 4, 8, 16, >256 against MRSA, MSSA, *A. baumannii*, and *E. coli*, respectively.

Given the activity against MRSA, we were interested in evaluating this library for its antimicrobial activity against various MRSA strains isolated from a nosocomial environment. MRSA has emerged as a major cause of illness and death in hospitals,[11] which includes lower respiratory tract infections, surgical site infections, cardiovascular infections, and pneumonia.[12] We obtained 9 different MRSA strains and screened for activity with lead compounds **4d** and **4o**. The lead compounds behaved consistently among the different MRSA strains recording MIC values as low as 2 μg/mL (Table 2). This antimicrobial activity is comparable to vancomycin (MIC 2 μg/mL), which is widely used to treat MRSA infections. Oxacillin, which these MRSA strains are resistant to, record MIC values of 64 μg/mL.[13]

In conclusion, we have established a modular approach to the synthesis of 1,4,5-substituted-2-aminoimidazoles, which allows rapid assembly and diversity from readily available building blocks. Lead compounds **4d** and **4o** were identified as antimicrobial reagents against Gram-positive bacterial strains. Given the biological activity of 1,4,5-substituted-2-aminoimidazoles, it is highly likely that more functionalized polysubstituted 2-aminoimidazoles will present enhanced antibiotic activity. These studies are ongoing in our lab and will be reported in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.090.

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