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One-Step Synthesis of Oxazoline and Dihydrooxazine Libraries

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Introduction

Oxazolines appear in numerous medicinally active compounds and natural products of biological significance.¹ Additionally, they are valuable as synthetic intermediates or protecting groups² in organic synthesis,³ and commonly appear in ligands for asymmetric synthesis (Figure 1).⁴ The most common mode of oxazoline synthesis involves preparation of a β -hydroxy amide followed by cyclization. Typical cyclization reagents include Burgess reagent,⁵ PPh_3/DIAD ,⁶ $\text{DIC}/\text{Cu}(\text{OTf})_2$,⁷ molybdenum oxide,⁸ and $\text{DAST}/\text{Deoxo-Fluor}$.⁹ The six-membered homologous dihydrooxazines have been prepared by various methods that include [4+2] cycloadditions between *N*-acyl imines and alkenes,¹⁰ 1,4-dipolar cycloaddition reactions between olefins and aminomethyl ions,¹¹ and from stereochemically defined *N*-thioacyl-1,3-amino alcohols in the presence of Bu_4NF and EtI .¹²

To date, three reports describe parallel synthesis of oxazolines, all of which entailed cyclization of β -hydroxy amides. Pirrung and coworkers described a catch and release strategy using polymer-bound tosyl chloride in their oxazoline library synthesis.¹³ Crosignani and coworkers reported a one-pot protocol using polymer-bound Mukaiyama reagent to facilitate formation of β -hydroxy amide, followed by in situ cyclization using either polymer-bound tosyl chloride or polymer-bound 2-fluoro-*N*-pyridinium triflate.¹⁴ Finally, Wipf and coworkers described a tandem condensation-cyclodehydration strategy using boronic acid as catalyst.¹⁵ Of these approaches, only that of Pirrung was extended to the synthesis of the homologous dihydrooxazines.¹³

Previous work in our laboratory has demonstrated that the reaction between aldehydes and 1,2- or 1,3-hydroxyalkyl azides in the presence of Lewis acid or protic acid results in a facile one-step construction of oxazolines or dihydrooxazines, respectively (Scheme I).¹⁶ Of several Lewis acids examined, $\text{BF}_3 \cdot \text{OEt}_2$ was found to be the most effective promoter for the cyclization. As part of a larger program in the application of hydroxyalkyl azides to parallel synthesis, we wished to adapt this reaction to library preparation. Herein, we report the realization of this plan, which involved the development of appropriate scavenging conditions to facilitate the removal of excess hydroxyalkyl azide prior to final purification.

The mechanism of the reaction (Scheme 2) involves initial hemiketal formation and subsequent elimination to form an oxenium ion, which is now set up for intramolecular attack by the azide. The resulting intermediate can then form the product by 1,2-hydride shift coupled with N_2 loss, followed by proton loss to give the oxazoline product.

Results and Discussion

The scope of the oxazoline/dihydroxazine synthesis had been demonstrated to include electron-rich and electron-deficient aromatic aldehydes as well as aliphatic aldehydes.¹⁵ Accordingly, we chose a subset of the various commercially available aldehydes that would represent a variety of these possibilities (Figure 2). *p*-Bromobenzaldehyde **1**{1} was included as it would serve as a handle for further cross-coupling and animation reactions. Indole-3-carboxyaldehyde **1**{3} represented heterocyclic aldehydes in our initial survey. We wished to include nitrogen-containing precursors that might enable us to generate “drug-like” scaffolds with attractive physiochemical properties. These include molecular weight, logP, pKa, and molecular polarizability. Unfortunately, attempts to carry out the reaction with 4-dimethylaminobenzaldehyde were unsuccessful. As alternatives, 4-acetoamido benzaldehyde **1**{9} and 3-nitrobenzaldehyde **1**{7} were chosen. Following some initial, experiments, the aliphatic aldehydes were not ultimately included in the final library as these substrates provided product in poor purities when adapted to parallel format. We suspect that these compounds underwent hydrolysis to amides upon workup, but this point was not extensively pursued.

With respect to the hydroxyalkyl azides, five 1,2-hydroxyalkyl azides and three 1,3-hydroxyalkyl azides were chosen to optimize the conditions in the parallel synthesis (Figure 3). The hydroxyalkyl azides were largely chosen to represent common amino acid side chains including phenylglycine, phenylalanine, leucine and valine. In addition, hydroxyethyl azide **2**{4} was also used; it formally corresponds to a D-amino acid due to its method of synthesis (see discussion below). To demonstrate the utility of the present method for the synthesis of dihydrooxazines, hydroxypropyl azides were identified for this project.

In general, 1,2-hydroxyalkyl azides were generated by azidation of the corresponding enantiomerically pure amino alcohols, which are derived readily from amino acids. Thus, the 1,2-hydroxyalkyl azides **2**{1-3} were synthesized by the reduction of the amino acid using TMSCl/LiBH₄ followed by conversion of the amino group to the corresponding azide using TfN₃.¹⁷ Compound **2**{4} was synthesized by direct azidation of (*S*)-serine benzyl ester, leading to the stereoisomer shown. The 1,3-hydroxyalkyl azide were either prepared by S_N2 displacement or Mitsunobu reaction.¹⁸ Compound **2**{6} was used as a 1:1 mixture of diastereomers (syn and anti).

We wished to retain our originally reported conditions utilizing BF₃•OEt₂ as the Lewis acid but required a streamlined workup procedure for parallel synthesis. Our first approach entailed the use of excess of aldehyde which was then scavenged using polymer-bound tosyl hydrazine (Scheme 3).¹⁹ A small 3×3 library was prepared, using aldehydes **1**{1-3} and hydroxyalkyl azides **2**{1-2} and **2**{3}; affording products in the range of 5–24%.

When the reaction was attempted with excess hydroxyalkyl azide, products were isolated in ≥50% yields (Scheme 4). In a small 3×3 library performed, using aldehydes **1**{1-3}, hydroxyalkyl azides **2**{1-2} and **2**{3}, products were isolated in the range of 22–69%. The excess hydroxyalkyl azide could be scavenged using polymer-bound triphenylphosphine, presumably as the Staudinger reaction adduct. This was determined by showing clean removal of azide from a test mixture of oxazoline and excess hydroxyalkyl azide (see experimental section for details).

The parallel synthesis techniques were applied to a series of four libraries. The reactions were carried out in Bohdan MiniBlock™ XT and subsequently quenched with saturated sodium bicarbonate. This was followed by parallel liquid-liquid extraction using hydrophobic frits, after which the excess hydroxyalkyl azide was scavenged using polymer-bound triphenylphosphine. The crude products were then subjected to preparative HPLC. Purities in

the range of 68–100% were achieved after this preparative LC purification. Thus, a series of disubstituted oxazolines and di- and trisubstituted dihydrooxazines were generated.

The results from the library syntheses are summarized in Tables 1–3. In total of 64 attempts, there were four failed reactions. Yields generally consistent across all the hydroxyalkyl azides, with the exception of the ester containing hydroxyalkyl azide **2**{4}. Of the aldehydes used, only indole 3-carboxyaldehyde was problematic; two of the failed reactions were with this aldehyde. The corresponding oxazoline products generated from this aldehyde were **3**{8} and **3**{16}. It is possible that the indole underwent competitive reaction under these conditions, but this point was neither supported by the data or pursued. As expected, diastereomeric mixtures of heterocycles were obtained when hydroxyalkyl azide **2**{6} was used; interestingly, a few dihydrooxazines were isolated from these reactions in slightly enhanced diastereomeric ratio, probably as an artifact of the purification protocol.

Due to our ongoing interest in preparing heterocycles for use in future high-throughput screening ventures, *in silico* screening of the library members was carried out to evaluate their accordance with Lipinski's "rule of five"²⁰ and Veber's rules.²² Thus, molecular weight, clogP, number of hydrogen bond donors and acceptors, and the number of rotatable bonds were either enumerated or calculated for each of the library members using the SYBYL²¹ program. The current library members are highly Lipinski compliant: 70% of the library members completely adhered to Lipinski's rules, while the rest of the library members had violation to only one of the parameters.

In conclusion, the reactions of 1,2- and 1,3-hydroxyalkyl with aldehydes allowed a simple, one-step construction of a 60-member library of disubstituted oxazolines and di- and trisubstituted dihydrooxazines. The material recovery of the library was in the range of 3–46 mg following purification by preparative HPLC. The average yield of the library was 39% and the average purity was 91%. The library members are currently being evaluated against various biological screens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Oxazolines in biologically active compounds.

Figure 2.
Aldehyde sublibrary.

Figure 3.
Sublibrary of hydroxyalkyl azides synthesized.

Scheme 1.

Scheme 2.

Scheme 3.

Scheme 4.

Table 1

Library data for compounds **3**{1-40}.

compound	R ¹	R ²	yield (%)	purity (%) ^a
3 {1}	4-BrC ₆ H ₄	CH ₂ Ph	26	98
3 {2}	4-OCH ₃ C ₆ H ₄	CH ₂ Ph	17	99
3 {3}	3-CH ₃ C ₆ H ₄	CH ₂ Ph	68	99
3 {4}	1 <i>H</i> -indole	CH ₂ Ph	0	NA
3 {5}	4-BrC ₆ H ₄	<i>i</i> -Pr	26	98
3 {6}	4-OCH ₃ C ₆ H ₄	<i>i</i> -Pr	22	98
3 {7}	4-CH ₃ C ₆ H ₄	<i>i</i> -Pr	34	98
3 {8}	1 <i>H</i> -indole	<i>i</i> -Pr	20	99
3 {9}	4-BrC ₆ H ₄	<i>i</i> -Bu	55	99
3 {10}	4-OCH ₃ C ₆ H ₄	<i>i</i> -Bu	54	95
3 {11}	4-CH ₃ C ₆ H ₄	<i>i</i> -Bu	44	99
3 {12}	1 <i>H</i> -indole	<i>i</i> -Bu	11	99
3 {13}	4-BrC ₆ H ₄	CO ₂ Bn	17	75
3 {14}	4-OCH ₃ C ₆ H ₄	CO ₂ Bn	10	99
3 {15}	4-CH ₃ -C ₆ H ₄	CO ₂ Bn	11	99
3 {16}	1 <i>H</i> -indole	CO ₂ Bn	0	NA
3 {17}	1-naphthyl	CH ₂ Ph	50	99
3 {18}	3,5-Cl ₂ C ₆ H ₄	CH ₂ Ph	89	99
3 {19}	3-NO ₂ C ₆ H ₄	CH ₂ Ph	52	98
3 {20}	4-AcNHC ₆ H ₄	CH ₂ Ph	0	NA
3 {21}	1-naphthyl	<i>i</i> -Pr	51	99
3 {22}	3,5-Cl ₂ C ₆ H ₄	<i>i</i> -Pr	52	99
3 {23}	3-NO ₂ C ₆ H ₄	<i>i</i> -Pr	55	92
3 {24}	4-AcNHC ₆ H ₄	<i>i</i> -Pr	10	89
3 {25}	1-naphthyl	<i>i</i> -Bu	42	95
3 {26}	3,5-Cl ₂ C ₆ H ₄	<i>i</i> -Bu	31	98
3 {27}	3-NO ₂ C ₆ H ₄	<i>i</i> -Bu	30	93
3 {28}	4-AcNHC ₆ H ₄	<i>i</i> -Bu	85	96
3 {29}	1-naphthyl	CO ₂ Bn	15	89
3 {30}	3,5-Cl ₂ C ₆ H ₄	CO ₂ Bn	10	94
3 {31}	3-NO ₂ C ₆ H ₄	CO ₂ Bn	25	82
3 {32}	4-AcNHC ₆ H ₄	CO ₂ Bn	20	80
3 {33}	1-naphthyl	Ph	32	81
3 {34}	3,5-Cl ₂ C ₆ H ₄	Ph	20	71
3 {35}	3-NO ₂ C ₆ H ₄	Ph	47	67
3 {36}	4-AcNHC ₆ H ₄	Ph	12	78
3 {37}	4-BrC ₆ H ₄	Ph	40	88
3 {38}	4-OCH ₃ C ₆ H ₄	Ph	25	91
3 {39}	3-CH ₃ C ₆ H ₄	Ph	42	92
3 {40}	4-FC ₆ H ₄	Ph	43	89

^aUV purities determined at 215 nm after preparative HPLC.

Table 2

Library data for compounds 3{41-56}.

compound	R ¹	R ²	R ³	yield (%)	purity (%) ^a
3{41}	Ph	H	1-naphthyl	26	98
3{42}	Ph	H	3,5-Cl ₂ C ₆ H ₄	35	98
3{43}	Ph	H	3-NO ₂ C ₆ H ₄	68	99
3{44}	Ph	H	4-AcNHC ₆ H ₄	26	98
3{45}	Ph	H	4-BrC ₆ H ₄	20	98
3{46}	Ph	H	4-OCH ₃ C ₆ H ₄	32	91
3{47}	Ph	H	3-CH ₃ C ₆ H ₄	51	99
3{48}	Ph	H	4-FC ₆ H ₄	98	98
3{49}	H	CH ₃	4-BrC ₆ H ₄	33	100
3{50}	H	CH ₃	3-OCH ₃ C ₆ H ₄	31	95
3{51}	H	CH ₃	3-CH ₃ C ₆ H ₄	20	96
3{52}	H	CH ₃	4-FC ₆ H ₄	32	89
3{53}	H	CH ₃	1-naphthyl	61	98
3{54}	H	CH ₃	3,5-Cl ₂ C ₆ H ₄	20	72
3{55}	H	CH ₃	3-NO ₂ C ₆ H ₄	34	98
3{56}	H	CH ₃	4-NHAcC ₆ H ₄	25	91

^aUV purity determined at 215 nm after preparative HPLC.

Table 3Library data for compounds **3**{57–64}.

compound	R	yield(%)	purity(%)	diastereomeric ratio
3 {57}	4-BrC ₆ H ₄	34	91	single diastereomer
3 {58}	4-OCH ₃ C ₆ H ₄	0	NA	NA
3 {59}	3-CH ₃ C ₆ H ₄	51	99	1:1
3 {60}	1-naphthyl	12	91	1:1
3 {61}	3,5-Cl ₂ C ₆ H ₄	20	99	1.1:1
3 {63}	3-NO ₂ C ₆ H ₄	16	98	3.1:1
3 {64}	4-AcNHC ₆ H ₄	35	85	29:9:1

^a UV purity determined at 215 nm after preparative HPLC. Purity reflects mixture of diastereomers.

Table 4**In silico**

screening analysis of library members.

parameter	range
molecular weight	193.21–350.19
ClogP	1.76–5.70
number of hydrogen bond acceptors	1–7
number of hydrogen bond donors	1–4
number of rotatable bonds	1–6