Pergamon

Tetrahedron Letters, Vol. 38, No. 35, pp. 6149-6152, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01421-4

The Application of High-Throughput Synthesis And Purification To The Preparation Of Ethanolamines

Anthony J. Shuker,*[a] Miles G. Siegel,*[b] Donald P. Matthews[a] and Leland O. Weigel[c]

[a]Endocrine Research, [b]Research Technologies and Proteins and [c]Chemical Process R&D, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis IN 46285

Abstract: A 48 compound library of structurally diverse ethanolamines was prepared using a parallel synthesis approach. The synthetic paradigm employed a solution phase epoxide-opening reaction followed by rapid purification by ion exchange chromatography to yield products with near-analytical purity. An array of epoxides and primary amines, arranged in an 8x6 matrix, were reacted in the presence of an in situ silylating agent to form 48 individual compounds with an average yield of 75% and an average purity of 92.3%. © 1997 Elsevier Science Ltd.

Ethanolamines are important medicinal agents and pharmacological tools that have been applied to a variety of therapeutic areas.[1] In particular, ethanolamines of general structure **I** possessing a secondary amine have demonstrated utility as adrenergic receptor modulators.[2-4] In the course of a number of ongoing studies, we wished to develop a combinatorial method to prepare a structurally diverse library of optically pure ethanolamines for biological evaluation. Several syntheses of the general structure **I** have been reported, but to date no solution phase synthesis of chiral ethanolamine libraries has appeared in the literature.[5-7] We considered two well-established ethanolamine disconnections (**figure 1**): **path a**, alkylation of primary amines with epoxides, and **path b**, reductive amination of ketones with primary ethanolamines.

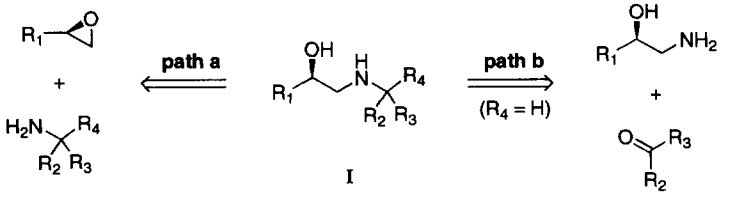
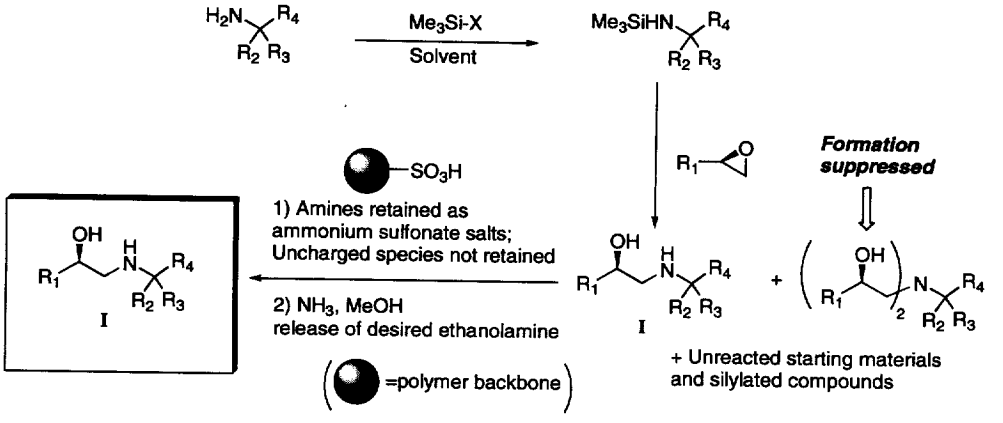


Figure 1

We initially examined the reductive amination route (**path b**) in combination with ion exchange purification[8-13] for the generation of targeted ethanolamine libraries;[14] this approach yielded a number of very exciting adrenergic compounds for further development. One limitation of **path b** however, is that it does not provide access to neopentyl amines (i.e. $R_4 \neq H$). Furthermore, **path a** affords a greater opportunity for structural diversity due to the increased availability of chiral epoxides as compared to chiral ethanolamines. In this communication, we present our results on the solution phase generation of ethanolamine libraries by the mono-alkylation of primary amines with epoxides.

The procedure described by **path a** generally requires an excess of amine to avoid undesired bis-alkylation. We felt that the removal of this impurity in a parallel synthesis format would be difficult to

achieve. Earlier reports from our laboratories, however, indicate that if the reacting primary amine is silylated in situ with TMS acetamide in DMSO, bis-alkylation is diminished or completely suppressed.[15] By coupling these reaction conditions with cation exchange purification, we felt that we could develop a general solution phase combinatorial methodology for ethanolamine libraries (**Scheme 1**).



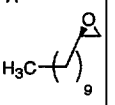
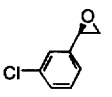
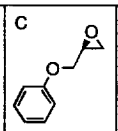
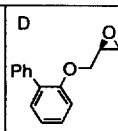
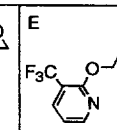
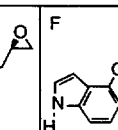
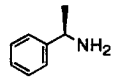
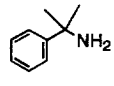
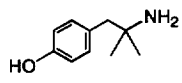
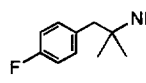
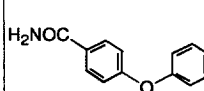
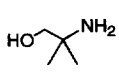
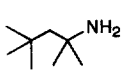
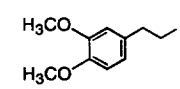
Scheme 1

In an effort to optimize product formation, we used a model system[16] to investigate the following reaction parameters: 1) silylating agent; 2) ratios of amine/epoxide/silylating agent; and 3) the ion exchange purification step. We found that bis-(trimethylsilyl)acetamide (BSA) suppressed bis-alkylation most efficiently[17] and that the optimum ratio of amine to epoxide was 1:1.2 in the presence of one equivalent of silylating agent.

We then examined the feasibility of utilizing strong ion-exchange chromatography (SCX) as a means of isolating the desired product. We performed the alkylation using our optimal silylating agent and reactant ratios. After consumption of starting amine, the reaction was quenched with 19:1 methanol/glacial acetic acid and placed on an SCX column.[18] The product amine was retained on the column while residual epoxide, silicon byproducts, and DMSO were removed by washing extensively with methanol. Product was then eluted with methanolic ammonia. The product ethanolamine was isolated in 95% yield, contaminated by 3% starting amine and no bis-alkylated side product. In subsequent experiments, we found we could elute the final product with either methanolic ammonia or methanolic HCl; in general, higher mass recoveries were obtained using ammonia in methanol.

We next attempted the construction of a representative ethanolamine library utilizing our finalized reaction conditions. Thus, an 8 x 6 reaction array employing eight different primary amines and six different epoxides was performed using our optimized protocol. The amines (**1-8**) and epoxides (**A-F**) were chosen to explore reaction scope and to generate diversity in our library (**Table 1**). All of the starting materials are commercially available with the exception of epoxide **F** and amines **3** and **5**.[19] The reactions were performed in screw-top vials in accordance with the procedure below and monitored by thin layer chromatography. Following ion exchange chromatography, the reaction products were analyzed by ion-spray mass spectrometry and either HPLC or ^{1}H NMR. All reactions produced the desired compounds, with an average yield of 75% and an average purity of 92.3%. We isolated up to 50 mg of each final product.

Table 1: Amine and epoxide reaction matrix (yield/ purity)

amines \ epoxides	A 	B 	C 	D 	E 	F 
1 	25/90	80/90	86/95	88/91	88/95	75/94
2 	14/95	52/95	71/100	67/100	87/95	72/95
3 	48/95	73/95	75/95	85/96	89/95	79/95
4 	27/90	66/95	79/93	91/99	97/95	90/96
5 	60/85	95/67	87/81	96/89	99/91	96/80
6 	22/90	82/95	95/95	81/96	95/95	87/95
7 	18/95	68/95	81/95	60/100	98/95	84/95
8 	56/95	99/90	86/70	97/97	88/80	83/89

All compounds were analyzed by ion spray mass spectrometry and displayed a molecular ion peak. Purity and structural confirmation were determined by ^{1}H NMR ($CDCl_3$, 300 MHz) for the following compounds: A1-A4, A6-A8, B1-B4, B6-B8, C1, C3, C6-C8, E1-E4, E6-E8, F6, F8. Purity was determined by HPLC for the remaining compounds (conditions: 20-100% acetonitrile/0.01%TFA over 35 minutes, C-18 Waters Symmetry column). Yields are based on mass balance.

Procedure for ethanolamine synthesis: Stock solutions of amines and epoxides were prepared (0.2 M in DMSO). To an 8x6 array of 1 dram screw cap vial was added amine stock solutions (500 μL, 0.1mmol) and BSA (0.05mmol). After gently shaking for thirty minutes, the epoxide stock solutions (600 μL 0.12mmol) were added. The vials were capped and the reaction heated at 80°C for 4-5 days. After cooling to room temperature, reactions were quenched with 1mL 5% aqueous acetic acid. Each vial was then diluted with 1mL methanol and then placed directly on a 500 mg Varian SCX ion exchange column. The columns were washed with 7mL methanol. The products were eluted by washing with 4mL 2N anhydrous ammonia in methanol. The product solutions were concentrated in tared vessels and analyzed by HPLC, ion-spray MS and ^{1}H NMR.[20]

In conclusion, we have developed a solution phase methodology for ethanolamine library construction via the monoalkylation of primary amines with epoxides. The reaction is fairly general for a variety of amines and epoxides, giving high purity products in good yield. These libraries are currently being examined for their potential as pharmacological agents, and these results will be reported elsewhere.

Acknowledgments: The authors wish to thank John Richardson, John Paschal and Larry Spangle for assistance in the acquisition of mass and ^{1}H NMR spectral data.

References and Notes

1. In 1995, thirteen of the top two hundred drugs ranked by prescription volume were ethanolamine-based compounds (source: Pharmacy Times, April 1996).
2. Hieble, J. P.; Bond, R. A. *TiPS* **1994,** *15*, 397.
3. Hieble, J. P.; Bondinell, W. E.; R.R. Ruffolo, J. *J. Med. Chem.* **1995,** *38*, 3415.
4. Ruffolo, R. R.; Bondinell, W. E.; Hieble, J. P. *J. Med. Chem.* **1995,** *38*, 3681.
5. Kick, E. K.; Ellman, J. A. *J. Med. Chem.* **1995,** *38*, 1427.
6. Wang, G. T.; Li, S.; Wideburg, N.; Krafft, G. A.; Kempf, D. J. *J. Med. Chem.* **1995,** *38*, 2995.
7. Rotella, D. P. *J. Am. Chem. Soc.* **1996,** *118*, 12246.
8. Siegel, M. G.; Hahn, P. J.; Dressman, B. A.; Fritz, J. E.; Grunwell, J. R.; Kaldor, S. W. *Tetrahedron Lett.* **1997,** *38*, 3357.
9. Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996,** *118*, 2567.
10. Lawrence, R. M.; Biller, S. A.; Fryszman, O. M.; Poss, M. A. *Synthesis* **1997**, 553.
11. Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1997,** *38*, 513.
12. Flynn, D. L.; Crich, J. Z.; Devraj, R. V.; Hockerman, S. L.; Parlow, J. J.; South, M. S.; Woodard, S. *J. Am. Chem. Soc.* **1997,** *119*, 4874.
13. Chucholowski, A.; Masquelin, T.; Obrecht, D.; Stadlwieser, J.; Villalgordo, J. M. *Chimia* **1996,** *50*, 525.
14. Siegel, M. G.; Shuker, A. J.; .Droste, C. A.; Hahn, P. J.; Jesudason, C. D.; McDonald III, J. H.; Matthews, D. P.; Rito, C. J.; Thorpe, A. J. *Mol. Diversity*, submitted.
15. Atkins, R. K.; Frazier, J.; Moore, L. L.; Weigel, L. O. *Tetrahedron Lett.* **1986,** *27*, 2451.
16. The reaction between epoxide C and amine 5 was used as a model in this case. The corresponding product was also prepared independently for structural validation.
17. Other silylating agents examined included hexamethyldisilazane (HMDS) and trimethylsilylacetamide.
18. Varian SCX columns are sulfonic acid residues covalently linked to silica gel. These prepacked columns are particularly convenient in that they readily fit off the shelf automated solid phase extraction equipment.
19. The preparation of these molecules is exemplified in EP 764640 and EP 7649632.
20. For example, compound **2B** exhibited the following: ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.43-7.10 (m, 9H), 4.61 (dd, *J*=6.1 and 10.9 Hz, 1H), 3.1 (br s, 1H), 2.64 (dd, *J*=6.8 and 13.6 Hz, 2H), 2.19 (dd, *J*=10.2 and 13.6 Hz, 2H), 1.46 (s, 3H), 1.44 (s, 3H).

(*Received in USA* 29 *May* 1997; *revised* 30 *June* 1997; *accepted* 10 *July* 1997)