Tetrahedron Letters, Vol. 34, No. 41, pp. 6513-6516, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A CONVENIENT SYNTHESIS OF CHIRAL *N*-BOC-AMINO ETHERS AS POTENTIAL PEPTIDE BOND SURROGATE UNITS

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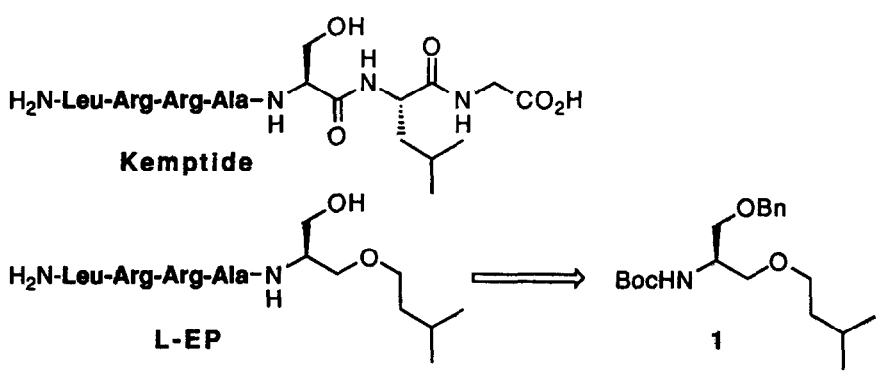
Abstract: *Boron trifluoride etherate and zinc triflate have been found to be effective catalysts for the synthetic route to chiral N-Boc-amino ethers via a Lewis acid-catalyzed ring-opening of N-acyl aziridines, derived from chiral amino acids.*

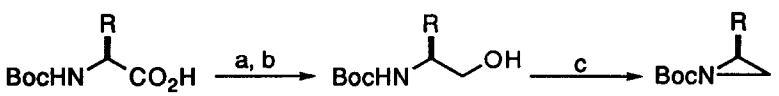
Peptide analogs containing ether-based peptide bond surrogate units have not been widely considered as a favorable approach for designing peptide antagonists, and there have been few reports on the synthesis of ether-containing peptides.[1,2,3] However, the use of ether-containing peptide analogs as potential pharmaceuticals warrants further consideration, because they could provide desirable drug properties, such as oral stability, protease resistance and dual solubility in aqueous and lipid environments. The latter property may potentially be of great value in the uptake of the peptide analogs into cells. Roubini et al.[1] has pointed out that there is some resemblance between the back bone of a polyethylene glycol and a polypeptide, although the polyether chain has a greater rotational freedom about the C-C-O-C bond than the corresponding amide bond of the polypeptide chain (2.7 kcal/mol vs. 21 kcal/mol). In cases where the amide is not involved in hydrogen bond, this conformational freedom may be beneficial for ether-based peptide analogs to achieve an optimal binding conformation at the enzyme active site. In our studies on the synthesis of an ether-based analog (**L-EP**) of Kemptide, a known substrate of cAMP-dependent protein kinase, we have found a convenient method for the preparation of chiral *N*-Boc-amino ethers, such as **1**, from chiral *N*-Boc-α-amino acids.



Existing procedures for the synthesis of ether-based peptide surrogate units have been based on Williamson's ether synthesis,[1,2,3] although a procedure using diazoacetate as the *O*-alkylating agent[4] has also been reported. For the purpose of synthesizing peptide analogs, these methods have limited utility due to the uncertainty of preserving chiral centers and side-chain functionalities. We have developed an alternative procedure based on a Lewis acid-catalyzed aziridine ring-opening. The attraction of this approach is that the aziridine intermediate can be prepared from a large pool of commercially available chiral α-amino acids and that only mild conditions are required for the ring-opening reaction.

As summarized in Table 1, several *N*-Boc-amino acids can readily be converted into *N*-Boc-amino alcohols via sodium borohydride reduction of their mixed anhydrides. We have found, contrary to published procedures, that this reduction step can be completed in one hour.[5] Although it had been suggested that the acidic component of the Mitsunobu reaction should have a $pK_a \leq 13$,[6] there are precedents for aziridine formation from an *N*-Boc-amino alcohol moiety under Mitsunobu's conditions.[7,8] We found that cyclization of *N*-Boc-amino alcohols **4a-4d** derived from the corresponding chiral α-amino acids **3a-3d** can be achieved with 1.2 to 1.5 equivalents of Mitsunobu's reagent using either THF or $CHCl_3$ as the solvent at 0°C to r.t. in two hours. We did not detect formation of oxazoline byproducts in this cyclization. Similar finding has been reported in β-lactam formation under the Mitsunobu's conditions[9] where oxazoline formation occurred only with a normal acylamino substituent, but not with a carbamate. This procedure for *N*-Boc-aziridine formation is compatible with not only aliphatic side chains but also ether and ester functionalities. The cyclization product of *N*-Boc-alaninol **4f** was too volatile to be easily handled or purified, and the glutamine-derived alcohol **4e** gave an unstable product, presumably **5e**, which gradually cyclized to a lactone (see discussion below) during the chromatographic purification process.

Table 1. Conversion of *N*-Boc-amino acids into *N*-Boc-aziridines.

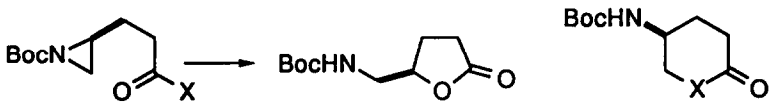


3a R=CH_2OBn	**4a** (98%, oil)	**5a** (73%, oil)
3b R=$CH_2CH_2CO_2Bn$	**4b** (75%, m.p. 76-77°C)	**5b** (74%, oil)
3c R=$CH_2CH_2CH(CH_3)_2$	**4c** (82%, oil)	**5c** (82%, oil)
3d R=$CH_2C_6H_5$	**4d** (93%, m.p. 95-96°C)	**5d** (86%, oil)
3e R=$CH_2CH_2CONH_2$	**4e** (83%, m.p. 117-118°C)	**5e** N.D.[d]
3f R=CH_3	**4f** (87%, m.p. 59-60°C)	**5f** N.D.

[a] i-BuOCOCl, Et_3N, THF, -10°C. [b] $NaBH_4$, H_2O. [c] Ph_3P, DEAD, THF or $CHCl_3$.
[d] Yields not determined.

BF_3·etherate catalyzed ring-opening of *N*-acylaziridinecarboxylates has been known to be an effective method for introducing nucleophiles into the β-position of α-amino acids.[10,11,12] We found that in the presence of BF_3·etherate, *N*-acyl aziridine **5a** can undergo ring-opening by the attack of isoamyl alcohol,

even without a carboxylate group present to activate the aziridine ring and to direct the regioselectivity of nucleophile attack. Two products, **1** and **2**, were obtained in a ratio of 3 : 2 corresponding to C-1 and C-2 attack. The stereochemistry of **2** has been tentatively assigned assuming that the ring-opening proceeded with inversion of the configuration. As shown, when the glutamate-derived *N*-Boc-aziridine **5b** was subjected to similar conditions (method A), no ether product was observed. By NMR analysis the major product from **5b** was found to be identical with the cyclization product that occurred during the purification process after cyclization of glutaminol **4e**. Elemental analysis ruled out the possibility of a δ-lactam product **7**, and suggested the product could be a lactone, either **6** or **8**. ^{1}H NMR COSY confirmed it to be the γ-lactone **6**.



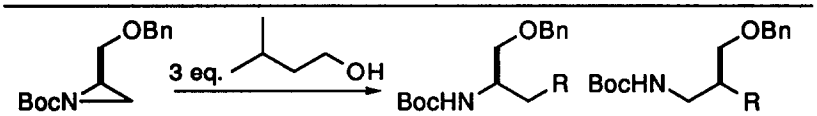
5e X=NH_2
5b X=OBn

6

7 X=NH
8 X=O

We have also investigated other Lewis acids as catalysts for *N*-Boc-aziridine ring-opening. Zinc chloride has been used effectively in catalyzing glycosidic bond formation via an epoxide ring-opening.[13] With zinc chloride as the catalyst, we found that the two major products from ring-opening of **5a** were the chlorides **9** and **10**, albeit with an improved selectivity (5 : 1) for C-1 attack. This suggested that other Lewis acids with non-nucleophilic ligands might be good candidates for our purpose. Titanium (IV) isopropoxide was found to be totally ineffective. Zinc triflate has been used to catalyze the ring-opening of *N*-acyl aziridinecarboxylates by indole nucleophiles.[11] It turned out that $Zn(OTf)_2$ also catalyzed the ring-opening of **5a** to form **1** and **2** in a ratio similar to that of BF_3-catalyzed reaction (see Table 2). This suggested that the ring-opening of *N*-acyl aziridine proceeds, with S_N1 characteristics in the presence of alcohol nucleophiles, through a common intermediate either with BF_3 or $Zn(OTf)_2$ as the catalyst. A notable advantage for using $Zn(OTf)_2$ is that less than stoichiometric amounts of catalyst are needed[14] and the rigorous effort in excluding moisture associated with the use of BF_3-etherate can be avoided.

Table 2. Ring-Opening of *(2R)*-*N*-Boc-2-benzoxymethylaziridine.



5a

Method A[a]	R=$OCH_2CH_2CH(CH_3)_2$	**1**(49%)	**2**(32%)
Method B[b]	R=Cl	**9**(58%)	**10**(11%)
Method C[c]	R=$OCH_2CH_2CH(CH_3)_2$	**1**(31%)	**2**(22%)

[a] Method A: 0.5% BF_3·Et_2O in $CHCl_3$, r.t., 3 hr. [b] Method B: 2 eq. $ZnCl_2$ in $CHCl_3$, r.t., 2.5 hr. [c] Method C: 0.2 eq. $Zn(OTf)_2$ in $CHCl_3$, r.t., 20 hr.

Our synthesis of chiral *N*-Boc-amino ethers could be used as a convenient alternative to the existing procedures for ether-containing peptide bond surrogate units. The versatility of this method also allows the introduction of a variety of chiral 1,3-dialkoxy-2-amino-propanes, for instance potentially as inhibitors of phospholipase A_2.[15]

Acknowledgment is made to the American Association of Colleges of Pharmacy and the American Heart Association, New York State Affiliate for support of this research, to Dr. A. J. Solo for his helpful comments and to Ms. Weiheng Wang for her technical assistance.

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(Received in USA 7 July 1993; accepted 16 August 1993)