One-Step Synthesis of Oxazoline and Dihydrooxazine Libraries

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The reactions of 1,2- and 1,3-hydroxyalkyl azides and aldehydes in the presence of Lewis acid result in the one-step construction of oxazolines and dihydrooxazines, respectively. The reaction was adapted to parallel synthesis using a polymer-bound phosphine to scavenge excess hydroxyalkyl azide. Thus, a 60-member library of various disubstituted oxazolines and di- and trisubstituted dihydrooxazines was generated.

Introduction

Oxazolines appear in numerous medicinally active compounds and natural products of biological significance.[1] Additionally, they are valuable as synthetic intermediates[2] or protecting groups in organic synthesis[3] and commonly appear in ligands for asymmetric synthesis (Figure 1).[4] The most common mode of oxazoline synthesis involves the preparation of a β-hydroxy amide followed by cyclization. Typical cyclization reagents include Burgess reagent,[5] PPh_3/DIAD,[6] DIC/$Cu(OTf)_2$,[7] molybdenum oxide,[8] and DAST/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 co-workers described a catch and release strategy using polymer-bound tosyl chloride in their oxazoline library synthesis.[13] Crosignani and co-workers 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 co-workers 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 1).[16] Of several Lewis acids examined, $BF_3{\cdot}OEt_2$ 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.

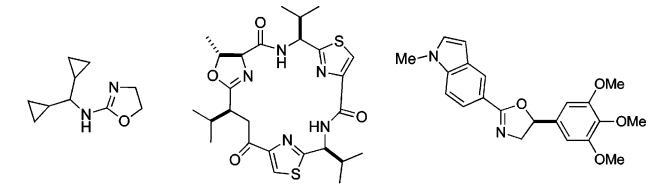
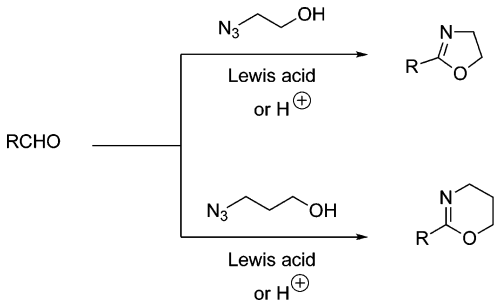
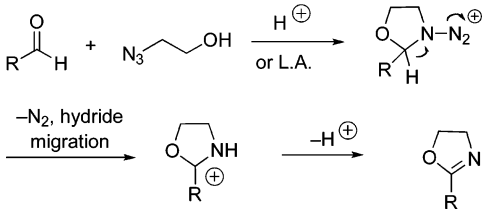


Figure 1. Oxazolines in biologically active compounds.

Scheme 1



Scheme 2



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

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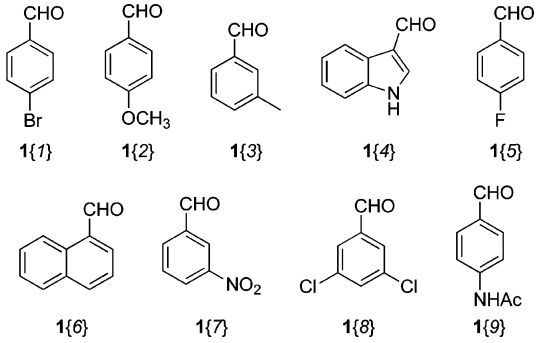


Figure 2. Aldehyde sublibrary.

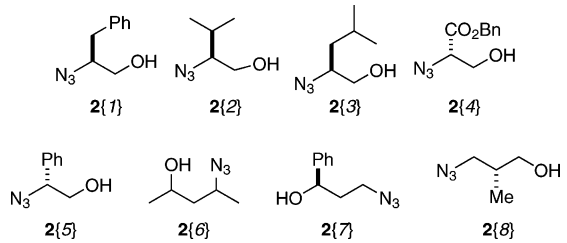


Figure 3. Sublibrary of hydroxyalkyl azides synthesized.

product via a 1,2-hydride shift, coupled with N_2 loss, followed by proton loss to give the oxazoline product.

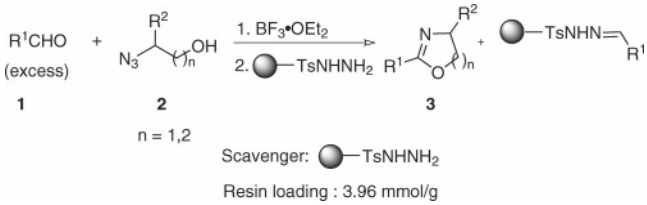
Results and Discussion

The scope of the oxazoline/dihydrooxazine 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).

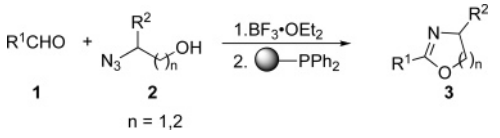
p-Bromobenzaldehyde **1**{*1*} was included because it would serve as a handle for further cross-coupling and amination reactions. Indole-3-carboxyaldehyde **1**{*4*} represented heterocyclic aldehydes in our initial survey. We wished to include nitrogen-containing precursors that might enable us to generate druglike scaffolds with attractive physiochemical properties. These include molecular weight, log *P*, pK_a, 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. After some initial experiments, the aliphatic aldehydes were not ultimately included in the final library because these substrates provided the 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 because of 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.

Scheme 3



Scheme 4



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/$LiBH_4$, followed by conversion of the amino group to the corresponding azide using TfN_3.[17] Compound **2**{*4*} was synthesized by direct azidation of (*S*)-serine benzyl ester, leading to the stereoisomer shown. The 1,3-hydroxyalkyl azides were either prepared by S_N2 displacement or by the Mitsunobu reaction.[18] Compound **2**{*6*} was used as a 1:1 mixture of diastereomers (syn and anti).

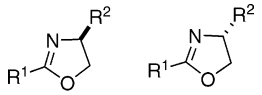
We wished to retain our originally reported conditions, using BF_3·OEt_2 as the Lewis acid, but we needed a streamlined workup procedure for parallel synthesis. Our first approach entailed the use of excess of aldehyde, which was then scavenged using polymer-bound tosyl hydrazine (Scheme 3).[19] A small 3 × 3 library was prepared, using aldehydes **1**{*1*−*3*} and hydroxyalkyl azides **2**{*1*−*2*} and **2**{*3*}, affording products in yields of 5−24%.

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

Parallel synthesis techniques were applied to a series of four libraries. The reactions were carried out in the 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 67−100% 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. The yields were generally consistent across all the

Table 1. Library Data for Compounds **3**{*1*−*40*}

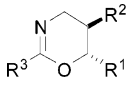


3{*1-29*} **3**{*30-40*}

compound	R^1	R^2	yield (%)	purity[a] (%)
3{*1*}	4-BrC_6H_4	CH_2Ph	26	98
3{*2*}	4-$CH_3OC_6H_4$	CH_2Ph	17	99
3{*3*}	3-$CH_3C_6H_4$	CH_2Ph	68	99
3{*4*}	1*H*-indole	CH_2Ph	0	
3{*5*}	4-BrC_6H_4	*i*-Pr	26	98
3{*6*}	4-$CH_3OC_6H_4$	*i*-Pr	22	98
3{*7*}	3-$CH_3C_6H_4$	*i*-Pr	34	98
3{*8*}	1*H*-indole	*i*-Pr	20	99
3{*9*}	4-BrC_6H_4	*i*-Bu	55	99
3{*10*}	4-$CH_3OC_6H_4$	*i*-Bu	54	95
3{*11*}	3-$CH_3C_6H_4$	*i*-Bu	44	99
3{*12*}	1*H*-indole	*i*-Bu	11	99
3{*13*}	4-BrC_6H_4	CO_2Bn	17	75
3{*14*}	4-$CH_3OC_6H_4$	CO_2Bn	10	99
3{*15*}	3-$CH_3C_6H_4$	CO_2Bn	11	99
3{*16*}	1*H*-indole	CO_2Bn	0	
3{*17*}	1-napthyl	CH_2Ph	50	99
3{*18*}	3,5-$Cl_2C_6H_4$	CH_2Ph	89	99
3{*19*}	3-$NO_2C_6H_4$	CH_2Ph	52	98
3{*20*}	4-$AcNHC_6H_4$	CH_2Ph	0	
3{*21*}	1-napthyl	*i*-Pr	51	99
3{*22*}	3,5-$Cl_2C_6H_4$	*i*-Pr	52	99
3{*23*}	3-$NO_2C_6H_4$	*i*-Pr	55	92
3{*24*}	4-$AcNHC_6H_4$	*i*-Pr	10	89
3{*25*}	1-napthyl	*i*-Bu	42	95
3{*26*}	3,5-$Cl_2C_6H_4$	*i*-Bu	31	98
3{*27*}	3-$NO_2C_6H_4$	*i*-Bu	30	93
3{*28*}	4-$AcNHC_6H_4$	*i*-Bu	85	96
3{*29*}	1-napthyl	CO_2Bn	15	89
3{*30*}	3,5-$Cl_2C_6H_4$	CO_2Bn	10	94
3{*31*}	3-$NO_2C_6H_4$	CO_2Bn	25	82
3{*32*}	4-$AcNHC_6H_4$	CO_2Bn	20	80
3{*33*}	1-napthyl	Ph	32	81
3{*34*}	3,5-$Cl_2C_6H_4$	Ph	20	71
3{*35*}	3-$NO_2C_6H_4$	Ph	47	67
3{*36*}	4-$AcNHC_6H_4$	Ph	12	78
3{*37*}	4-BrC_6H_4	Ph	40	88
3{*38*}	4-$CH_3OC_6H_4$	Ph	25	91
3{*39*}	3-$CH_3C_6H_4$	Ph	42	92
3{*40*}	4-FC_6H_4	Ph	43	89

[a] UV purities determined at 215 nm after preparative HPLC.

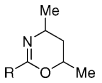
Table 2. Library Data for Compounds **3**{*41*−*56*}



compound	R^1	R^2	R^3	yield (%)	purity[a] (%)
3{*41*}	Ph	H	1-napthyl	26	98
3{*42*}	Ph	H	3,5-$Cl_2C_6H_4$	35	98
3{*43*}	Ph	H	3-$NO_2C_6H_4$	68	99
3{*44*}	Ph	H	4-$AcNHC_6H_4$	26	98
3{*45*}	Ph	H	4-BrC_6H_4	20	98
3{*46*}	Ph	H	4-$CH_3OC_6H_4$	32	91
3{*47*}	Ph	H	3-$CH_3C_6H_4$	51	99
3{*48*}	Ph	H	4-FC_6H_4	98	98
3{*49*}	H	CH_3	4-BrC_6H_4	33	100
3{*50*}	H	CH_3	4-$CH_3OC_6H_4$	31	95
3{*51*}	H	CH_3	3-$CH_3C_6H_4$	20	96
3{*52*}	H	CH_3	4-FC_6H_4	32	89
3{*53*}	H	CH_3	1-napthyl	61	98
3{*54*}	H	CH_3	3,5-$Cl_2C_6H_4$	20	72
3{*55*}	H	CH_3	3-$NO_2C_6H_4$	34	98
3{*56*}	H	CH_3	4-$AcNHC_6H_4$	25	91

[a] UV purity determined at 215 nm after preparative HPLC.

Table 3. Library Data for Compounds **3**{*57*−*64*}



compound	R	yield (%)	purity (%)	diastereomeric ratio
3{*57*}	4-BrC_6H_4	34	91	single diastereomer
3{*58*}	4-$CH_3OC_6H_4$	0		
3{*59*}	3-$CH_3C_6H_4$	51	99	1:1
3{*60*}	1-napthyl	12	91	1:1
3{*61*}	3,5-$Cl_2C_6H_4$	20	99	1.1:1
3{*63*}	3-$NO_2C_6H_4$	16	98	3.1:1
3{*64*}	4-$AcNHC_6H_4$	35	85	2.9:1

[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
C log *P*	1.76−5.70
no. of hydrogen bond acceptors	1−7
no. of hydrogen bond donors	1−4
no. of rotatable bonds	1−6

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. It is possible that the indole underwent competitive reaction under these conditions, but this point was neither supported by the data nor was it 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 a slightly enchanced diastereomeric ratio, probably as an artifact of the purification protocol.

Because of 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, clog *P*, 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 SYBYL[21] program (Table 4). 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 a violation of 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.

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Supporting Information Available. Experimental details, characterization of library members, and ^{1}H and ^{13}C NMR spectra of selected library members. This material is available free of charge via the Internet at http://pubs.acs.org.

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