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Synthesis of pyrrole-imidazole polyamide oligomers based on a copper-catalyzed cross-coupling strategy

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ABSTRACT

Pyrrole-imidazole (Py-Im) polyamides are useful tools for chemical biology and medicinal chemistry studies due to their unique binding properties to the minor groove of DNA. We developed a novel method of synthesizing Py-Im polyamide oligomers based on a Cu-catalyzed cross-coupling strategy. All four patterns of dimer fragments could be synthesized using a Cu-catalyzed Ullmann-type cross-coupling with easily prepared monomer units. Moreover, we demonstrated that pyrrole dimer, trimer, and tetramer building blocks for Py-Im polyamide synthesis were accessible by combining site selective iodination of the pyrrole/pyrrole coupling adduct.

Pyrrole-imidazole (Py-Im) polyamides are synthetic ligands originally developed as 2:1 ligand–DNA complexes based on the binding properties of distamycin A to A/T sequences in the minor groove of DNA (Fig. 1).[1] Hairpin-like structures consisting of two polyamide strands with a γ-amino butyric acid linkage bind to the minor groove of DNA in a sequence-specific manner, downregulating the gene expression by disrupting transcription factor/DNA interactions. The specificity is achieved by the rules that an antiparallel Py/Py motif recognizes A·T or T·A base pairs while the Im/Py and Py/Im motifs recognize G·C and C·G base pairs, respectively.[2] Various Py-Im polyamides,[3] including functionalized polyamides conjugated with a bioactive molecule,[4] have been developed and applied to chemical biology and medicinal chemistry studies.

Py-Im polyamides are generally prepared using solid-phase synthetic methods, which have advantages for the divergent preparation of Py-Im polyamide libraries on a milligram scale.[5] Applying solid-phase synthetic methods to large-scale syntheses, however, is intrinsically difficult. Solution-phase syntheses were investigated to realize gram-scale production of this class of polyamide molecules by utilizing convergent synthetic approaches with pre-assembled oligoamide building blocks.[6] Despite steady progress toward developing a method to elongate Py-Im polyamide chains using condensation reagents,[7] the preparation of monomer units has basically relied on the conventional synthetic methods developed by Dervan et al. in the mid of 1990s.[5a] Introduction of the nitrogen functionality at the 4-position of the pyrrole and imidazole cores was achieved by an arduous nitration of 2-trichloroacetylpyrrole/imidazole derivatives using fuming HNO_3 in impractical solvent systems (e.g., acetic anhydride or H_2SO_4). Disagreeable experimental procedures (e.g., slow addition of fuming HNO_3, etc.) also hampered large-scale synthesis (Scheme 1). On the other hand, Tor and co-workers

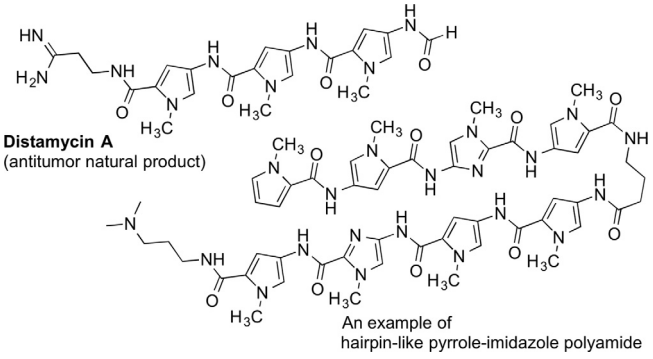

Fig. 1. Distamycin A and an example of pyrrole-imidazole polyamide.

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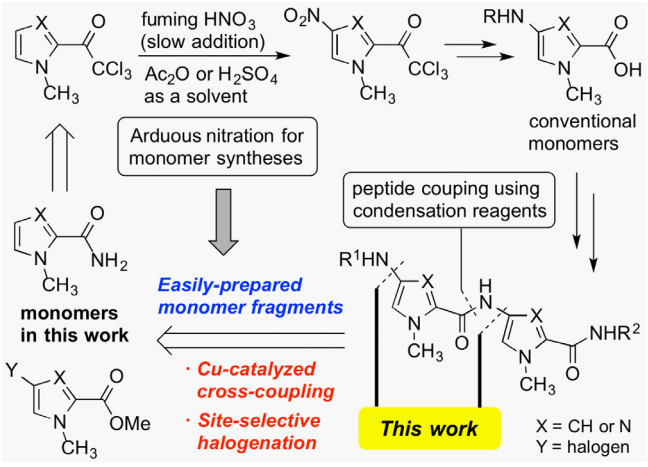


Scheme 1. Background and novel synthetic strategy for this work.

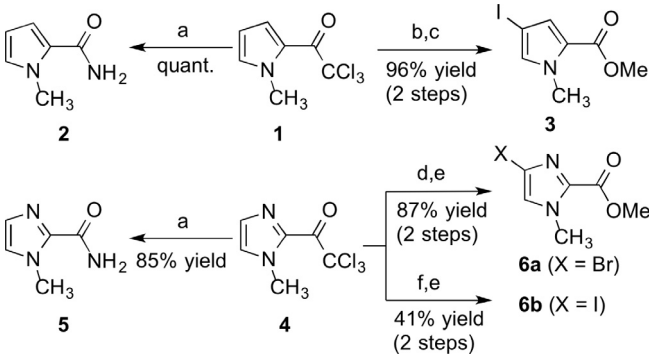
reported the synthesis of a pyrrole monomer unit using a Cu-catalyzed Ullmann-type cross-coupling reaction between the bromopyrrole derivative and *t*-butyl carbamate ($BocNH_2$), although the same strategy was not applicable to the synthesis of an imidazole monomer unit.[8] This background led us to launch a project to develop a novel synthetic approach to Py-Im polyamides based on a cross-coupling strategy using easily available pyrrole/imidazole amide nucleophiles and halopyrrole/imidazole electrophiles. We hypothesized that the development of coupling processes in combination with site-selective halogenation of the coupling adducts would provide efficient access to oligoamide building blocks. Herein, we report our primary efforts on the synthesis of Py-Im polyamide oligomers based on a Cu-catalyzed Ullmann-type cross-coupling strategy.

We began by preparing monomer units for this study (Scheme 2). *N*-Methyl-2-trichloroacetylpyrrole **1**[9] was treated with ammonia solution to give amido-pyrrole monomer **2** in quantitative yield. Site-selective iodination of **1** proceeded efficiently in the presence of 10 mol % of $In(OSO_2CF_3)_3$ and 1.1 equiv of *N*-iodosuccinimide (NIS),[10] and the corresponding product was obtained in 98% yield. Subsequent methanolysis under basic conditions afforded iodopyrrole monomer **3** in 98% yield. Imidazole monomers were similarly prepared. 1-Methyl-2-trichloroacetylimidazole **4**[9] was reacted with ammonia solution to give amido-imidazole monomer **5** in 85% yield. Site-selective bromination of **4** proceeded using 0.6 equiv of 1,3-dibromo-5,5-dimethylhydantoin (DBH), affording the mono-bromo imidazole derivative in 91% yield, which was then transformed by methanolysis into compound **6a** in 96% yield. Site-selective iodination of **4** proceeded in the presence of 10 mol % of $In(OSO_2CF_3)_3$ and 1.1 equiv of 1,3-diiodo-5,5-dimethylhydantoin (DIH), affording the mono-iodo imidazole derivative in 45% yield.[11] Methanolysis of the product proceeded smoothly to give compound **6b** in 92% yield.

Cu-catalyzed Ullmann-type coupling between **2** and **3** was first examined to synthesize pyrrole dimer fragment **7** (Table 1). The reaction conditions were optimized using 5 mol % of CuI, 10 mol % of *N*,*N*′-dimethylethylenediamine (DMEDA), and 1.5 equiv of Cs_2CO_3 in several solvent systems. The desired pyrrole dimer **7** was obtained in 68% yield when the reaction was performed in dioxane at 110 °C (entry 3). K_3PO_4 was also an effective base for this reaction and compound **7** was produced in a slightly higher yield than when using Cs_2CO_3 (entry 4). The yield of **7** was further improved by performing the reaction with 2 equiv of base. The coupling adduct **7** was obtained in 92% yield using either Cs_2CO_3 or K_3PO_4 as a base (entries 5 and 6). The present catalysis could be performed on a gram scale (entry 6).

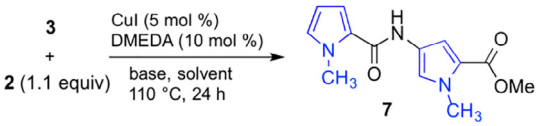
We next examined a coupling reaction using an amido- imidazole monomer **5** and iodopyrrole monomer **3** (Scheme 3). Optimization of the reaction conditions were based on those for pyrrole-pyrrole coupling revealed that 10 mol % of CuI, 40 mol % of DMEDA, and 1.5 equiv of Cs_2CO_3 in dioxane at 110 °C were the best conditions for this purpose.[12] The desired imidazole-pyrrole heterodimer **8** was obtained in 74% yield. In striking contrast, coupling reactions between **2** and **6a** or **6b** never provided the desired product **9**. When haloimidazole derivatives **6a** and **6b** were treated with the coupling reaction conditions in the absence of **2**, both compounds were decomposed and TLC analysis revealed the formation of highly polar by-products. On the other hand, imidazole amide derivative **8** was stable under the reaction conditions, leading us to hypothesize that the target reaction would proceed using haloimidazole amide derivatives as substrates. Thus, we prepared benzylamide derivative **10a** and **10b** from **4**[12] and applied the coupling processes. The coupling reaction of **10b** with 1.1 equiv of amido-pyrrole **2** proceeded using 10 mol % of CuI, 40 mol % of DMEDA, and 2.0 equiv of Cs_2CO_3 in dioxane at 110 °C, affording pyrrole-imidazole heterodimer **11** in 80% yield.[12,13] Compound **10b** was also applicable to the imidazole-imidazole coupling. The coupling reaction of **10b** with 1.2 equiv of amido-imidazole **5** proceeded using 10 mol % of CuI, 40 mol % of DMEDA, and 1.5 equiv of Cs_2CO_3 in dioxane at 110 °C, affording compound **12** in 54% yield.[12] The use of iodoimidazole derivative **10b** gave the products in higher yield than when using bromoimidazole derivative **10a** in both cases.

Elongation of the amide chain using the present coupling strategy required site-selective introduction of a halide group to the



Scheme 2. Synthesis of monomer units. (a) 25% aq. NH_3, CH_3CN, rt; (b) $In(OSO_2CF_3)_3$ (10 mol %), NIS (1.1 equiv), CH_3CN, 0 °C; (c) NaH, MeOH, 0 °C to rt; (d) DBH (0.6 equiv), CH_3CN, 0 °C to rt; (e) DMAP (40 mol %), MeOH, rt; (f) $In(OSO_2CF_3)_3$ (10 mol %), DIH (1.1 equiv), CH_3CN, 0 °C to rt.

Table 1
Optimization of the reaction conditions.



Entry	Base (equiv)	Solvent	Yield[a]
1	Cs_2CO_3 (1.5)	DMF	51%
2	Cs_2CO_3 (1.5)	Toluene	46%
3	Cs_2CO_3 (1.5)	Dioxane	68%
4	K_3PO_4 (1.5)	Dioxane	76%
5	Cs_2CO_3 (2.0)	Dioxane	92%
6	K_3PO_4 (2.0)	Dioxane	92% (80%)[b]

[a] Isolated yield.
[b] Reaction scale: 1.32 g of **3** was used.