Amino Acid Derived Epoxide Ring Opening under Microwave Irradiation

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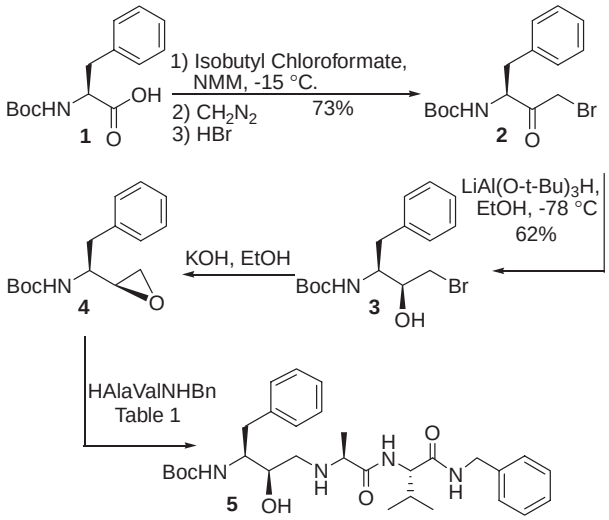
A solvent-free microwave-assisted methodology for the obtainment of the hydroxyethylamine (HEA) isostere is described. A phenylalanine derived aminoalkyl epoxide is allowed to react with a dipeptide amine using basic alumina partially deactivated with water under microwave irradiation. The HEA is obtained in very short time (3 min). This methodology is amenable to application in a parallel or automatic sequential format.

Hydroxyethylamine (HEA) transition state analogues have been widely exploited in the design of potent protease inhibitors,[1–5] in virtue of its capability of mimicking the tetrahedral intermediate that leads to the cleavage of amide bonds.[6] The synthetic stereoselective methods generally employed for the obtainment of the HEA isostere employ the opening of the corresponding protected aminoalkyl epoxide with amines under base-catalyzed conditions.[4,7] Best results are obtained with soluble low molecular weight amines while peptidic or high molecular weight amines react more difficultly, because of the scarce solubility that prevents the use of large excess.[8] Furthermore, erythro epoxides are less prone towards reaction compared to threo stereoisomers and often do not lead to the hydroxyethylamine isoster.[9] Tucker and co-workers[8] have attempted the opening of phenylalanine derived erythro epoxide **4** with a peptidic amine using several conditions (metal salt catalysis, Lewis acid catalysis, heating in protic solvents), but none succeed in providing the desired product. The same authors described a modification of the procedure by Posner and Rogers[10] using basic alumina partially unactivated by water and in this case the product was obtained with low to moderate yields (15–40%) and long reaction times (24–48 h). In the course of our studies on BACE inhibitors we met similar difficulties in the opening of the phenylalanine derived epoxide **4** with a peptide derived amine (HAlaValNHBn). In fact by using conventional conditions (Table 1, Entry A) the HEA compound **5** could not be isolated, instead by applying Tucker's procedure (Entry C) the final product was isolated in moderate yields, but reaction time was quite long (48 h). The synthetic pathway used to prepare erythro epoxide **4** is outlined in Scheme 1. Boc-phenylalanine (**1**) was transformed by treatment with isobutylchloroformate and diazomethane in the correspondent diazomethylketone, which successively was transformed in bromomethylketone **2** as described by Rotella.[11] Bromomethylketone **2** was subsequently reduced stereoselectively to (*S*,*S*)-bromohydrin **3** with $LiAl(O\text{-}t\text{-}Bu)_3H$ in EtOH at −78 °C, as described by Hoffman et al.[12] The stereochemical outcome of the reaction was determined by ^1H NMR.[13] Finally the erythro epoxide **4** was obtained by treatment of bromohydrin **3** with ethanolic KOH.[11]

Microwaves technology offers several advantages: first of all reaction times are reduced from hours to minutes, compared with that necessary using conventional heating; furthermore microwaves heating minimize collateral reactions and can be easily adapted to a parallel or automatic sequential format commonly applied in the process of drug-discovery.[14,15]



Scheme 1.

Recently, the opening of alkyl epoxides with anilines[16] or protected amino acids[17] has been obtained under microwaves irradiation using a Lewis acid catalyst improving yields and reaction times. The opening of amino acids derived epoxides by application of microwaves irradiation under basic catalysis has not yet been reported and in view of the failure in the obtainment of product **5** (Table 1, Entry A) by conventional heating, microwaves irradiation was attempted. Yet in this case, to our disappointment, the product was not obtained (Entry B); instead by using microwaves irradiation and Tucker's conditions (Entry D) at 80 °C complete disappearance of starting material was obtained after 45 min and after silica-gel chromatography and digestion, the final product was isolated in 32% yields

Table 1. Summary of reaction conditions and yields

Entry	Catalyst and Solvent	Temperature	Time	Yields[a]
A	TEA, *i*-PrOH	65 °C	48 h	—
B	TEA, *i*-PrOH	150 °C, MW	5 min	—
C	Al_2O_3, H_2O, THF	50 °C	48 h	33%
D	Al_2O_3, H_2O, THF[20a]	80 °C, MW	45 min	32%
E	Al_2O_3, H_2O, THF[20a]	150 °C, MW	20 min	29%
F	Al_2O_3 deactivated[20b]	150 °C, MW	3 min	27%
G	Al_2O_3	150 °C, MW	3 min	—

[a]After silica-gel chromatography and digestion, the final product was isolated in 32% yields (Entry D) calculated from bromohydrin **3**.

(Entry D). Following these encouraging results we considered important to further reduce reaction time and therefore the temperature was increased at 150 °C (Entry E). Under these conditions the starting product disappeared after 20 min and HEA **5** was isolated in 29% yields. ^{1}H NMR and H–H COSY spectra were in agreement with the structure and showed no sign of epimerization.[18] Solvent-free microwaves-assisted reactions provide an opportunity to work with open vessels, thus avoiding the risk of high-pressure development and increasing the potential of such reactions to upscale.[19] Organic reactions under solvent-free conditions are accomplished by adsorbed organic compounds on the surface of inorganic oxides and by heating with the use of microwaves. Solvent-free conditions were therefore applied (Entry F) to a sample prepared as Entry (E) after removal of solvents. Complete disappearance of epoxide was obtained after 3 min and HEA **5** was isolated in 27% yields. The importance of deactivating alumina is clearly demonstrated by Entry (G) in which the same conditions of Entry (F) were applied but alumina was not deactivated by the addition of water. In this case, extensive decomposition was observed and the HEA compound **5** was not obtained.

Protease inhibitors containing the HEA transition state analogues are an important class of molecules and have been applied to the discovery of BACE, HIV–protease and renine inhibitors. The synthesis of these molecules is difficult especially when the erythro epoxide is opened with insoluble amines, thus jeopardizing the application of these molecules to the process of drug discovery. In this paper, we described an improved methodology for the obtainment of the HEA isoster amenable of application in parallel or automatic sequential format applied to the process of drug-discovery. We thank Professor Ermanno Valoti for the microwaves oven CEM discovery.

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18 Compound **5**: ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$ 95:5) δ 0.89 (6H, m); 1.27 (9H, s); 1.30 (3H, d); 2.02 (1H, m); 2.52–2.78 (3H, m); 3.06 (1H, m); 3.22 (1H, m); 3.46 (1H, m); 3.76 (1H, m); 4.04 (1H, d); 4.36 (2H, m); 7.12–7.29 (10H, m).
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20 Basic alumina (870 mg), deactivated by H_2O (21 μL), was added to a solution of HAlaValNHBn (161 mg, 0.42 mmol) in THF (1 mL) and the mixture was stirred for 15 min. Successively the epoxide **4** (100 mg, 0.38 mmol) in THF (1 mL) was added and the mixture was either heated under microwaves irradiation (20a) or concentrated and successively heated under MW (20b), according to Table 1. After completion of the reaction, as indicated by TLC, the reaction was diluted with MeOH and the suspension was filtered. The solution was concentrated in vacuo and the crude product purified by silica-gel chromatography (CH_2Cl_2/MeOH 99:1 → 98:2 → 97:3) followed by digestion with Et_2O.

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