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Synthesis of Multifunctional 2-Aminobenzimidazoles on DNA via Iodine-Promoted Cyclization

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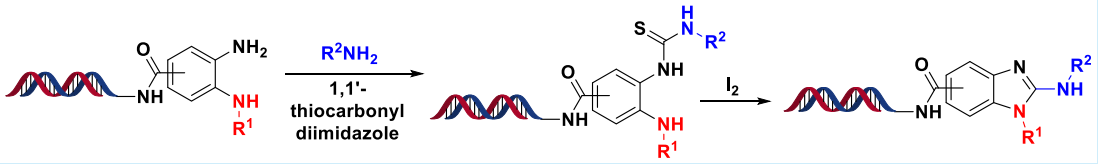

ABSTRACT: 2-Aminobenzimidazole cores are among the most common structural components in medicinal chemistry and can be found in many biologically active molecules. Herein, we report a mild protocol for the synthesis of multifunctional 2-aminobenzimidazoles on-DNA with broad substrate scopes. The reaction conditions expand our ability to design and synthesize 2-aminobenzimidazole core-focused DNA-encoded libraries.

DNA-encoded libraries (DELs) have emerged in the pharmaceutical industry as one of the most powerful hit generation sources for early drug discovery.[1] These combinatorial chemical libraries can be designed to access new chemical space in dramatically larger library sizes, compared to conventional screening collections. As a result of the increased application of encoded libraries in drug discovery, a growing number of DEL-originated hit compounds are emerging in the scientific literature.[2] Several drug candidates that originated from their corresponding initial DEL hits have entered into clinical studies.[3]

One key attribute for a DEL to provide useful chemical starting points for medicinal chemistry is the structural diversity of accessible structures displayed by DNA. The success is dependent not only on the number and diversity of the building blocks or scaffolds used for the DEL construction, but also on a chemical methodology for assembling these building blocks and scaffolds. Although there has been an increasing number of reports describing DNA-compatible transformations,[4] the number of published chemical reactions on DNA is still quite limited, compared with traditional medicinal chemistry.

Nitrogen heterocycles are among the most important structural components in biologically active molecules. Assessment of FDA approved drugs reveals that 59% of unique small-molecule drugs contain at least one nitrogen heterocycle.[5] Therefore, it is attractive to encompass these common structural cores into DNA-encoded libraries via development of DNA-compatible chemical transformations. A recent example from our laboratory is the synthesis of C3-alkylated indole derivatives on DNA via indolyl alcohol formation, followed by metal-free transfer hydrogenation.[6]

2-Aminobenzimidazole has been recognized as an important structural motif and is distributed widely in compounds with diverse pharmaceutical properties (Figure 1).[7] Although a

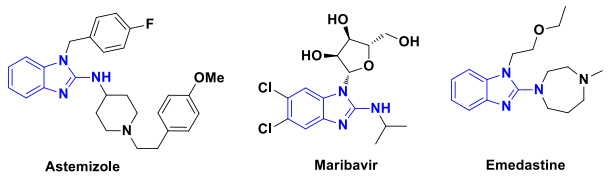

Figure 1. Pharmaceuticals containing 2-aminobenzimidazole.

variety of synthetic pathways have been reported for the synthesis of 2-aminobenzimidazole (Figure 2),[8] few examples have emerged for 2-aminobenzimidazole derivatives with N-1 substitution. For use in DEL, the chemical reactions must be

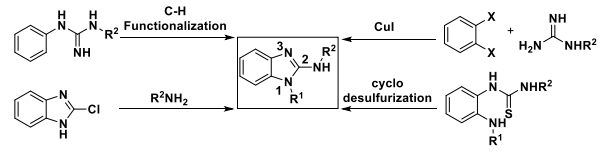

Figure 2. Approaches for synthesizing 2-aminobenzimidazoles.

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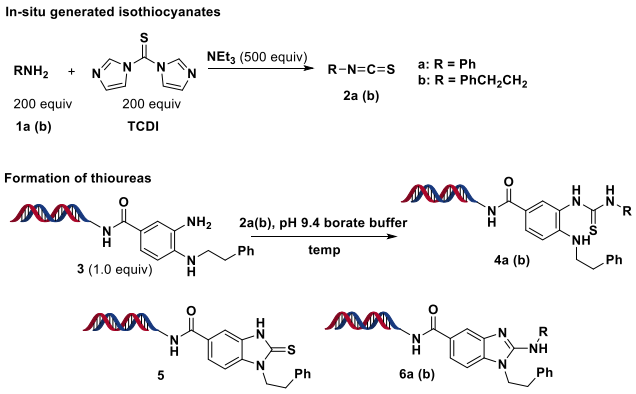
robust, high yielding, cover a broad reactant scope, and preserve the integrity of the DNA barcodes. To this end, we hypothesized that a cyclodesulfurization approach could be a viable option in the presence of DNA. First, enhanced molecular diversity of the library can be easily achieved from readily accessible isothiocyanates and N-substituted *o*-diaminoarenes as substrates. Second, among reported desulfurization agents including HgO,[9] $PhI(OAc)_2$,[10] iodine,[11,12] etc., some are potentially amenable to an aqueous system. Third, the ring closure is an intramolecular reaction. The annulation should be kinetically promoted by large amounts of desulfurization agents to generate active carbodiimide intermediates, although DNA is present in diluted concentration (typically 1 mM or less).

Large numbers of structurally diverse, commercially available building blocks typically underlie the chemical foundation of library diversity. We proposed that isothiocyanates **2a**/**2b** (see Table 1) could be generated in situ from primary amines **1a**/**1b**

Table 1. Condition Optimization for Thiourea Formation



entry[a]	1	temperature (°C)	3[b] (%)	4[b] (%)	5[b] (%)	6[b] (%)
1	**1a**	30	0	26	18	49
2	**1b**	30	46	49	3	0
3	**1b**	60	15	60	0	4
4	**1b**	80	5	72	11	4

[a]Amine (4 μmol in 20 μL MeCN:H_2O = 1:1, 200 equiv), TCDI (4 μmol in 10 μL DMSO, 200 equiv) and Et_3N (10 μmol in 10 μL MeCN, 500 equiv) were premixed and reacted at rt for 5 h. The obtained crude mixture was added to conjugate **3** (20 nmol in 20 μL borate buffer (250 mM in H_2O, pH 9.4) and reacted for 16 h; [b]Conversion was determined by LC-MS.

and 1,1′-thiocarbonyldiimidazole (TCDI). We selected aniline and phenethylamine as model substrates to represent aromatic and aliphatic amines. Crude isothiocyanates **2a**/**2b** were obtained by premixing a 1:1 equiv ratio of primary amines and TCDI in the presence of triethylamine at room temperature for 5 h. The resulting crude isothiocyanate solution was then treated with conjugate **3** in pH 9.4 borate buffer for 16 h at 30 °C. Interestingly, aniline and phenethylamine gave significantly different results. For aniline, 26% desired product **4a**, along with 49% cyclization product **6a** and 18% cyclized byproduct **5**, were observed. By comparison, 49% desired product **4b** was observed for phenethylamine, with 46% starting material **3** remaining. The formation of large amounts of both conjugate **5** and conjugate **6a** for aniline can be possibly attributed to carbodiimide formation promoted by excess unreacted 1,1′-thiocarbonyldiimidazole[13] (see control experiments described in the Supporting Information). Fortunately, increasing the temperature to 60 °C boosted the formation of **4b** to 60% for phenethylamine as a substrate, and, ultimately, application of the same system at 80 °C resulted in 72% conversion to the desired thiourea **4b** and 4% conversion to cyclized **6b**.

Next, we set out to optimize the reaction condition for the cyclodesulfurization (Table 2). Since almost half of the thiourea

Table 2. Condition Optimization for Cyclodesulfurization

entry[a]	desulfurization agent (equiv, solvent)	reaction time (min)	6b[b] (%)
1[c]	TsCl (200, 0.2 M in MeCN)	60	15
2[d]	IBX (50, 0.5 M in DMSO)	60	31
3[d]	I_2 (50, 0.5 M in DMSO)	60	61
4[d]	I_2 (50, 0.5 M in DMSO)	30	68
5[d]	I_2 (20, 0.2 M in DMSO)	30	70

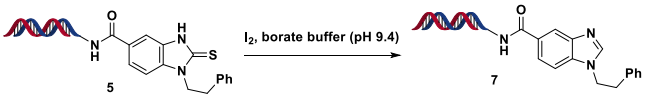
[a]All the reactions were carried with conjugate **4b** (20 nmol, 1.0 equiv) in 20 μL buffer and desulfurization agents. The reaction was performed at room temperature (rt). [b]Conversion was determined by liquid chromatography (LC-MS). [c]Conjugate **4b** was dissolved in pH 7.1 phosphate buffer (0.2 M in dd-H_2O). [d]Conjugate **4b** was dissolved in pH 9.4 borate buffer (0.25 M in dd-H_2O).

4a had been converted to 2-aminobenzimidazole product **6a** in the step of thiourea formation, we decided to optimize the cyclodesulfurization using **4b** as the substrate. The substrate **4b** was directly obtained from the last step with only ethanol precipitation. Since various desulfurization agents have been reported in small molecule synthesis,[8−11] we started to develop the DNA compatible chemistry with well-known desulfurization agents. The use of tosyl chloride resulted in only 15% product **6b** over two steps starting from material **3**. A better conversion (31% conversion; see Table 2, entry 2) was achieved when IBX was used as a desulfurization agent. Switching to iodine enhanced the conversion to 61% over two-step reactions. Finally, the use of 20 equiv of iodine over 30 min reaction time at room temperature provided **6b** in 70% conversion over two steps (from **3** to **6b**; see Table 2, entry 5).

During the condition optimization, we found that the byproduct **5**, which was generated in the step of thiourea formation, disappeared after iodine treatment. A new desulfurization product (**7**) was observed instead. To understand the mechanism, we set up a control experiment by treating pure conjugate **5** with iodine in borate buffer, conjugate **7** was obtained with 77% conversion (see Scheme 1).[14]

With the established conditions in hand, we explored the scope of the reactions with a range of substrates (see Scheme 2)

Scheme 1. Byproduct Generation in the Cyclodesulfurization Step[a]



[a]Conditions: iodine (400 nmol in 2 μL DMSO, 20 equiv) were added to 20 μL conjugate **5** (20 nmol, 1 mM in pH 9.4 borate buffer (0.25 M in dd-H_2O), 1.0 equiv). The reaction was allowed to proceed at rt for 30 min.

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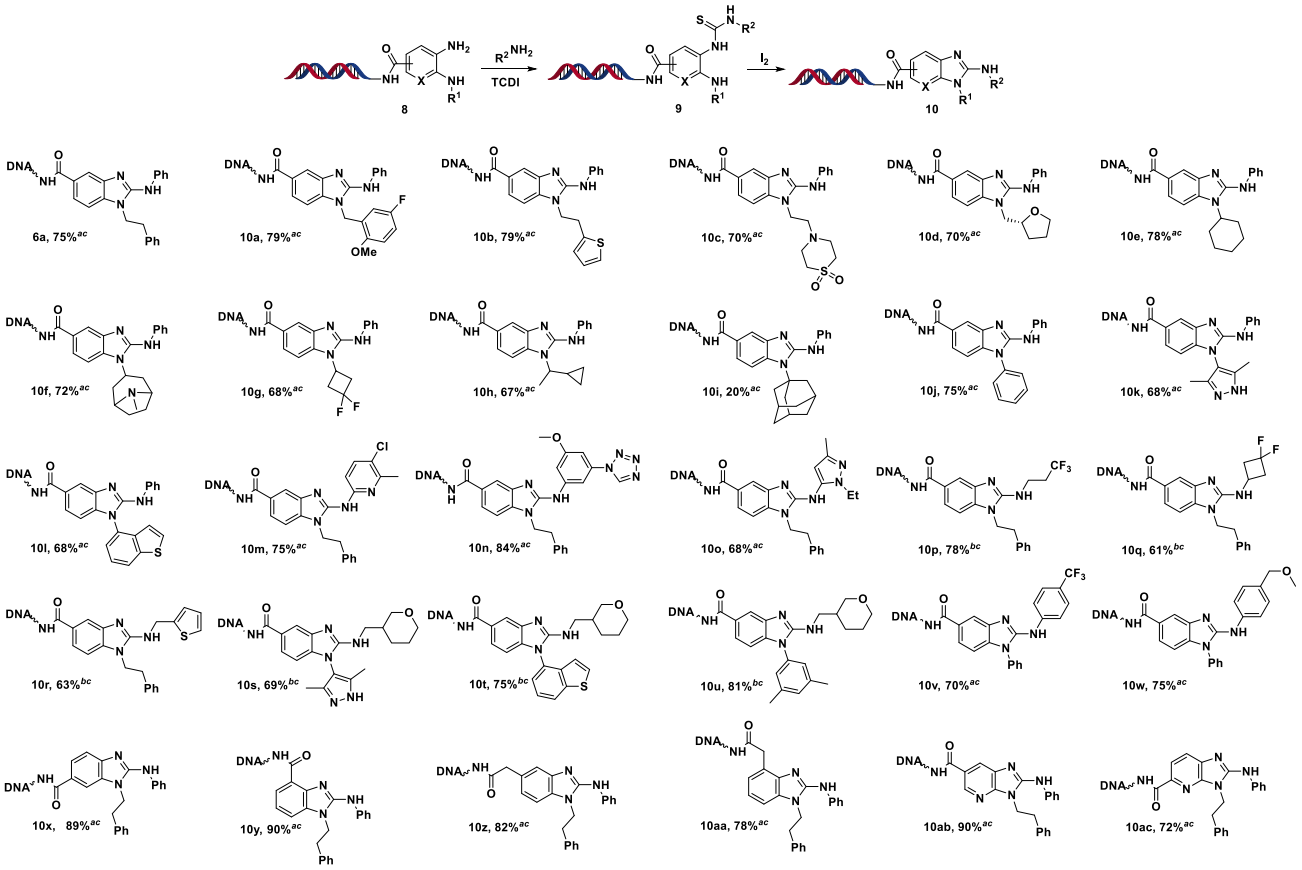
Scheme 2. Substrate Scope of Thiourea Formation and I_2-Promoted Cyclodesulfurization*



*Conditions were as follows: [a]Condition of step 1 for aromatic amine (R^2NH_2): amine (4 μmol in 20 μL MeCN:H_2O = 1:1, 200 equiv), 1,1′-thiocarbonyldiimidazole (4 μmol in 10 μL DMSO, 200 equiv) and Et_3N (10 μmol in 10 μL MeCN, 500 equiv) were premixed at rt for 5 h to give the crude isothiocyanates; the mixture then was added to conjugate **8** (20 nmol in 20 μL borate buffer (250 mM in H_2O, pH 9.4), 1.0 equiv) and reacted at rt for 16 h. [b]Condition of step 1 for aliphatic amine (R^2NH_2): amine (4 μmol in 20 μL MeCN:H_2O = 1:1, 200 equiv), 1,1′-thiocarbonyldiimidazole (4 μmol in 10 μL DMSO, 200 equiv) and Et_3N (10 μmol in 10 μL MeCN, 500 equiv) were premixed at rt for 5 h to give the crude isothiocyanates; the mixture then was added to conjugate **8** (20 nmol in 20 μL borate buffer (250 mM in H_2O, pH 9.4), 1.0 equiv) and reacted at 80 °C for 16 h. [c]Condition of step 2: conjugate **9** (20 nmol in 20 μL borate buffer (250 mM in H_2O, pH 9.4), 1.0 equiv), I_2 (400 nmol in 2 μL DMSO, 20 equiv), rt, 30 min.

by (1) studying the effects of R^1 with constant R^2 (R^2 = Ph, **6a**, **10a−10l**); (2) studying effects of R^2 with constant R^1 (R^1 = CH_2CH_2Ph, **10m−10r**); (3) studying the effects of different combinations of R^1 and R^2 (**10s−10w**); and (4) studying the effects of various phenyldiamine structures (**10x−10ac**). Gratifyingly, the standard conditions were found to be tolerant of various functional groups on both R^1 and R^2, giving moderate to excellent conversions. However, if R_1 was sterically hindered (**10i**), the conversion was found to be low. Besides desired products, the conjugate **7** was observed as the major and common byproduct for all substrates over two-step reactions. Furthermore, diverse scaffolds were screened by studying effects of DNA tagging positions and electronic effects. Notably, these scaffolds were found to be tolerable to the standard conditions (**10x−10ac**). These results gave us enormous confidence to plan a library using the developed chemistry.

Employing the newly developed conditions, we validated a collection of primary amine building blocks (1342 R^1NH_2 and 2423 R^2NH_2) on designed model substrates and reactions, as shown in Schemes 3 and 4. 1342 R^1NH_2 were studied through four-step reactions to evaluate the efficiency of SNAr and their effects on ring closures. The conversions were determined by LC/MS over four steps (Scheme 3). With the similar protocol, 2423 R^2NH_2 were validated over two-step reactions (Scheme 4), by evaluation of the efficiency of urea formation and cyclodesulfurization. The results of conversion distribution showed that a large set of amines gave acceptable conversions for library synthesis. Unfortunately, so far, it has been difficult to make clear conclusions regarding which types of building blocks gave favorable conversions.

The co-injection experiment by LC-MS and HPLC of **6a** from on-DNA synthesis and authentic sample **18** from off-DNA synthesis, followed by the installation of DNA, was performed (see Scheme 5). Two samples gave identical LC-MS and HPLC traces (see detailed information in the Supporting Information). This method indirectly confirmed the characterization of desired on-DNA product **6a**.

Under the newly developed conditions, a DEL with 2-aminobenzimidazole cores was synthesized using a split and pool approach (see Scheme 6). Introducing three cycles of diversity brought expected library diversity to 7.34 million compounds using commercially available building blocks, as shown in Scheme 6.

In conclusion, an efficient strategy to construct on-DNA 2-aminobenzimidazoles was reported. We demonstrated that 2-aminobenzimidazoles can be constructed from thio-urea

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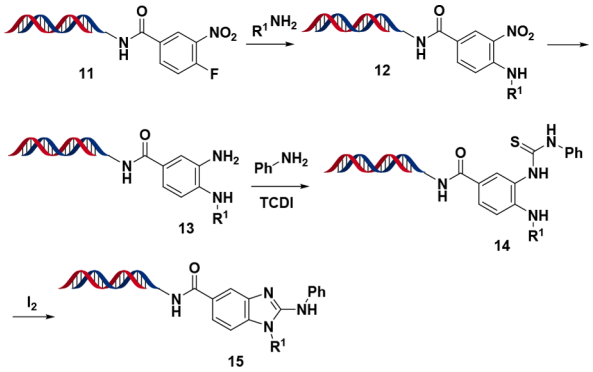
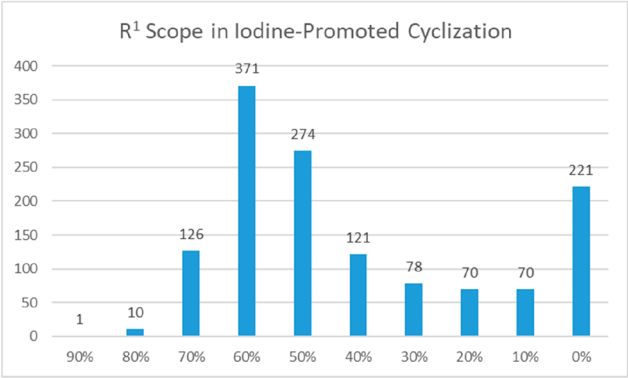
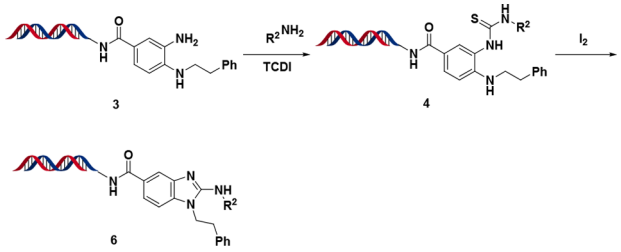
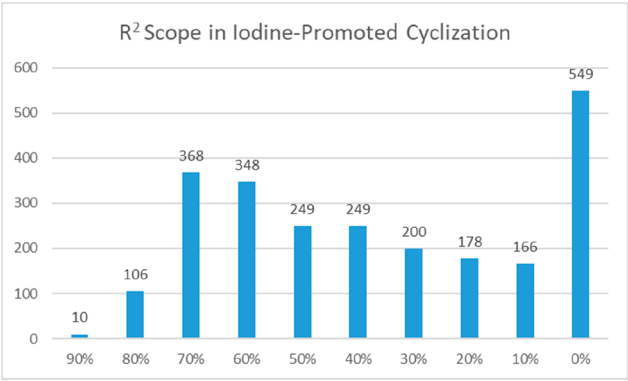
Scheme 3. R^1 Scope in Iodine-Promoted Cyclization



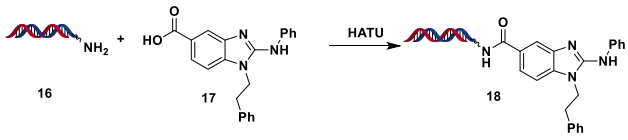


Scheme 4. R^2 Scope in Iodine-Promoted Cyclization



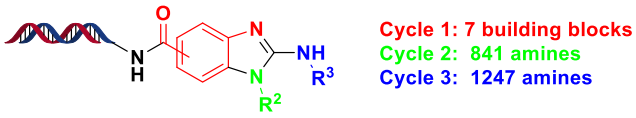


Scheme 5. Off-DNA Synthesis of Authentic Sample 17



formation, followed by I_2-promoted cyclodesulfuration. This enables the production of a very attractive library from simple amines and commercially available scaffolds, which would provide considerable diversity. Continued efforts to transform this robust and efficient chemistry to DEL construction will be reported in due course.

Scheme 6. A DNA-Encoded Library with 2-Aminobenzimidazole Cores



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04578.

Details of experimental procedures, copies of HPLC traces, MS, NMR spectra, and q-PCR experiments (PDF)

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Notes

The authors declare no competing financial interest.

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