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Synthesis of 3-Alkoxyazetidin-2-ones: Dipeptide Mimics

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Abstract:Several dipeptide mimics, 3-alkoxyazetidin-2-ones, were prepared in a diastereoselective fashion by the direct displacement of a scalemic triflate with 3-hydroxyazetidin-2-ones. The scope and limitation are presented.

An important step in therapeutics design and discovery is the functional minimization of large peptides and proteins or, in other words, the distillation of these large molecules into small functional units (domains). Quite often, the functional domains contain key peptide secondary structures such as reverse turns, α-helices and β-strands. For several years we have been involved in the area of design and synthesis of secondary structure mimetics as therapeutic drugs and as important tools for understanding biological processes.[1]

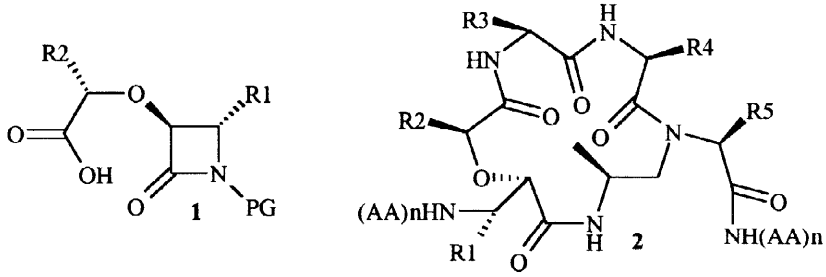

Fig.1 Azetidin-2-one **1** and reverse-turn mimetic **2**

Azetidin-2-ones are key components in our modular synthesis of β-turn and β-bulges mimetics. As a part of a project to explore the role of CTLA-4 (a costimulatory receptor that is expressed on activated T cells) in cellular signaling, we needed access to a series of azetidin-2-ones of the general structure **1** (Fig. 1) for the synthesis of mimetics of generic structure **2** (Fig. 1). 3-Alkoxyazetidin-2-ones are generally accessible via the Staudinger imine-acyl chloride condensation reaction[2] or the ester enolate-imine condensation variant. However, except for a few cases,[3] the reaction works best for imines derived from aromatic, heteroaromatic or allylic aldehydes. In most instances the cis compound is the predominant isomer which is the undesired one in our case.[4] Since we were interested in using stereochemically defined components in our syntheses, we explored alternative

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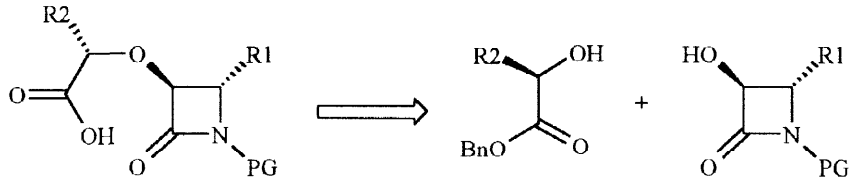
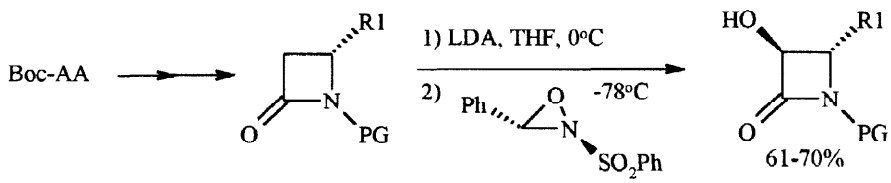
pathways to these azetidin-2-ones. Herein we present a new approach for the synthesis of the dipeptide mimetics 3-alkoxyazetidin-2-ones, **1**, based on the nucleophilic displacement of a triflate with a azetidin-2-one-derived alkoxide. The scope and limitation of this new approach will also be discussed.

Nucleophilic displacement of triflates in a stereoselective or stereospecific fashion has been described in literature.[5] The nucleophiles were either amines, hydroxyl amines or carbon-based nucleophiles. It became apparent to us that alcohols, with adequate activation[6], should also be able to participate in a triflate-displacement reaction to afford ethers (Scheme 1). Indeed, we found that the sodium salt of 3-hydroxyazetidin-2-ones displaces triflates in a diastereoselective fashion to afford the corresponding ethers. 3-Hydroxyazetidin-2-



Scheme 1

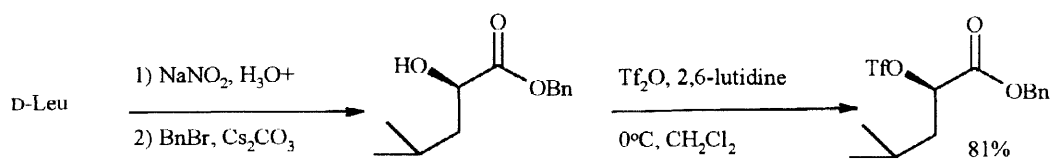
one is prepared from the corresponding azetidin-2-one by treatment of the lithium enolate with trans-2-(phenylsulfonyl)-3-phenyloxaziridine[7] (Scheme 2). The hydroxylation reaction proceeds in good chemical yield (61-70%) and stereochemical control [diastereomeric ratio ranged from 4:1 to 18:1 (trans:cis isomers)].



Scheme 2

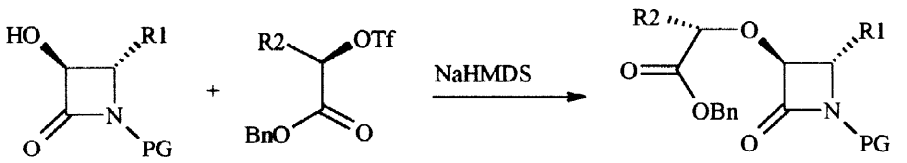
The relative stereochemistry of the 3- and 4-substituents was easily ascertained from the characteristic coupling constant of ~2 Hz for trans substituted azetidin-2-one (cis-substituted azetidin-2-ones have a coupling constant of ~5 Hz).

In general, the hydroxy esters were prepared from the corresponding amino acids. The triflates were easily prepared, quantitatively, from the corresponding alcohols by treatment with triflic anhydride and 2,6-lutidine as shown in Scheme 3.



Scheme 3

The displacement reaction (Scheme 4) was run in THF at -45 to -55 °C to RT using NaHMDS as a base for the deprotonation of the hydroxyl moiety. In every case, 20-30% of starting 3-hydroxyazetidin-2-one was recovered. Subsequent hydrogenolysis of the benzyl ester afforded the TBS protected carboxylic acids.



Scheme 4

Table 1. Displacement of Triflates with 3-Alkoxyazetidin-2-ones

Entry	R1	R2	Yield	Diastereomeric ratio
1	iBu	cyclohexyl	20%	50:50
2	iBu	CH_2CH_2Br	42%	64:36
3	iBu	CH_2-2-benzothiazole	44%	54:46
4	iBu	CH_2-cyclohexyl	40%	90:10
5	iBu	CH_2-2-thiazole	22%	71:29
6	iBu	CH_2-Ph	38%	96:4
7	iBu	Ph	0%	N/A
8	iBu	$CH_2CH_2SCH_3$	0%	N/A
9	H	$CH_2(CH_2)_2CH_2NZ_2$	25%	N/A
10	Me	$CH_2(CH_2)_2CH_3$	54%	98:2
11	Me	trans-$CH_2CHCHCH_3$	41%	75:25
12	Me	$CH_2CH_2SO_2CH_3$	48%	92:8
13	(S)-sBu	(S)-$CH_2CH(CH_3)_2$	44%	98:2
14	(S)-sBu	(R)-$CH_2CH(CH_3)_2$	35%	98:2

For compounds with hydrogenolysis-sensitive functionality, basic hydrolysis was employed. The hydrolysis was accompanied by shedding of the TBS protecting group. The resultant acids were used in the coupling reaction without further purification.

Inspection of Table 1 reveals few trends in this reaction. The unoptimized yields for this transformation ranged from 0% to 54%. The triflates were freshly prepared and were only exposed to aqueous workup protocol. When the triflate was relatively stable the chemical yields were acceptable (entries 2, 3, 4, 6, 10, 11, 12 and 13) however, when the triflate had a weakly nucleophilic moiety associated with it (entries 5 and 8[8]), or was destabilized by the presence of an aromatic ring (entry 7) the yields were low.

The diastereoselectivity of this displacement is very good (in most cases) and is determined by the enantiomeric purity of the hydroxy esters. In the case of simple triflates derived from the corresponding amino acids, the diastereomeric ratio (DR) was excellent (entries 4, 6, 10, 12, 13 and 14). However, in the case of functionalized triflates (entries 3 and 5) or triflates whose origin was not a natural amino acid (entries 1, 2 and 11) the DR was low and reflected the scalemic nature of the corresponding alcohol. The high reactivity of the triflate precludes the side chain from possessing a nucleophilic functionality (entries 5 and 8). In these cases intramolecular substitution and decomposition prevailed.

A new synthesis of an important dipeptide mimetic component was presented. The synthesis is based on the diastereoselective displacement of a triflate with a azetidin-2-one derived alkoxide. The resultant azetidin-2-

one ethers were used in the construction of turn-bulges library. The synthesis of this library and the bioassay results will be discussed elsewhere.

Acknowledgments:

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3) For example see, Palomo, C.; Aizpurua, J. M.; Cabre, F.; Cuevas, C.; Munt, S.; Odriozola, J. M. *Tetrahedron Lett.* **1994**, *35*, 2725.

4) For an exception see, Endo, M.; Droghini, R. *Bioorg. Med. Chem. Lett.* **1993**, *1*, 2483.

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7) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org Syn* **1987**, *66*, 203.

8) This compound was prepared via a different route, for details see Kim, H.-O.; Lum, C.; Lee, M. S. *Tetrahedron Lett.* **1997**, *38*, 4935.