Non Lewis acid catalysed epoxide ring opening with amino acid esters†

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The ring opening of epoxides by various amino acid esters is described in refluxing trifluoroethanol without any catalyst. Under these simple conditions the corresponding β-amino alcohols are obtained in good to excellent yields in relatively short reaction times compared to previously reported methods.

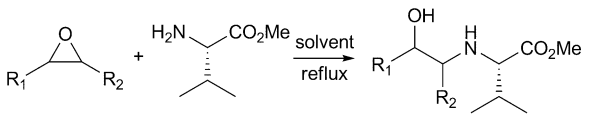
The direct ring opening of epoxides with amino acids should be the most straightforward synthetic route to functionalised peptidomimetics, in particular to hydroxyethylamine peptide isosteres which are widely exploited in the design of potent protease inhibitors.[1] However, this reaction is not very efficient due to the low nucleophilicity of amino acids. According to the scale of nucleophilicity reported by Mayr *et al.*,[2] the reactivity of amino acids towards epoxides is expected to be comparable to that of aromatic amines and thus to require an activator. Indeed, without any catalyst, β-amino alcohols were reported to be obtained in very low yields (8–14%).[3] To improve the reaction, the use of Lewis acids (Al_2O_3,[4] $Yb(OTf)_3$[5] or $LiClO_4$[6]), excess of reactants, or other activation such as microwave irradiation is required.[7] Despite these successful examples, drawbacks such as prolonged reaction times and moderate yields still remain, depending on the substrate. This indicates that there are no efficient general conditions for the success of the reaction. To our knowledge, only one preparative systematic study involving substoichiometric quantities of $Ca(OTf)_2$ in hot acetonitrile has been reported with terminal oxiranes.[8]

Recently, efficient ring opening of oxiranes with amines has been reported in protic solvents without any catalyst. For example, aliphatic amines react easily in water[9] while aromatic amines have been proved to be more reactive with oxiranes in fluoro alcohols as solvents.[10] In connection with this, we now report the successful opening of epoxides with a variety of amino acids in trifluoroethanol.

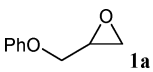
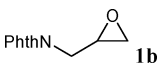
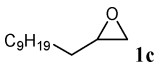
First of all, the evaluation of the effect of various protic solvents has been performed with the phenoxymethyl oxirane **1a** and the L-valine methyl ester.‡ The reaction was conducted at reflux with 2 eq. of valine and prolonged until disappearance of the epoxide. Performing the reaction in water did not result in the formation of the β-amino alcohol **2a** (Table 1, entry 1). The same reaction was then carried out in ethanol and methanol: the desired compound was obtained in good yields after around 2 h as a 1:1 mixture of two diastereoisomers (Table 1, entries 2 and 3). Our efforts were then focused on fluoro alcohols. As strong H-bond donors, the latter can be activators of oxirane opening with weak nucleophiles[10] while with strong nucleophiles, they form complexes,[11] thus inhibiting the reaction. The ring opening of **1a** in refluxing hexafluoroisopropanol (HFIP, b.p. = 58 °C) resulted in the formation of the β-amino alcohol **2a** isolated in good yield (77%) after only 10 min (Table 1, entry 4). A similar result was obtained in refluxing trifluoroethanol (TFE, b.p. = 78 °C), with a higher yield (92%). The reaction time was considerably increased when the reaction was performed at room temperature (Table 1, entry 6). The reaction could also be achieved at reflux with only 1 eq. of amino acid (Table 1, entry 7) but with a lower isolated yield (73%). In all solvents, a complete regioselectivity was observed, leading to the β-amino alcohol corresponding to the nucleophilic attack at the less hindered carbon of the epoxide.

From these results, clearly amino acids are not so reactive as aliphatic amines since the reaction failed in water. Nevertheless amino acids exhibit a better reactivity than aromatic amines that

Table 1 Ring opening of mono and disubstituted epoxides with L-H-Val-OMe in protic solvents



1a-d **2a-d**

Entry	Epoxide **1**	Solvent	Time	Product (yield[a] [%])
1	 **1a**	H_2O	—	**2a** (0)
2		EtOH	2 h	(97)
3		MeOH	2.5 h	(89)
4		HFIP	10 min	(77)
5		TFE	10 min	(92)
6		TFE (r.t.)	18 h	(87)
7		TFE	2 h[b]	(73)
8	 **1b**	TFE	1 h	**2b** (82)
9		EtOH	5.5 h	(85)
10	 **1c**	TFE	3 h	**2c** (96)
11		EtOH	24 h	(88)
12	 **1d**	TFE	18 h	**2d** (64)
13		EtOH	48 h	(36)
14		HFIP	18 h	(60)
15		*i*PrOH	48 h	(14)

[a] Isolated yields, 1:1 mixture of 2 diastereoisomers. [b] Reaction carried out with 1 eq. of amino acid.

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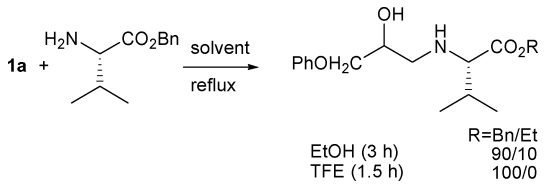
† Electronic supplementary information (ESI) available: Experimental procedure and characterization data (^1H, ^{13}C NMR and MS) of the products **2a–12b**. See DOI: 10.1039/b902081k

usually hardly react with oxiranes at refluxing EtOH and TFE.[10a] The latter appeared to be the best solvent for the reaction, in combined terms of reaction time and yield. Furthermore, due to its poor nucleophilicity, TFE is not prone to be involved in a transesterification reaction. This has been demonstrated by performing the reaction with the L-valine benzyl ester: no transesterification occurred in refluxing TFE whereas 10% of transesterification was observed after 3 h in ethanol at reflux (Scheme 1).



Scheme 1 Ring opening with L-H-Val-OBn.

The efficiency of these conditions (2 eq. of amino acid in refluxing TFE) was then evaluated with different epoxides: the phthalimide *N*-protected epoxide **1b** for an access to peptidomimetics, the decyl epoxide **1c** as a lipophilic substrate and the cyclopentyl epoxide **1d** for an example of 1,2-disubstituted epoxide. With **1b** and **1c**, corresponding β-amino alcohols **2b** and **2c** were obtained in high yield after 1 h and 3 h respectively (Table 1, entries 8 and 10). With the disubstituted epoxide **1d**, the reaction was more difficult and required 18 h to yield 64% of **2d** (entry 12). Taking into account our previous results on facile disubstituted epoxides ring opening with anilines in HFIP,[10a,12] the reaction was carried out in refluxing HFIP (Table 1, entry 14). Surprisingly, no improvement was observed.

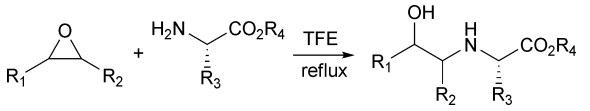
In all cases, the beneficial effect of TFE compared to EtOH was again observed[13] and is particularly crucial for the disubstituted epoxide **1d** (only 36% yield in EtOH after 48 h). To our knowledge the ring opening of 1,2-disubstituted oxiranes with amino acids had not been previously reported except when an activated substituent was present.[6a]

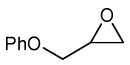
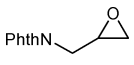
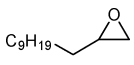
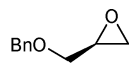
The reaction was then extended to various amino acids by choosing TFE as solvent. In all cases, 2 eq. of enantiopure C-protected amino acids were used. The results are summarized in Table 2.

With **1a–c**, the reaction was successful whatever the side chain and the protection of amino acids were, except with glycine. In most cases, reactions were complete within less than 2 h. Functionalised amino acids such as protected tyrosine or aspartic acid were also reactive under these uncatalysed conditions (entries 3 and 11). Interestingly, the reaction also gave rise to corresponding β-amino alcohols from the disubstituted epoxide **1d** albeit in a lower yield. When long reaction times were needed, no transesterification was observed using the benzyl, *t*-butyl, methyl or ethyl ester of the amino acids. No racemization occurred by treating the enantiopure epoxide **1e** with a chiral amino acid, since in this case only one product was formed (Table 2, entry 18).

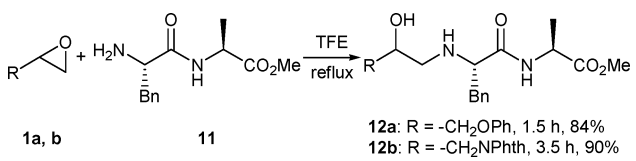
As an example for an access to more elaborated peptidomimetics, the ring opening of **1a** and **1b** was also investigated with the dipeptide **11** in refluxing TFE, and led to the corresponding β-peptidyl alcohol derivatives **12a**,**b** in good yields and within reasonable reaction times (Scheme 2).

Table 2 Reactions of epoxides with various amino acids at refluxing TFE



Entry	Epoxide **1**	Amino acid	Time	Product (yield [%])[a]
1	 **1a**	L-H-Val-OMe	10 min	**2a** (92)
2		L-H-Val-OBn	1.5 h	**3a** (92)
3		L-H-Tyr(Bn)-OMe	1.5 h	**4a** (96)
4		L-H-Leu-O*t*Bu	10 min	**5a** (92)
5		L-H-Phe-OMe	45 min	**6a** (85)
6		H-Gly-OEt	24 h[b]	**7a** (54)
7	 **1b**	L-H-Val-OMe	1 h	**2b** (82)
8		H-Gly-OEt	1 h	**7b** (52)
9		L-H-Phe-OBn	2 h	**8b** (72)
10		L-H-Ile-OBn	1.5 h	**9b** (83)
11		L-H-Asp(OMe)-OMe	3.5 h	**10b** (68)
12	 **1c**	L-H-Val-OMe	3 h	**2c** (96)
13		L-H-Val-OBn	4 h	**3c** (78)
14		L-H-Leu-O*t*Bu	2.5 h	**5c** (90)
15	 **1d**	L-H-Val-OMe	18 h	**2d** (64)
16		L-H-Val-OBn	18 h	**3d** (54)
17		L-H-Ile-OBn	18 h	**9d** (79)
18	 **1e**	L-H-Val-OMe	45 min	**2e** (80)[c]

[a] Isolated yields, 1:1 mixture of 2 diastereoisomers. [b] Carried out at room temperature. [c] Only one diastereoisomer.



Scheme 2 Reaction of epoxides **1a** and **1b** with the dipeptide **11**.

We have demonstrated that trifluoroethanol is a highly efficient solvent for the direct epoxide ring opening with amino acids, leading to the corresponding β-amino alcohols in high yields and total regioselectivity. The reaction could be generalised to various amino acids and structural patterns of epoxides, including 1,2-disubstituted ones. Our results clearly show the advantageous effect of TFE. Compared with previously reported methods, significant improvements were achieved: simple reaction conditions, no need for catalyst or Lewis acid, reasonable reaction times, increased yields and no by-product.

These conditions are very attractive for the synthesis of hydroxyethylamine scaffolds which are widely used as transition-state protease inhibitors.

Acknowledgements

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Notes and references

‡ A typical procedure is as follows (Table 1, entry 5): L-H-Val-OMe·HCl salt (1.5 mmol, 0.251 g) and K_2CO_3 (2.5 mmol, 0.345 g) were suspended in water (3 mL). The free amino acid was extracted with diethyl ether (3 × 15 mL). The organic phase was then dried with $MgSO_4$ and concentrated under reduced pressure at ambient temperature. The free amino acid (0.76 mmol, 0.099 g) was immediately diluted in 1.25 mL of trifluoroethanol. Then, epoxide **1a** (0.38 mmol, 0.058 g) was added. The reaction mixture was stirred at reflux until the disappearance of the epoxide (monitored by TLC). After 10 min of heating, the reaction medium was concentrated under reduced pressure and the resulting oil was then purified by chromatography on silica gel (cyclohexane/AcOEt : 8/2). The product **2a** (0.098 g, 92%) was obtained as a colourless oil, as a mixture of two diastereoisomers in a 1:1 ratio.

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11 J. F. Berrien, M. Ourévitch, G. Morgant, N. E. Ghermani, B. Crousse and D. Bonnet-Delpon, *J. Fluorine Chem.*, 2007, **128**, 839.

12 Reaction of 1.1 eq. of aniline with cyclopentene oxide in refluxing HFIP afforded after 9 hours the corresponding β-amino alcohol in 88% yield.

13 For another comparison between EtOH and TFE, the reaction was performed in refluxing EtOH and was quenched after the time required for completion in refluxing TFE. Product, **2a** was isolated in 34% after 10 min; product **2b** in 56% after 1 hour; product **2c** in 39% after 3 hours.

