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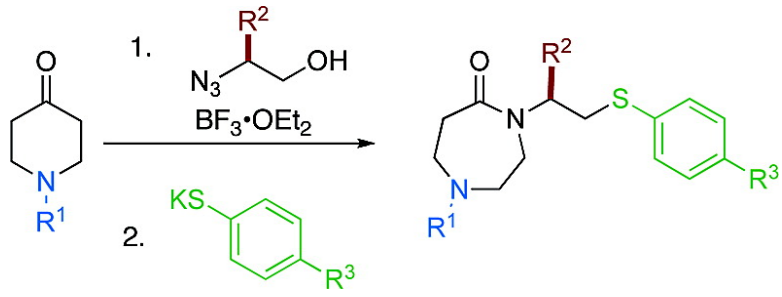
J. Comb. Chem., **2008**, 10 (2), 230-234• DOI: 10.1021/cc700174c • Publication Date (Web): 07 February 2008



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Three-Component Synthesis of 1,4-Diazepin-5-ones and the Construction of γ-Turn-like Peptidomimetic Libraries

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Received October 30, 2007

The parallel synthesis of γ-turn-inspired peptidomimetic libraries has been demonstrated through two approaches toward the preparation of 1,4-diazepin-5-ones. In the first approach, 1,4-diazepin-5-ones scaffolds were prepared on gram scale and subsequently diversified to produce libraries. In a second approach, libraries of 1,4-diazepin-5-ones were produced directly through a three-component strategy that maximizes the diversity obtained in a single step.

Introduction

Peptide mimicry has been an important goal of chemical biology for over a quarter of a century.[1] Although many early peptidomimetics were based on the faithful reproduction of backbone angles in turns, other workers have focused more on the optimization of side chain−target interactions.[2] This approach permits greater flexibility in the choice of turn scaffolds but often requires a researcher to identify optimal structures through screening. Accordingly, the development of libraries of turn mimics based on turn structures is a desirable goal.[3]

Substituted 1,4-diazepin-5-ones have interesting biological properties that include inhibition of the lymphocyte function-associated antigen-1 LFA-1 in inflammation and autoimmune diseases,[4] anticonvulsant activity,[5] and inhibition of reverse transcriptase of HIV-1.[6] In addition, we[7] and others[8] have suggested that compounds containing a diazepinone ring may function as turn mimics (Figure 1). To facilitate the utility of these units in medicinal chemistry, we wished to develop routes to 1,4-diazepin-5-one libraries that permit the easy incorporation of peptide side chain equivalents, as well as the incorporation of additional reactive moieties. Two approaches that allow for this are presented here. In the first, 1,4-diazepin-5-one scaffolds were prepared in gram quantities and subsequently modified to incorporate a variety of side chain moieties. In a second method, we report the application of a recently developed one-pot, three-component approach to the semiautomated synthesis of 1,4-diazepin-5-ones libraries.[9]

Results and Discussion

Synthesis of 1,4-Diazepin-5-one Scaffolds and Subsequent Diversification. We first set about preparing a set of *N*-hydroxyethyl-1,4-diazepin-5-ones using a ring-expansion protocol developed in this laboratory (Scheme 1).[7,9] Thus, treatment of an *N*-benzylpiperidone **1** with a substituted azidoethanol afforded an iminium ether that was converted to the desired lactam by subsequent treatment with aqueous base. Although the enantiomeric purity of the resulting lactams was not checked in this work, we have not observed epimerization in using this reaction for asymmetric synthesis applications.[7b,c] One advantage of the 1,4-diazepinone skeleton was that it contained a masked secondary amine that could be deprotected and subsequently substituted. The hydroxyethyl azides **2** were derived from amino acids to serve as *i*+*2* side chain mimics; the alcohol also presents a useful functional group for additional diversification.

With the *N*-hydroxyethyl-1,4-diazepin-5-ones scaffolds **4** in hand, we turned toward library preparation. We began by

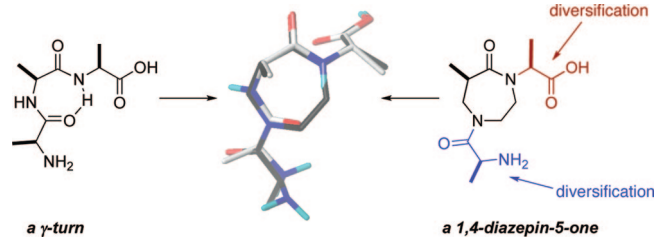

Figure 1. Overlay of an idealized γ-turn (white) with the 1,4-diazepin-5-one skeleton (black), both derived from Ala−Ala−Ala, and the peptide side chain diversifications of interest in the 1,4-diazepin-5-one.[7]

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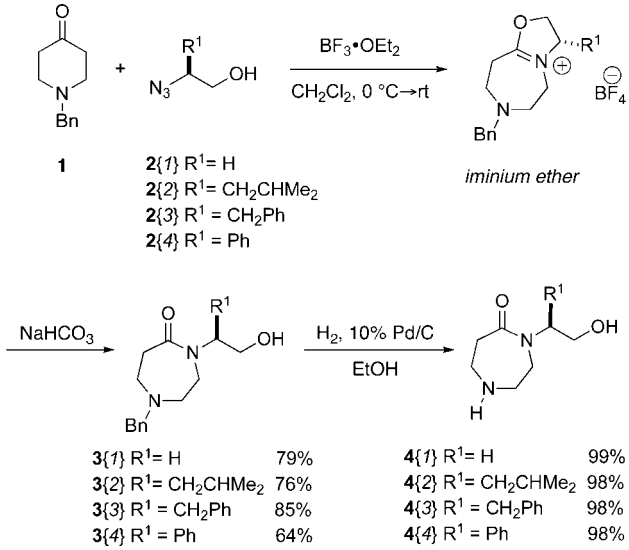
10.1021/cc700174c CCC: $40.75
Published on Web 02/07/2008

Scheme 1. *N*-Hydroxyethyl-1,4-diazepin-5-one Scaffold Synthesis

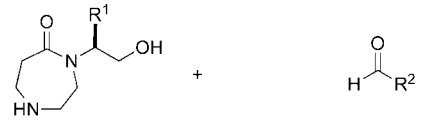


1

2{*1*} R^1= H
2{*2*} R^1= CH_2CHMe_2
2{*3*} R^1 = CH_2Ph
2{*4*} R^1 = Ph

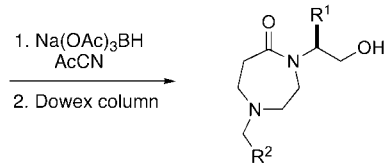
3{*1*} R^1= H	79%	**4**{*1*} R^1= H	99%
3{*2*} R^1= CH_2CHMe_2	76%	**4**{*2*} R^1= CH_2CHMe_2	98%
3{*3*} R^1 = CH_2Ph	85%	**4**{*3*} R^1 = CH_2Ph	98%
3{*4*} R^1 = Ph	64%	**4**{*4*} R^1 = Ph	98%

Scheme 2. Reductive Amination Library



4{*1*} R^1= H
4{*2*} R^1= CH_2CHMe_2
4{*3*} R^1 = CH_2Ph
4{*4*} R^1 = Ph

5{*1*} R^2= C_2H_5
5{*2*} R^2= C_6H_{13}
5{*3*} R^2= $CHMe_2$
5{*4*} R^2= CH_2CH_2Ph
5{*5*} R^2= Ph
5{*6*} R^2= 4-OMe-C_6H_4
5{*7*} R^2= 4-OH-C_6H_4
5{*8*} R^2= 4-Br-C_6H_4
5{*9*} R^2= 4-CN-C_6H_4
5{*10*} R^2= 4-NO_2-C_6H_4
5{*11*} R^2= 3,4-$(OMe)_2$-C_6H_3
5{*12*} R^2= 3-pyridine

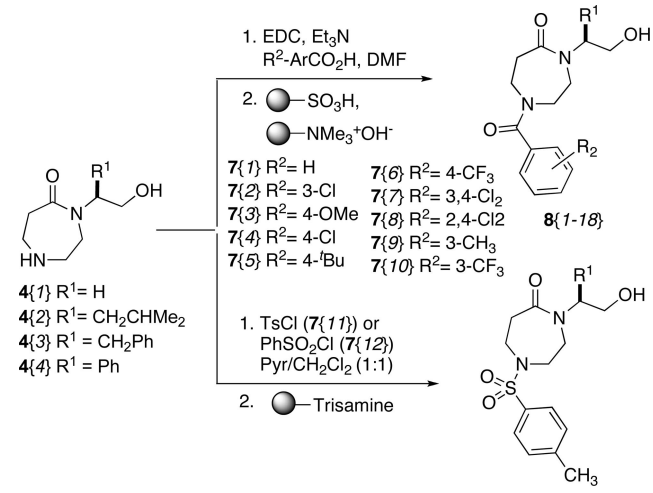


6{1-48}

constructing a straightforward reductive amination library, in which the scaffolds **4** were reacted with twelve various aldehydes **5** using the standard conditions shown in Scheme 2. Upon completion of the reaction, the crude mixtures were treated with 10% TFA/methanol and filtered through an acid resin column to remove excess aldehyde, followed by eluting the reductive amination products with 10% triethylamine/methanol. Further purification was achieved through the use of preparative HPLC. A total of 48 compounds were prepared with unoptimized yields in the range of 7–56% with 46 of the reactions providing material in ≥85% purity (details of all library preparations are provided in Supporting Information).[10]

The secondary amine of **4** was then subjected to acylation using variously substituted benzoic acids **7** in the presence of EDC and triethylamine. Purification was achieved by removing excess EDC and benzoic acid derivatives with Amberlyst 15 and Amberlite 400, providing 18 compounds with purities of ≥85%[10] and yields in the range of 59–89% (Scheme 3). Similarly, the secondary amine of the four *N*-hydroxyethyl-1,4-diazepin-5-ones scaffolds **4** was sulfonylated to provide four more compounds. Upon completion of these reactions, excess sulfonyl chloride was removed using solid-bound trisamine reagent to provide the desired compounds in 65–78% yields and >90% purity.[10] In addition to provision of a set of target compounds, these two

Scheme 3. *N*-Acylation and *N*-Tosylation Libraries



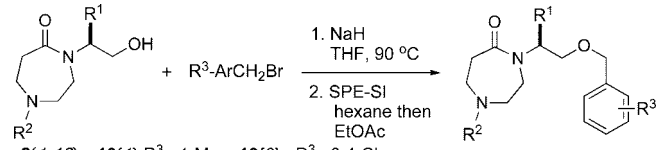
4{*1*} R^1= H
4{*2*} R^1= CH_2CHMe_2
4{*3*} R^1 = CH_2Ph
4{*4*} R^1 = Ph

7{*1*} R^2= H
7{*2*} R^2= 3-Cl
7{*3*} R^2= 4-OMe
7{*4*} R^2= 4-Cl
7{*5*} R^2= 4-^{t}Bu
7{*6*} R^2= 4-CF_3
7{*7*} R^2= 3,4-Cl_2
7{*8*} R^2= 2,4-Cl2
7{*9*} R^2= 3-CH_3
7{*10*} R^2= 3-CF_3

8{*1-18*}

9{*1-4*}

Scheme 4. *O*-Alkylation Library

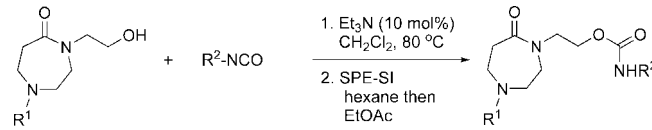


8{*1-18*}
9{*1-4*}

10{*1*} R^3= 4-Me
10{*2*} R^3= 3-Me
10{*3*} R^3= 4-CF_3
10{*4*} R^3= 3-CF_3
10{*5*} R^3= 3-F
10{*6*} R^3= 3-Cl
10{*7*} R^3= 4-OMe
10{*8*} R^3= 4-F
10{*9*} R^3= 3,4-Cl_2
10{*10*} R^3= 3,5-Cl_2
10{*11*} R^3= 2,4-Cl_2
10{*12*} R^3= 2-Me
10{*13*} R^3= H
10{*14*} R^3= 3-OMe
10{*15*} R^3= 4-NO_2
10{*15*} R^3= 4-Cl

11{1-76}

Scheme 5. Carbamate Library



9{*1*} R^1= Ts
3{*3*} R^1= Bn

12{*1*} R^2= 4-Me-C_6H_4
12{*2*} R^2= 4-OMe-C_6H_4
12{*3*} R^2= 4-Ac-C_6H_4
12{*4*} R^2= 2-Me-C_6H_4
12{*5*} R^2= 3,4-Me_2-C_6H_3
12{*6*} R^2= 3-Me-5-I-C_6H_3
12{*7*} R^2= Ph
12{*8*} R^2= 3-CF_3-C_6H_4
12{*9*} R^2= 4-Cl-C_6H_4
12{*10*} R^2= 3-Cl-C_6H_4
12{*11*} R^2= 3-OMe-C_6H_4
12{*12*} R^2= 4-F-C_6H_4
12{*13*} R^2= Cy
12{*14*} R^2= thienyl
12{*15*} R^2= Bn
12{*16*} R^2= CH_2-4-OMe-C_6H_4

13{1-26}

Scheme 6. Three-Component Approach to the Synthesis of 1,4-Diazepin-5-ones

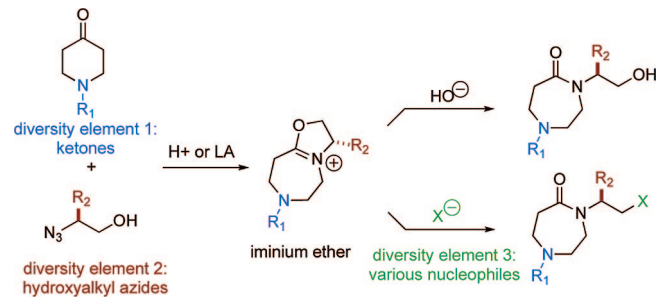
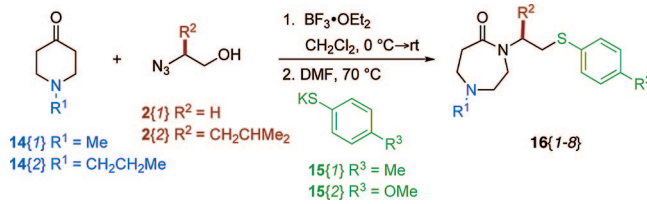


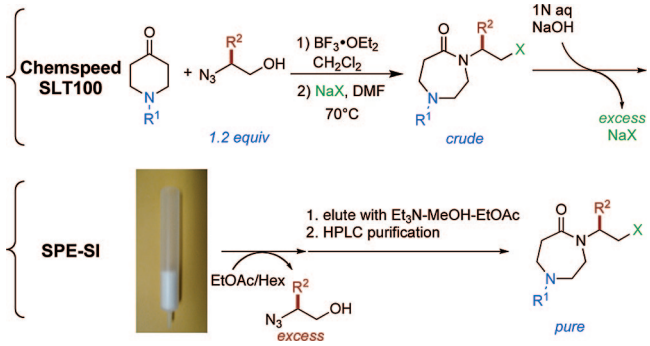
Table 1. Rehearsal 2 × 2 × 2 Library Synthesis of 1,4-Diazepin-5-ones using the Bohdan MiniBlock XT and the Chemspeed SLT100[a]



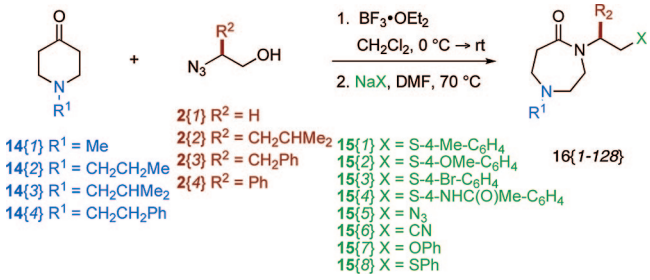
					Bohdan MiniBlock XT		Chemspeed SLT100	
entry	ketone	N_3R	ArSK	product	yield(%)[b]	purity(%)[c]	yield(%)[b]	purity(%)[c]
1	**14**{*1*}	**2**{*1*}	**15**{*1*}	**16**{*1*}	58	100	61	100
2	**14**{*2*}	**2**{*1*}	**15**{*1*}	**16**{*2*}	46	92	49	100
3	**14**{*1*}	**2**{*2*}	**15**{*1*}	**16**{*3*}	38	91	55	100
4	**14**{*2*}	**2**{*2*}	**15**{*1*}	**16**{*4*}	56	99	58	99
5	**14**{*1*}	**2**{*1*}	**15**{*2*}	**16**{*5*}	55	98	56	100
6	**14**{*2*}	**2**{*1*}	**15**{*2*}	**16**{*6*}	57	98	52	100
7	**14**{*1*}	**2**{*2*}	**15**{*2*}	**16**{*7*}	85	99	47	100
8	**14**{*2*}	**2**{*2*}	**15**{*2*}	**16**{*8*}	47	90	52	92

[a] Reaction conditions: $BF_3 \cdot OEt_2$ (4.00 mmol), ketone **14** (0.80 mmol), hydroxyalkyl azides **2** (1.00 mmol), RT, 12 h, then ArSK **15** (2.00 mmol), DMF (2 mL), 70 °C, 24 h. [b] Purified by an automated preparative reverse phase HPLC (detected by mass spectroscopy). [c] Purity was determined by HPLC with peak area (UV) at 214 nm.

Scheme 7. Synthesis and Purification of 1,4-Diazepinon-5-ones Using a Semiautomated Process



Scheme 8. Three-Component Library Synthesis of 1,4-Diazepin-5-ones



sequences also provided *N*-functionalized scaffolds for the preparation of additional libraries (see below).

At this point, we focused our attention toward diversifying the *N*-hydroxyethyl side chains using the sulfonylated and benzoyl products (**8** and **9**) as scaffolds. In the first such library, alkylation of the hydroxyl with benzyl bromides **10** was attempted. Initial experiments revealed that the alkylation could be achieved rapidly (under 1 h) and in good yield when the reaction was performed at elevated temperatures (90 °C) in screwcap vials; these conditions also eliminated the need for a promoter such as sodium iodide (Scheme 4). Upon completion of this reaction, a straightforward prepurification process was performed to remove the relatively nonpolar benzyl bromides from product using solid-phase extraction (SPE-Si), affording the desired alkylated 1,4-diazepin-5-one products with >85% purity[10] and yields in the 45–93% range. Using this protocol, we synthesized a library of 76 compounds.

A library of carbamates was then prepared by the treatment of the 1,4-diazepin-5-one alcohols with various arylisocyanates. This was achieved in screwcap vials using a catalytic amount of triethylamine in methylene chloride solvent at 80 °C (Scheme 5). Upon completion of this reaction, the relatively nonpolar excess phenylisocyanates were removed using solid-phase extraction (SPE-Si), affording the desired alkylated 1,4-diazepin-5-one products with >85% purity[10] and yields in the 38–77% range. Using this protocol, we synthesized a library of 26 compounds.

Altogether, four readily prepared γ-turn nuclei were converted into 172 examples of structurally divergent 1,4-diazepin-5-ones using simple chemistry. Although certainly useful as a demonstration of concept, the full realization of the ring-expansion approach to γ-turn-inspired molecules required a more aggressive approach to subunit incorporation in the 1,4-diazepin-5-one synthesis reaction itself.

Three-Component Synthesis of 1,4-Diazepin-5-ones. As noted above, the primary product in the preparation of *N*-hydroxyethyl-1,4-diazepin-5-ones is an iminium ether, which was hydrolyzed to the corresponding alcohol in all of the above examples. However, iminium ethers are known to react with a variety of nucleophiles.[11] Most stabilized, heteroatom-containing nucleophiles add kinetically but reversibly to the iminium cationic center, ultimately affording a product resulting from S_N2 attack at the *O*-alkyl carbon. We had also previously investigated this electrophilic property in *N*-alkyloxazolinium bicycle ring systems obtained from the reaction of cyclohexanones with hydroxyalkyl azides[9] and recently developed a process which combines the nucleophilic addition step to the ring-expansion reaction in a single pot.[9b] We considered this one-pot reaction to be an attractive platform for library synthesis because it would permit combining the diversification of three different

reaction components, piperidone, hydroxyalkyl azide, and nucleophile, in a single step (Scheme 6).

Four nucleophiles were chosen to maximize the utility of the resulting 1,4-diazepin-5-ones. Aza−Wittig or reductive amination could allow for terminal azide derivatives to be further elaborated to substituted amines, while nitriles have been used as warheads in cysteine protease inhibitors.[12] In addition, substituted phenoxides or thiophenoxides could lead to additional diversity using aryl-substituted versions. The viability of each of these nucleophiles in the iminium ether-opening step has been previously established.[9]

Two related protocols for adapting this reaction to library synthesis were developed. First, a rehearsal 2 × 2 × 2 library was prepared using piperidones **14**{*1*} and **14**{*2*}, hydroxyalkyl azides **2**{*1*} and **2**{*2*}, and substituted thiophenoxides **15**{*1*} and **15**{*2*} (Table 1). The eight reactions were carried out in a Bohdan MiniBlock XT. Upon their completion, excess thiophenoxide was scavenged using polymer-bound phenylisocyanate and excess hydroxyalkyl azide was scavenged using a polymeric triphenylphosphine equivalent.[13] After initial prepurification using SPE-Si, the crude products **16** were subjected to preparative HPLC. Yields in the range of 46–85% were achieved with 90–100% purity (Table 1). The same reactions were repeated using a Chemspeed SLT100 automated synthesizer. The results listed in Table 1 show similar yield (47–61%) and purity ranges (92–100%) when compared to those using the MiniBlock method.

Having established a viable approach for the synthesis of small libraries, we devised a streamlined approach that obviated the need for scavenging agents. Thus, the crude liquids within the individual Chemspeed reactors were washed with 1 N NaOH to remove excess nucleophile as a water-soluble salt. The reactions were removed from the synthesizer and subjected to separation of the relatively nonpolar hydroxyalkyl azide from product using solid-phase extraction (SPE-Si) as shown in Scheme 7. Final purification was performed using preparative HPLC.

Two 4 × 4 × 4 libraries of 1,4-diazepin-5-ones were made using the semiautomated process described (Scheme 8). In one library, the standard nucleophiles used in the method development work were used to provide functional group diversity in the finishing step. For the second, structural diversity was obtained by using four substituted thiophenoxides. In total, we attempted the synthesis of the 128 compounds using the building blocks shown in Scheme 8.

Of the 128 attempted library reactions, 117 reactions provided 1,4-diazepin-5-ones in larger than 20 mg quantities (using 0.400 mmol of piperidone starting material), and 113 reactions provided material with ≥85% purity.[10] In general, higher yields were obtained for reactions using hydroxyalkyl azide **2**{*1*} (R^2 = H), whereas lower yields were obtained for those in which **2**{*4*} (R^2 = Ph) was used, suggesting a possible steric influence on these reactions. The average yields were 43 mg and 30% purity, with purified compounds having an average purity of 92%.

In conclusion, we have successfully demonstrated two approaches to 1,4-diazepin-5-ones library synthesis. In the first, *N*-hydroxyethyl-1,4-diazepin-5-ones were prepared in usable quantities and shown to be viable scaffolds for diversification in a library synthesis format. In the second, a more direct three-component approach to 1,4-diazepin-5-ones from piperidones, hydroxyalkyl azides and various nucleophiles was demonstrated. These experimentally straightforward approaches can be readily adapted to library synthesis using either block technology or an automated synthesizer (the latter of which greatly facilitates iterative library synthesis). In this way, substantial amounts of product pure enough for downstream biological screening were made available. Future efforts will concentrate on targeted libraries and their biological evaluation.

Acknowledgment. Financial support of this work by the Institute of General Medical Sciences is gratefully acknowledged (PO50-GM069663 and P41 GM076302-01).

Supporting Information Available. Experimental procedures, tabulated results for all libraries, and full characterization data for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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