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Epoxide opening with amino acids: improved synthesis of hydroxyethylamine dipeptide isosteres

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Abstract—The amino acid opening of epoxides, catalyzed by calcium trifluoromethanesulfonate with short reaction times is described. The method can be used in a straightforward route for the preparation of hydroxyethylamine dipeptide isosteres.

Proteases are peptide bond cleaving enzymes that control protein synthesis, turnover and function. The inhibition of proteases has found numerous therapeutic applications, including the treatment of high blood pressure, stroke and AIDS.[1,2] Reactions catalyzed by proteases proceed via a tetrahedral transition-state, which results from nucleophilic attack by a water molecule on the peptide bond carbonyl group. Different functional groups can mimic this transition state by their tetrahedral geometry and charge distribution, leading to potent transition-state analogue enzyme inhibitors. Phosphinates,[3] statines,[4] hydroxyethylenes,[5] hydroxyethylamines[6] and many other types[2,7] of protease inhibitor have been developed using this concept.

We focused our attention on the hydroxyethylamine (HEA) isostere (Fig. 1), which is the fundamental moiety utilized in inhibitors of renin,[7] HIV protease,[8] angiotensin converting enzyme[9] and malarial proteases.[10] Different synthetic approaches for the preparation of HEA isosteres have been described. Although the most straightforward synthetic route appears to be the ring opening of the appropriate epoxide by an amino acid, in the majority of reported methods epoxides were not used.[8,11,12] They were used in the synthesis of HEA isosteres only in reactions with secondary amines, which have a higher nucleophilicity than amino acids.[13] Typically, direct ring opening of epoxides using C-protected amino acids is achieved by using an excess of the amine, high temperatures and prolonged reaction times.[14–24] For example, Erhardt et al. opened the epoxides with ethyl glycinate in refluxing ethanol with only 8% yield.[14] The yield was improved to 43% by reaction in refluxing dimethoxyethane,[23] however, the presence of a catalyst such as $LiClO_4$ did not further improve the yields of this interesting reaction.[17]

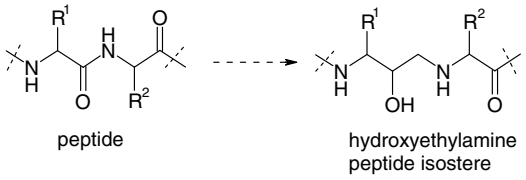

Figure 1. Hydroxyethylamine peptide isostere.

In our hands, these procedures gave yields that were too low and irreproducible to be used in the early steps of complex syntheses of enzyme inhibitors. We therefore sought an improved synthetic route to the HEA dipeptide isostere mimetics that would be generally applicable to the preparation of transition-state analogue enzyme inhibitors. A number of catalysts have been published for epoxide ring opening with different aliphatic and aromatic amines.[25] In this letter we report the application of calcium trifluoromethanesulfonate ($Ca(OTf)_2$) as a catalyst for epoxide ring opening by carboxyl-protected amino acids, which provides higher yields and the shortest reaction times reported so far.

Keywords: Proteases; Hydroxyethylamine dipeptide isosteres; Aminolysis; Calcium trifluoromethanesulfonate; Epoxides; Peptidomimetics.
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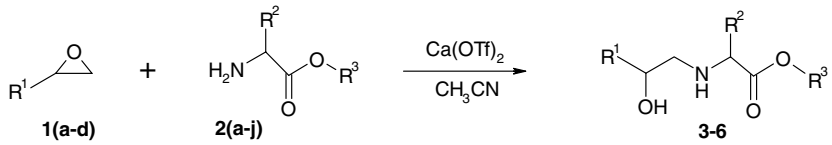

Scheme 1. Calcium trifluoromethanesulfonate catalyzed opening of epoxides with C-protected amino acids.

In order to test the general applicability of our reaction, a series of HEA dipeptide mimetics (**3**–**6**, Scheme 1) was synthesized from various amino acid esters **2**(**a**–**j**) and epoxides **1**(**a**–**d**). The reaction was optimized with respect to solvent, reaction time and temperature. Given the reaction type and solubility problems, it is not surprising that only a few solvents were found to be appropriate. Using the most commonly reported solvent, methanol,[15,16,20,24] transesterification occurred to a large extent whenever amino acid esters other than methyl were used as starting compounds. Acetonitrile led to the smallest amounts of side products and to moderate to high yields. The yields were highly dependent on the reaction time and temperature. At low temperatures and long reaction times only small amounts of the desired products were obtained. On the other hand, at refluxing temperatures and prolonged reaction times more side products were observed.

In a typical procedure, 2 mmol of the amino acid ester, 1 mmol of epoxide and 0.5 mmol of $Ca(OTf)_2$ were suspended in 15 ml of acetonitrile and refluxed for 4 h. After cooling to room temperature, the catalyst was removed by filtration and the solvent was removed under reduced pressure, giving a crude product, which was purified by circular chromatography.

The starting epoxides **1**(**a**–**d**), protected amino acids **2**(**a**–**j**), products **3**–**6** and final yields are listed in Table 1. The reaction can be used with different protected epoxides and amino acid esters, since yields were satisfactory regardless of the type of protection used. The products were fully characterized by IR, MS and NMR (^{1}H, HMQC, COSY) spectroscopy.[30] NMR spectra indicated that in reactions where racemic epoxides **1**(**a**–**d**) and enantiomerically pure amino acid esters were used as starting compounds, the products were equimolar mixtures of two diastereoisomers. In cases where racemic amino acid esters were used, the products were equimolar mixtures of four diastereoisomers (products **4d**, **4e** and **5a**). The reaction was also shown by NMR to be highly regioselective, giving only the desired products.

In conclusion, a direct and efficient synthetic method is presented for the preparation of HEA dipeptide isosteres from amino acid esters and epoxides. The method offers many advantages over the previously reported procedures for the synthesis: fewer reaction steps are involved, reaction times are shorter and yields are higher. The use of this method in the multi-step synthesis of complex HEA transition-state analogue inhibitors is currently underway in our laboratories and will be published in due course.

Acknowledgements

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Table 1. Hydroxyethylamine dipeptide isosteres obtained via Scheme 1

Entry	Epoxide (R^1)	Protected amino acid (R^2, R^3)	Product	Yield[a] (%)
1	$PhOCH_2$ (**1a**)	CH_3, Bn (L-Ala) (**2a**)	**3a**	61
2		CH_3, Et (L-Ala) (**2b**)	**3b**	68
3		CH_3, *t*-Bu (L-Ala) (**2c**)	**3c**	54
4		CH_2Ph, Me (L-Phe) (**2d**)	**3d**	65
5		$CH(CH_3)_2$, Bn (L-Val) (**2e**)	**3e**	76
6	$PhtCH_2$ (**1b**)[b]	H, Bn (Gly) (**2f**)	**4a**	52
7		CH_3, Bn (L-Ala) (**2a**)	**4b**	74
8		$CH(CH_3)_2$, Bn (L-Val) (**2e**)	**4c**	63
9		$(CH_2)_2SCH_3$, Et (D,L-Met) (**2g**)	**4d**	72
10		$(CH_2)_2SCH_3$, Bn (D,L-Met) (**2h**)	**4e**	67
11		CH_2Ph, Et (L-Phe) (**2i**)	**4f**	62
12		CH_3, *t*-Bu (L-Ala) (**2c**)	**4g**	61
13	$PhtCH_2CH_2O$ (**1c**)[b,c]	$(CH_2)_2SCH_3$, Et (D,L-Met) (**2g**)	**5a**	71
14		CH_3, Bn (D-Ala) (**2j**)	**5b**	53
15	$Bn_2NCH(CH_3)$ (**1d**)[d]	CH_3, Bn (L-Ala) (**2a**)	**6**	77

[a] Refers to yields of isolated diastereoisomeric mixtures after circular chromatography.
[b] Pht = Phthalimido group.
[c] **1c** was synthesized according to reported procedures.[26,27]
[d] **1d** was synthesized according to reported procedures.[28,29]

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30. Representative examples. Compound **3c**: white solid; mp 60–65 °C; IR (KBr, cm^{-1}): 3286, 2980, 1726, 1600, 1499, 1369, 1253, 1160, 1081, 851, 759, 694; ^1H NMR (300 MHz, $CDCl_3$): (two diastereoisomers)* δ (ppm) = 1.29 (1.30)* (d+d, 3H, $J = 7.0$ Hz, CH_3), 1.49 (s, 9H, $3 \times CH_3$), 1.98 (br s, 1H, OH), 2.64 (2.85)* (dd+dd, 1H, $J = 12.2$, 7.2 Hz, CH_aCH), 2.76 (2.98)* (dd+dd, 1H, $J = 12.2$, 3.7 Hz, CH_bCH), 3.25 (3.26)* (q+q, 1H, $J = 7.0$ Hz, CH–COO), 3.93–4.09 (m, 3H, O–CH_2–CH), 6.88–7.02 (m, 3H, Ph–H), 7.25–7.34 (m, 2H, Ph–H); MS (EI) *m/z*: 296 $(MH)^+$; MS (FAB) *m/z*: 296 $(MH)^+$; HRMS calcd for $C_{16}H_{26}NO_4$ *m/z*: 296.186184 $(MH)^+$, found 296.187020. Compound **4c**: colourless oil; IR (NaCl, cm^{-1}): 3470, 2961, 1773, 1714, 1467, 1395, 1154, 1031, 725; ^1H NMR (300 MHz, $CDCl_3$): (two diastereoisomers)* $\delta = 0.89$–0.95 (*m*, 6H, $CH(CH_3)_2$), 1.60 (br s, 1H, OH), 1.97 (m, 1H, CH), 2.37 (2.71)* (dd+dd, 1H, $J =$ 12.5, 7.3 Hz, CH_aCH), 2.53 (2.89)* (dd+dd, 1H, $J = 12.4$, 3.8 Hz, CH_bCH), 3.04 (dd, 1H, $J = 5.9$, 3.0 Hz, CH–COO), 3.21 (br s, 1H, NH), 3.67–3.81 (m, 2H, CH_2Pht), 3.85–3.93 (m, 1H, CHOH), 5.15 (s, 2H, CH_2–Ph), 7.30–7.36 (m, 5H, Ph–H), 7.70–7.73 (m, 2H, Pht–H), 7.84–7.87 (m, 2H, Pht–H) ppm; MS (EI) *m/z*: 411 $(MH)^+$; MS (FAB) *m/z*: 411 $(MH)^+$; HRMS calcd for $C_{23}H_{27}N_2O_5$ *m/z*: $(MH)^+$ 411.191997, found 411.193150.