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Multistep Synthesis of 1,2,4-Oxadiazoles *via* DNA-Conjugated Aryl Nitrile Substrates

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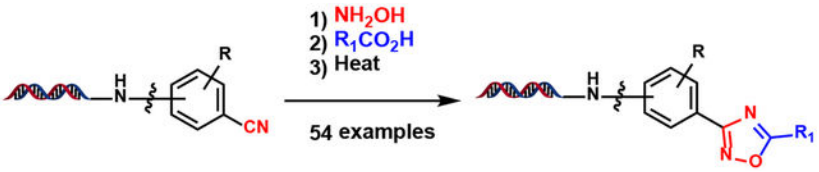
Abstract

A multistep protocol for the synthesis of 3,5-disubstituted 1,2,4-oxadiazoles on DNA-chemical conjugates has been developed. A set of six DNA-connected aryl nitriles were converted to corresponding amidoximes with hydroxylamine followed by the *O*-acylation with a series of aryl and aliphatic carboxylic acids. After cyclodehydration of the *O*-acyl amidoximes by heating at 90 °C in pH 9.5 borate buffer for two hours, the desired oxadiazole products were observed in 51—92% conversion with the cleavage of *O*-acylamidoximes as the major side-product. The reported protocol paves the way for the synthesis of oxadiazole core-focused DNA-encoded chemical libraries.

Graphical Abstracr



INTRODUCTION

DNA-encoded chemical libraries (DECLs) are collections of small molecules covalently linked to a unique, structure-identifying DNA tag which enables screens of large pools of library members for binders to biological targets.[1–7] DECLs constructed by a split-and-pool[8] strategy (i.e., iterative rounds of molecule functionalization, DNA-tag ligation and pooling) may routinely contain millions of encoded small molecule structures, and if used with post-screen high-throughput DNA sequencing,[9–11] can interrogate enormous amounts of chemical space.[12] However the success of DECL screening campaigns is influenced by the

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Author Contributions
H.D. optimized reaction conditions, prepared substrates, explored substrate scope, conducted ligation tests, and helped prepared the manuscript. M.B. optimized reaction conditions and explored substrate scope. N.S. advised experiments and helped prepared the manuscript. M.M.M. helped prepared the manuscript.

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Supporting Information
The Supporting Information is available free of charge on the ACS Publications website.
Details of experimental procedures and DNA structures.

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inherent diversity and fidelity of small molecule structures available within the DECL collection[13,14] and many common synthetic transformations have not yet been demonstrated in solution-phase DECL production.[15,16] This is due in part to stability and solubility limitations imposed by the presence of DNA within partially aqueous medium,[13,14] and thus adaptation of synthetic transformations to DECL-friendly conditions is needed to further enhance the diversity of future DECL productions.

Oxadiazoles represent a privileged class of heterocycles that are frequently featured in discovery screening collections,[17,18] are present in several approved pharmaceutical drugs,[19,20] and have robust solution- and solid-phase synthetic methods.[21–31] In particular, the on-DNA formation of 1,2,4-oxadiazoles is an attractive DECL combinatorial methodology as 1,2,4-oxadiazoles may be constructed from nitriles and carboxylic acids, compound building block sets that have wide commercial-availability and diversity.[32] A typical route to 1,2,4-oxadiazoles is through a three step process in which a nitrile **1** is converted to amidoxime **2** with hydroxylamine, coupled with a carboxylic acid to form *O*-acylamidoxime **3**, and cyclodehydrated to the 1,2,4-oxadizole **4** (Figure 1).

RESULTS AND DISCUSSION

To the best of our knowledge, this transformation has not been demonstrated on DNA-chemical conjugates aimed towards use in a DECL production. This may be partly due to presumed difficulties associated with the ultimate dehydration step in aqueous medium, as well as potential competing hydrolysis of synthetic sequence intermediates.[33,34] To address these concerns, we initiated studies on the formation of 1,2,4-oxadiazoles from six DNA-attached aryl nitriles **1a**–**1f** connected to a DNA construct through common functional handle transformations. We chose to utilize a DNA-connected nitrile rather than carboxylic acid to enable direct observation of all steps on a DNA-conjugate, to avoid the need to pre-form amidoximes, and to allow use of general carboxylic acid stocks as this is a common building block for many DECL designs.[32] Nitriles may be converted to amidoximes through attack of hydroxylamine under basic conditions[35] and a survey of basic buffers (e.g. borate, phosphate) and bases (e.g., Na_2CO_3, NaOAc, Cs_2CO_3, NaOH, *N*,*N*-Diisopropylethylamine, triethylamine) generally showed comparable conversions of nitriles **1** to the amidoxime **2**, albeit with prolonged reactions times (see Supporting Information for full details). Although heating could shorten the required reaction time, this led to mild decomposition of the DNA-chemical conjugates through formation of hydroxylamine DNA adducts and was avoided.[36] Ultimately, use of pH 8.2 borate buffer with addition of a small amount of Na_2CO_3 cleanly provided the amidoximes **2a**–**2f** in excellent yield (Scheme 1).

With the on-DNA amidoximes in hand, we next sought to find conditions that enabled the formation of the *O*-acylamidoximes **3**, using amidoxime **2b** and benzoic acid as a model system. Unfortunately, use of water-soluble DMTMM, a common coupling agent in DECL synthesis,[37] resulted in negligible formation of the *O*-acylamidoxime **3b1**. In other DECL studies, we have found DEPBT cleanly provides amidation products if the carboxylic acid is preactivated with coupling agent and Hunig's base in acetonitrile.[38] Application of this preactivation condition to **2b** in several different buffers all provided **3b1** in modest yield. Previously EDC/HOAt has been described as an efficient reagent system for this

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transformation[39] and applying this reagent combination provided **3b1** in 72–75% conversion (Table 1, entries 5–7). Switching to HATU under preactivation conditions further enhanced the conversion to 85–93% (Table 1, entries 8–10) but ultimately use of PyAOP without preactivation proved superior, providing **3b1** in excellent yield with pH 8.0 buffer and a slightly lessened yield with pH 9.5 buffer (Table 1, entries 11–12).

Using the optimal PyAOP/pH 8.0 condition (Table 1, entry 11), we investigated the *O*-acylation of amidoximes **2a**–**2f** with a range of aryl and aliphatic carboxylic acids (Table 2). Gratifyingly, nearly all of the *O*-acylamidoximes were formed in very good to excellent conversion, with only slightly decreased conversions observed with electron-deficient amidoxime nucleophiles **2d**–**2f**. Notably, both aryl and aliphatic carboxylic acids could be coupled, including electron deficient pyridyl carboxylic acids and sterically-encumbered secondary and tertiary aliphatic carboxylic acids (Table 2). With this collection of *O*-acylamidoximes, we next turned towards optimizing the final cyclodehydration step of amidoxime formation on the model substrate **3b1**. Typically, this cyclodehydration has been performed under basic, anhydrous, aprotic conditions at prolonged elevated temperature.[26] Although stable under ambient conditions,[40] heating *O*-acylamidoximes **3** in basic buffers may induce hydrolytic cleavage or elimination to ultimately provide a mixture of unreacted acylamidoxime **3**, desired oxadiazole **4**, amidoxime **2**, and cyanide **1**.

Our initial tests concentrated on the use of pH 9.5 borate buffer at elevated temperatures, as we have found this to be an optimal basic buffer system that maintains DNA and amide bond integrity for other reactions which require prolonged heating.[41] Use of this buffer alone or with a variety of additives produced the desired oxadiazole in fair yields, although with significant amounts of hydrolysis product **2b** (Table 3, entries 1–6). Lowering the starting pH of the buffer system suppressed hydrolysis to **2b** but led to large amounts of unreacted **3b** even after 16 h (Table 3, entries 7–8). Increasing the temperature to 80 °C in pH 9.5 borate buffer with *N,N*-diisopropylethylamine as an additive[42] boosted formation of **4b** to 83% after only 1.5 h, and ultimately application of the same system at 90 °C resulted in slightly improved conversion to the desired oxadiazole (Table 3, entries 9–10). Encouraged by this result, we applied this cyclodehydration condition to our collection of *O*-acylamidoximes **3a1**–**3f9** which produced all oxadiazoles **4a1**–**4f9** in fair to very good yields (Table 4). Although lowered conversion and significant hydrolysis was observed for all electron-deficient pyridyl substrates **3d1–3d9**, overall a variety of electronically-diverse aryl and alkyl substituted oxadiazoles were prepared through this multistep protocol.

Finally to further corroborate the formation of the DNA-conjugated oxadiazole product, we sought to compare the synthesis of amide-bound 1,2,4-oxadizole ataluren derivative **6b** prepared through our four-step process with the ataluren derivative **6a** prepared through direct acylation of commercially-obtained ataluren (Scheme 2). Formation of **6a** and **6b** proceeded smoothly through both synthetic routes and both were found to have identical retention on LC-MS during co-injection studies. To simulate the late-stage use of this process in a DECL production, these studies were performed on elongated DNA **5** (56 b.p.). No DNA degradation was detected and post-reaction **6b** efficiently ligated with a duplexed pair of 12 b.p. DNA oligomers (see Supporting Information for full details).

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CONCLUSIONS

In summary, we have demonstrated an efficient multistep synthesis of diverse 3,5-disubstituted 1,2,4-oxadiazoles on DNA-chemical conjugates. DNA-conjugated aryl nitriles were converted to 1,2,4-oxadiazoles through a four step process featuring conversion to the amidoxime, amidoxime *O*-acylation with a variety of aryl and aliphatic carboxylic acids, and cyclodehydration of *O*-acylamidoxime intermediates. This protocol produced a variety of electronically- and sterically-substituted oxadiazoles, utilizes building blocks that are widely commercially-available, and preserves the integrity of DNA. Efforts to apply this method within a full-scale DECL synthesis are ongoing and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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36. Hydroxylamine can induce downstream mutagenic PCR effects generally through substitution of DNA base amino groups with hydroxylamine. However under our optimized conditions these covalent adducts were not significant detected by LC-MS (< 5%).

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40. Samples of *O*-acyl amidoximes left at room temperature in neutral water for one week were found to be fully intact by LC-MS.

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42. The reactions appeared to have comparable conversions with or without the addition of DIPEA. However, the LC-MS trace seemed to be slightly cleaner in the presence of DIPEA.

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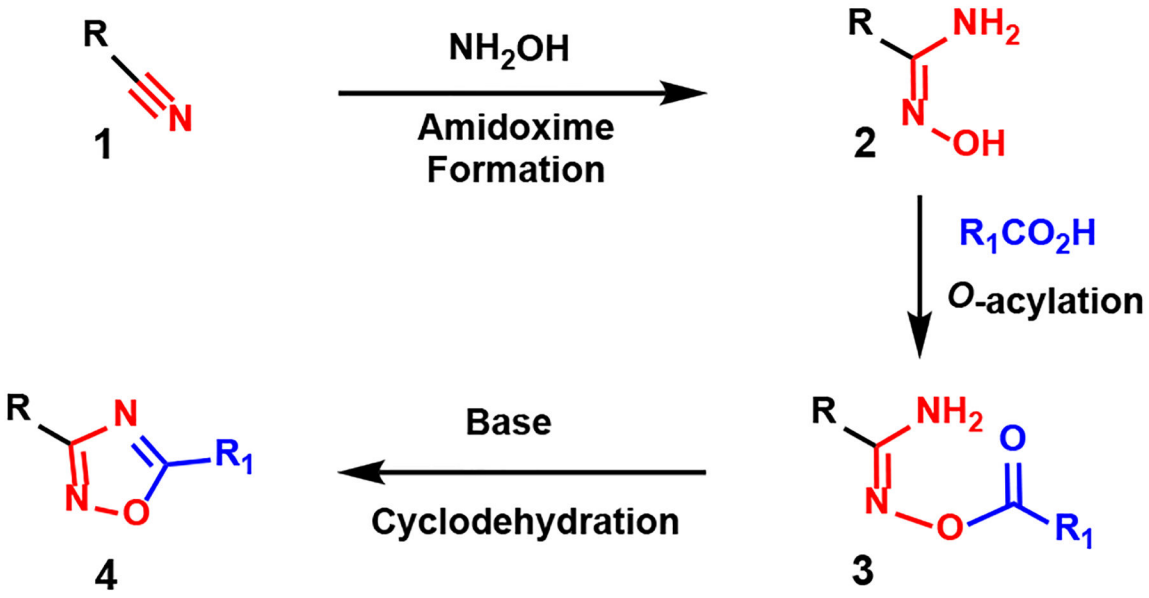

Figure 1.
General synthetic route of 1,2,4-oxadiazoles in conventional chemistry.

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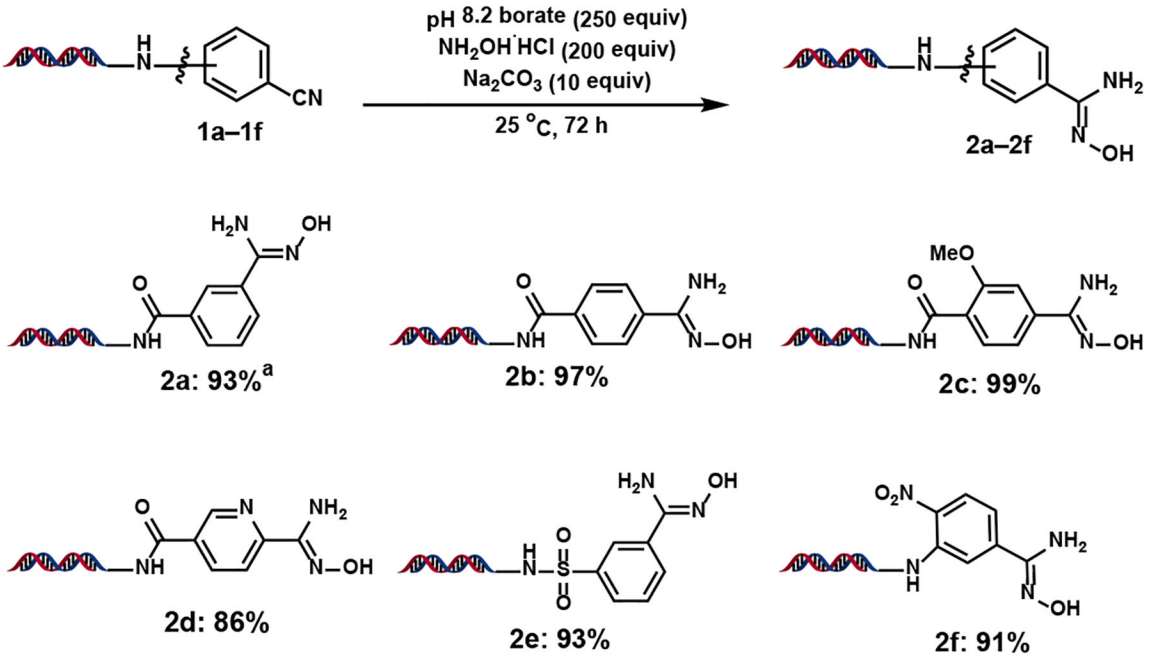

Scheme 1.

Amidoxime formation from DNA-conjugated nitriles.

[a]Conversions determined by LC-MS.

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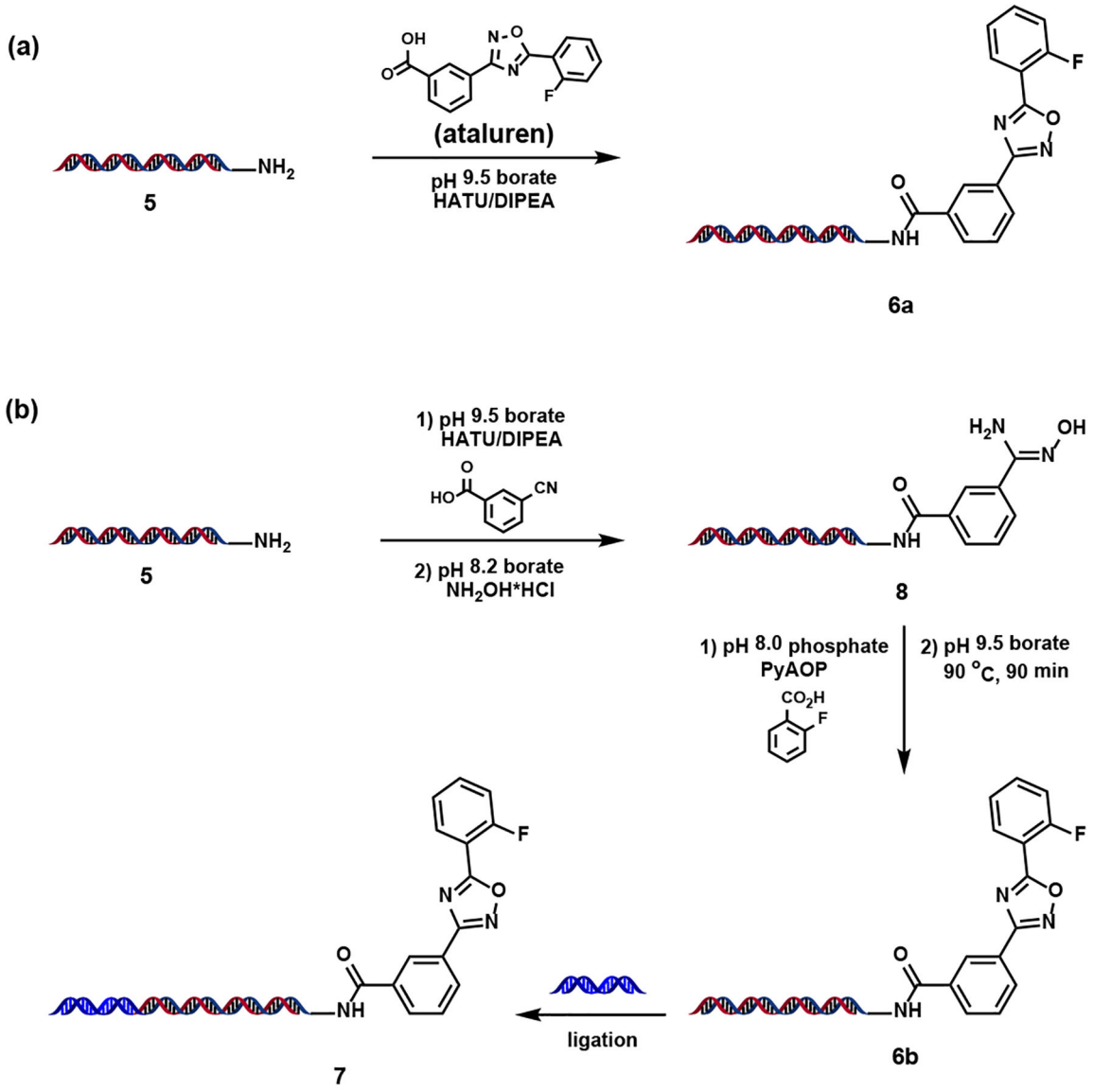

Scheme 2.

(a) Synthesis of DNA-conjugate **6a** via acylation with ataluren. (b) Multistep synthesis of 1,2,4-oxadiazole **6b** and enzymatic ligation.

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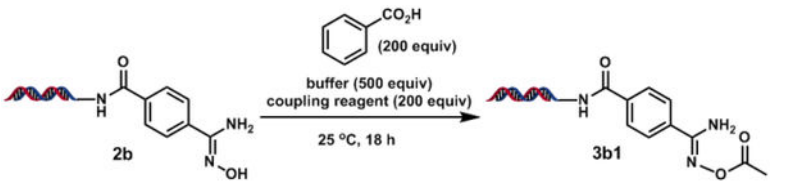
Table 1.

Optimization of *o*-acylation of amidoxime **2b**.



entry	buffer	coupling reagent	3b1[a] (%)
1	pH 8.0 phosphate	DMTMM[b]	< 5%
2[c]	pH 8.0 phosphate	DEPBT[d]	61%
3[c]	pH 8.2 borate	DEPBT	54%
4[c]	pH 9.5 borate	DEPBT	63%
5[c]	pH 8.0 phosphate	EDC[e]/HOAt[f]	75%
6[c]	pH 8.2 borate	EDC/HOAt	72%
7[c]	pH 9.5 borate	EDC/HOAt	74%
8[c]	pH 8.0 phosphate H	HATU[g]	85%
9[c]	pH 8.2 borate	HATU	90%
10[c]	pH 9.5 borate	HATU	93%
11	pH 8.0 phosphate	PyAOP[h]	95%
12	pH 9.5 borate	PyAOP	85%

[a]Conversions determined by LC-MS.

[b]4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methyl-morpholinium chloride.

[c]Carboxylic acid was preactivated by mixing with DIPEA (200 equiv) and coupling agent (200 equiv) in CH_3CN for 15 min at 25 °C prior to use.

[d]3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one.

[e]1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide.

[f]1-Hydroxy-7-azabenzotri-azole.

[g]1-[Bis-(di-methylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxid hexafluorophosphate.

[h](7-Azaben-zotriazol-1-yloxy) tripyrrolidinophophonium hexafluorophosphate.

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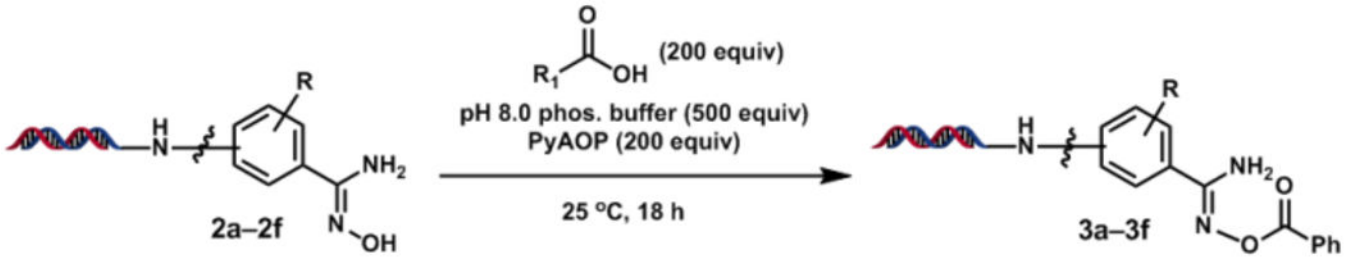
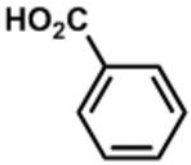
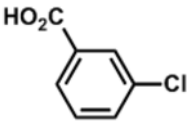
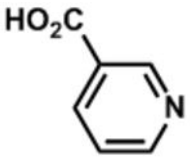
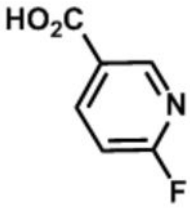
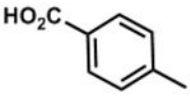
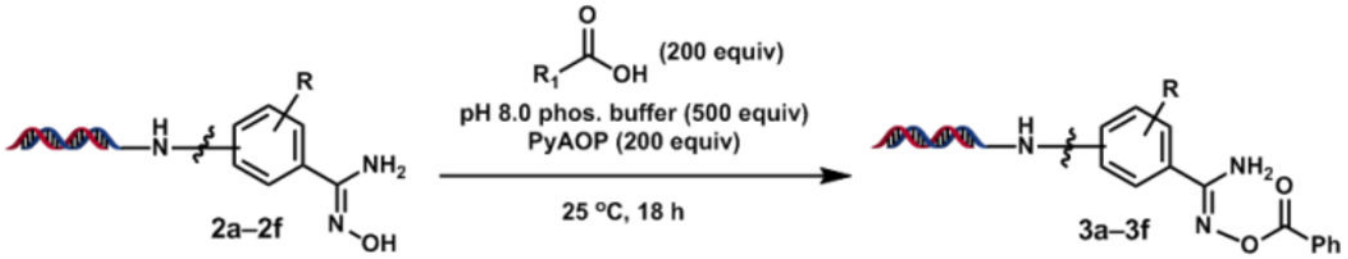
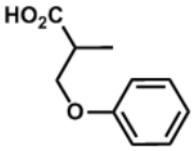
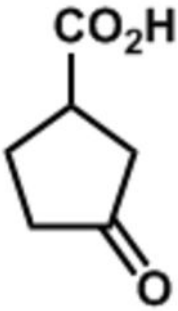
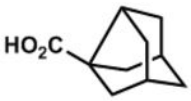
Table 2.

Substrate scope of *o*-acylation with carboxylic acids.[a]



		2a	2b	2c	2d	2e	2f
1		**3a1**: 94%	**3b1**: 95%	**3c1**: 95%	**3d1**: 92%	**3e1**: 99%	**3f1**: 92%
2		**3a2**: 97%	**3b2**: 98%	**3c2**: 95%	**3d2**: 92%	**3e2**: 99%	**3f2**: 90%
3		**3a3**: 94%	**3b3**: 95%	**3c3**: 94%	**3d3**: 92%	**3e3**: 98%	**3f3**: 96%
4		**3a4**: 89%	**3b4**: 96%	**3c4**: 94%	**3d4**: 90%	**3e4**: 96%	**3f4**: 88%
5		**3a5**: 91%	**3b5**: 97%	**3c5**: 95%	**3d5**: 84%	**3e5**: 97%	**3f5**: 81%



	2a	2b	2c	2d	2e	2f
6 	**3a6**: 90%	**3b6**: 99%	**3c6**: 94%	**3d6**: 89%	**3e6**: 98%	**3f6**: 87%
7 	**3a7**: 81%	**3b7**: 90%	**3c7**: 94%	**3d7**: 88%	**3e7**: 90%	**3f7**: 73%
8 	**3a8**: 97%	**3b8**: 97%	**3c8**: 96%	**3d8**: 94%	**3e8**: 99%	**3f8**: 91%
9	**3a9**: 97%	**3b9**: 99%	**3c9**: 94%	**3d9**: 93%	**3e9**: 98%	**3f9**: 93%

[a]Conversions determined by LC-MS.

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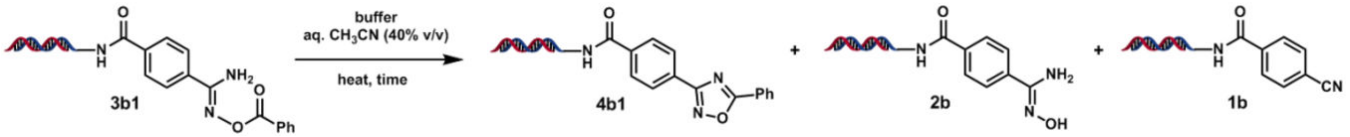
Table 3.

Optimization of cyclodehydration of acylamidoximes conditions.



entry	buffer[a]	base[b]	temperature	time	4b1[c] (%)	2b[c] (%)	3b1[c] (%)	1b[c] (%)
1	pH 9.5 borate	None	60 °C	16 h	54%	28%	9%	Trace
2	pH 9.5 borate	NaOAc[d]	60 °C	16 h	53%	26%	10%	Trace
3	pH 9.5 borate	Cs_2CO_3[e]	60 °C	16 h	59%	24%	9%	Trace
4	pH 9.5 borate	$NaHCO_3$[f]	60 °C	16 h	54%	25%	10%	Trace
5	pH 9.5 borate	Et_3N[g]	60 °C	16 h	57%	23%	20%	Trace
6	pH 9.5 borate	DIPEA[h]	60 °C	16 h	60%	27%	13%	Trace
7	pH 8.2 borate	DIPEA	60 °C	16 h	52%	11%	37%	Trace
8	pH 8.0 phosphate H	DIPEA	60 °C	16 h	53%	8%	39%	Trace
9	pH 9.5 borate	DIPEA	80 °C	1.5 h	83%	17%	Trace	Trace
10	pH 9.5 borate	DIPEA	90 °C	1.5 h	86%	14%	Trace	Trace

[a] 500 equiv used.

[b] 100 equiv used.

[c] Conversions determined by LC-MS.

[d] Sodium acetate.

[e] Cesium carbonate.

[f] Sodium bicarbonate.

[g] Triethylamine.

[h] *N,N*-diisopropylethylamine.

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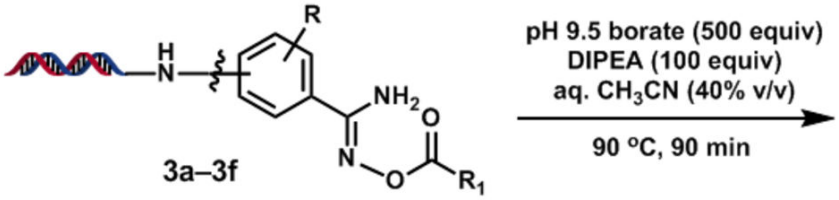
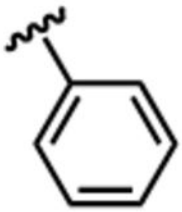
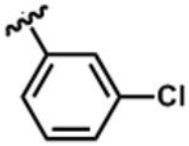
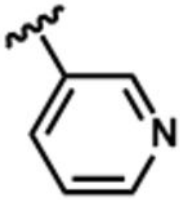
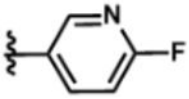
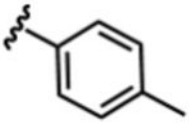
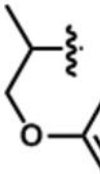
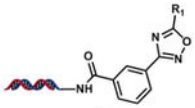
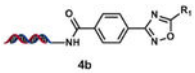
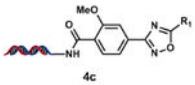
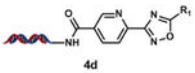
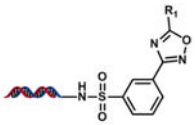
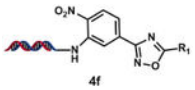
Table 4.

The synthesis of 1,2,4-oxadiazoles via cyclodehydration of acylamidoximes.[a,b]



Products	R_1= 					
 4a	**4a1**: 79%	**4a2**: 69%	**4a3**: 69%	**4a4**: 66%	**4a5**: 82%	**4a6**: 69%
 4b	**4b1**: 82%	**4b2**: 78%	**4b3**: 77%	**4b4**: 74%	**4b5**: 82%	**4b6**: 71%
 4c	**4c1**: 89%	**4c2**: 86%	**4c3**: 81%	**4c4**: 83%	**4c5**: 92%	**4c6**: 81%
 4d	**4d1**: 68%	**4d2**: 62%	**4d3**: 60%	**4d4**: 63%	**4d5**: 67%	**4d6**: 56%
 4e	**4e1**: 81%	**4e2**: 77%	**4e3**: 76%	**4e4**: 77%	**4e5**: 85%	**4e6**: 74%
 4f	**4f1**: 86%	**4f2**: 84%	**4f3**: 80%	**4f4**: 85%	**4f5**: 92%	**4f6**: 80%

[a]Conversions determined by LC-MS.

[b]Trace amount to 10% of cyanides **1a—1f** were also observed.