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Synthesis of a 2-Aminoimidazole Library for Antibiofilm Screening Utilizing the Sonogashira Reaction

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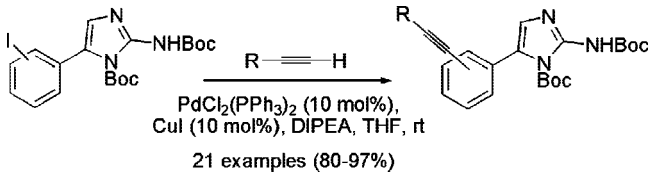

The divergent synthesis of a 21-member library composed of 2-aminoimidazole compounds for evaluation as novel antibiofilm molecules is presented. The Sonogashira reaction was employed with three regioisomeric aryl iodides and 11 different alkynes to generate variously substituted diverse ring systems. Good to excellent yields (80−97%) for the reaction were obtained, and the products provide adequate handles for further manipulation into more advanced analogues.

Bacterial biofilms have recently been estimated by the NIH as being responsible for upward of 80% of microbial infections in the human body.[1] They also possess increased resistance to basic host immune responses, antiseptics, and antibiotics, often representing a significant challenge to overcome as evident by the increased morbidity and mortality rates of numerous biofilm-mediated diseases.[2,3] Biofilms are described as highly organized structures composed of a complex matrix of bacteria and biomolecules.[4] They form when planktonic bacteria irreversibly bind to a surface suitable for growth and initiate the formation of a microcolony. On a global scale, biofilm-related costs incur billions of dollars to the agricultural, engineering, and medical sectors of the economy. Recently, there has been an intense effort to investigate small molecules that either retard biofilm development or, more importantly, disperse existing biofilms in hopes of providing a therapeutic tool in combating the serious problems they underpin.[5–7]

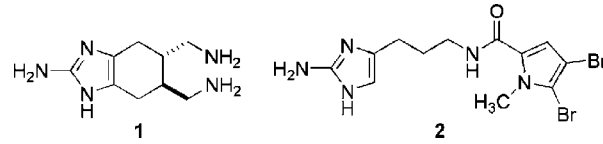

FIGURE 1. Previously reported 2-AI biofilm modulators.

Our group has been actively investigating the effects that simple sponge-derived marine alkaloids and their derivatives have upon biofilm development and maintenance in medically relevant bacteria.[8,9] The 2-aminoimidazole (2-AI) motif, prevalent in all members of the oroidin family of natural products,[10] serves as the inspiration in the design and evaluation of these analogues (Figure 1). In order to generate additional diversity around the 2-AI scaffold, new avenues for the synthesis of large numbers of compounds are needed.

Despite this need for 2-AI based motifs that would provide a suitable handle for rapid analogue construction and evaluation as antibiofilm agents, there remains a lack of known methods for their quick generation. It was therefore a goal to take advantage of palladium-catalyzed cross-coupling reactions in aiding the synthesis of these aforementioned chemical libraries. Among the known palladium-catalyzed carbon−carbon bond-forming reactions, the Sonogashira reaction[11] is known to proceed under fairly mild conditions[12,13] and would give the option of simultaneously providing entrance into further advanced analogues through exploitation of the triple bond into alkene and alkane based derivatives. It was also envisioned that by performing the couplings at various positions along the core phenyl ring, the position effect of the alkynyl appendage on activity could be evaluated. Herein we report the synthesis of a 21-member library that employs a high-yielding Sonogashira reaction on three aryl iodide protected 2-aminoimidazole scaffolds to generate novel small molecules applicable for screening as antibiofilm agents.

Access to the desired aryl halide intermediates for the Sonogashira coupling was executed through the commercially available ortho, meta, and para substituted iodobenzoic acid derivatives **3**−**5** (Scheme 1). Each was first transformed into its acid chloride before being sequentially reacted with diazomethane and quenched with concentrated HBr. This afforded the requisite α-bromo ketones **6**−**8** in excellent yields. Installation of the 2-aminoimidazole subunit was achieved through condensation with Boc-guanidine[14] in the presence of NaI. Attempts at performing the Sonogashira reaction with interme-

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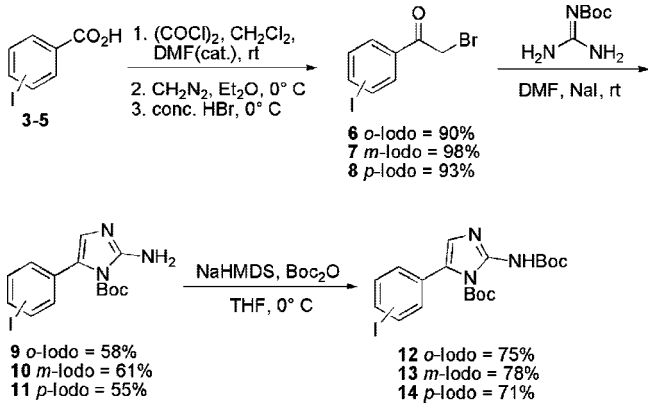
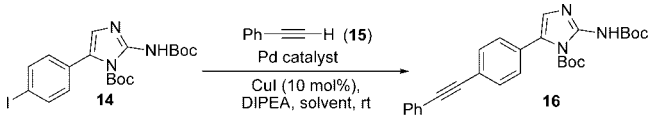
SCHEME 1. Construction of 2-AI Scaffolds



SCHEME 2. Sonogashira Optimization



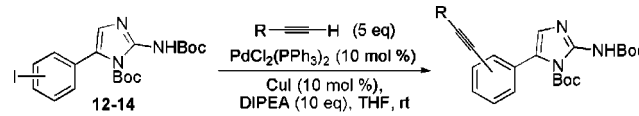
Entry	Catalyst	DIPEA	15	Solvent	Yield (%)[a]
1	$Pd(PPh_3)_4$ (5 mol%)	2 equiv	3 equiv	THF	48
2	$PdCl_2(PPh_3)_2$ (5 mol%)	2 equiv	3 equiv	THF	71
3	$PdCl_2(PPh_3)_2$ (5 mol%)	2 equiv	3 equiv	Dioxane	65
4	$PdCl_2(PPh_3)_2$ (5 mol%)	2 equiv	3 equiv	DMF	59
5	$PdCl_2(PPh_3)_2$ (5 mol%)	10 equiv	3 equiv	THF	78
6	$PdCl_2(PPh_3)_2$ (10 mol%)	10 equiv	5 equiv	THF	90

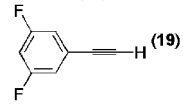
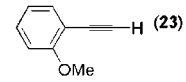
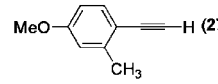
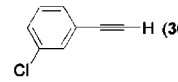
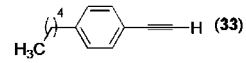
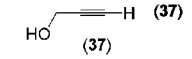
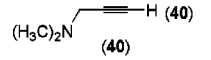
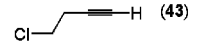
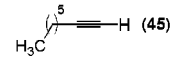
diate **11** proved futile due to its relative insolubility in all organic solvents except DMF. Low yields and difficulty in purification of the desired product were observed, however, when DMF was used in the reaction. It therefore became necessary to protect the exocyclic amine functionality, and this was accomplished by reaction of derivatives **9**−**11** with LiHMDS in the presence of Boc anhydride.[15] Despite the need for the extra synthetic step, scaffolds **12**−**14** were quickly prepared on multigram scales in just three synthetic operations.

Attention then was turned to a suitable catalyst system for the Sonogashira reaction. Lindel previously reported the use of $PdCl_2(PPh_3)_2$ as a catalyst for Heck- and Sonogashira-type reactions employing an imidazole-based iminophosphorane intermediate,[16] and this provided the starting point for catalyst screening and reaction condition optimization (Scheme 2). Conditions were screened using the *p*-iodo scaffold **14** and phenyl acetylene **15** as the alkyne. $PdCl_2(PPh_3)_2$ was found to be a better catalyst at promoting the coupling than $Pd(PPh_3)_4$ in every condition analyzed. Increasing the catalyst load to 10 mol% was found to be optimal, leading to complete consumption of the aryl iodide starting material. This was essential because incomplete conversion led to difficulty in removing unreacted starting material, which was laborious and led to reduced reaction yields. THF was the best solvent among the three scanned. Minor adjustments were also made in the amount of DIPEA used (10 equiv) and the alkyne coupling partner (5 equiv). With the conditions optimized on the trial system, the yield for the Sonogashira coupling was 90% and was deemed acceptable for the synthesis of the library.

Ten electronic and sterically diverse alkynes incorporating a number of synthetically relevant functionalities were then used

SCHEME 3. Library Synthesis



Entry	Substrate	Alkyne	Product (% Yield)
1	**12**	Ph—≡—H (**15**)	**17** (94%)
2	**13**	(**15**)	**18** (87%)
3	**12**	 (**19**)	**20** (97%)
4	**13**	(**19**)	**21** (91%)
5	**14**	(**19**)	**22** (94%)
6	**12**	 (**23**)	**24** (81%)
7	**13**	(**23**)	**25** (90%)
8	**14**	(**23**)	**26** (80%)
9	**12**	 (**27**)	**28** (92%)
10	**14**	(**27**)	**29** (85%)
11	**12**	 (**30**)	**31** (85%)
12	**13**	(**30**)	**32** (86%)
13	**13**	 (**33**)	**34** (91%)
14	**14**	TMS—≡—H (**35**)	**36** (85%)
15	**13**	 (**37**)	**38** (81%)
16	**14**	(**37**)	**39** (80%)
17	**13**	 (**40**)	**41** (86%)
18	**14**	(**40**)	**42** (90%)
19	**14**	 (**43**)	**44** (82%)
20	**14**	 (**45**)	**46** (84%)

to generate a small library of 2-AI analogues using the optimized coupling conditions (Scheme 3). Yields for all reactions were good to excellent (80−97%). The highest yielding reactions were those involving the 2,5-diflourophenyl alkyne derivative **19** (entries 3−5). TMS acetylene (entry 14) and propargyl alcohol (entries 15 and 16) were also shown to be suitable coupling partners under the extremely mild reaction conditions. Furthermore, consistently high yields were obtained when a single alkyne was coupled to all three regioisomers, thus indicating the robustness of the system.

In summary, the Sonogashira reaction was used to build a unique library of 21 complex 2-aminoimidazole based compounds that have the potential to provide access to numerous other more advanced analogues. The reaction proceeds in excellent yield regardless of the alkyne and aryl halide scaffold used. The biological screening of the analogues as modulators of biofilm growth and maintenance is currently underway, and our findings will be reported in due course. Additionally, other conditions are being investigated that take advantage of palladium-catalyzed cross-couplings to make other libraries of 2-AI based molecules for evaluation as novel antibiofilm agents.

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Experimental Section

Representative Procedure for Optimized Sonogashira Coupling. Aryl iodide **14** (0.100 g, 0.206 mmol) was dissolved in anhydrous THF (8 mL), and to this solution was added DIPEA (0.359 mL, 2.06 mmol), CuI (0.004 g, 0.021 mmol), and $PdCl_2(PPh_3)_2$ (0.014 g, 0.021 mmol). The solution was then degassed at ambient temperature for 10 min. During this time a solution of phenyl acetylene **15** (0.105 g, 1.03 mmol) in anhydrous THF (3 mL) was also degassed. The solution of alkyne was added dropwise to the solution of aryl iodide, and the reaction was stirred at room temperature for 12 h. The reaction was filtered through a Celite pad, and the filter cake rinsed with EtOAc (10 mL). The filtrate was washed with saturated NH_4Cl (2 × 10 mL) and brine (2 × 10 mL), and dried (Na_2SO_4). Filtration and evaporation afforded the crude product, which was purified via flash column chromatography (1:5 EtOAc/hexanes) to obtain the target product **16** (0.085 g, 90%) as a yellow solid: mp = 131−132 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.60 (s, 1H), 8.00 (s, 1H), 7.86 (d, 2H, J = 7.6 Hz), 7.42 − 7.57 (m, 7H), 1.58 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.9, 146.8, 139.9, 136.3, 133.0, 131.7, 131.4, 128.8, 124.9, 122.6, 126.8, 120.9, 113.7, 89.9, 89.5, 85.4, 80.1, 27.9, 27.3; HRMS (ESI) calcd for $C_{27}H_{29}N_3O_4Na$ (MNa^+) 482.2050, found 482.2051.

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Supporting Information Available: Experimental procedures, spectral characterization, and copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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