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Solution phase parallel synthesis of 1,2-phenethyldiamines

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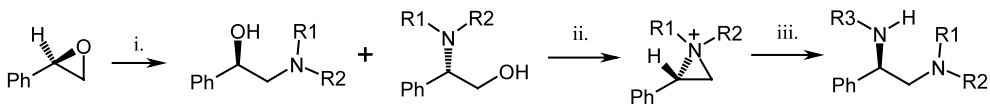
Abstract—A versatile solution phase synthesis for the preparation of 1,2-phenethyldiamines has been developed for the purpose of producing lead generation libraries. A facile strategy for the parallel purification of products provides high purity products suitable for SAR evaluation in high-throughput screening assays.

In recent years, the pharmaceutical industry has come to rely greatly on solution phase parallel synthesis[1] as a means of production for lead generation libraries of small molecules. Chemists working in this area are constantly looking for new reactions that can be readily converted from a single compound synthetic format to a parallel synthesis format. The 1,2-phenethyldiamine substructure provides an excellent core for a drug-like lead generation library. Furthermore, substituted 1,2-phenethyldiamines have proven to possess biological activities.[2]

The synthesis of 1,2-phenethyldiamines has been described in the literature.[3] In this procedure, chiral styrene oxides are opened with secondary amines to yield amino alcohol regioisomers. The alcohol products are then mesylated, whereupon the tertiary amine displaces the mesylate to form a relatively stable aziridinium intermediate. The aziridinium ion is opened regiospecifically with primary amines at the benzylic carbon to form the 1,2-phenethyldiamine products (Scheme 1). In this communication, we describe the parallel synthesis of 1,2-phenethyldiamines using (*R*,*S*) styrene oxide (**13**), (*R*) 3-chlorostyrene oxide (**14**),[4] 6,6a-dihydro-1a*H*-1-oxa-cyclopropa[*a*]indene (**15**),[5] and 2-naphthalen-2-yl-oxirane (**16**).[6] A representative 6×12 array of products is examined here.

The synthesis has proven to be rather versatile in that it allows opening of the aziridinium ion with anilines, amino alcohols, and hydrazides in addition to aliphatic primary amines. Virtually all of the nitrogen nucleophiles tested reacted successfully with the aziridinium intermediate. The scope of acceptable nucleophiles for this reaction has not even been fully evaluated at this point, but the versatility is sufficient to provide a broad range of reagent diversity. Consequently, product libraries can be designed with a relatively high degree of diversity.

The parallel synthesis procedure involves some deviations from the original literature procedure. While the literature procedure was a 'one-pot' reaction, the library synthesis was split into two steps. In the initial step, styrene oxides and secondary amines were combined neat in a 1–1 molar ratio and heated for 2–3 h at 90°C in a sealed 20 mL vial to afford the corresponding amino alcohols **A–F** (Fig. 1). Products were generally purified through trituration. Formation of the aziridinium ion and subsequent opening with nitrogen



Scheme 1. Synthesis of 1,2-phenethyldiamines. Literature procedure for single compounds:[3] *Reagents and conditions*: (i) secondary amine, EtOH, reflux; (ii) 3 equiv. Et_3N, 1.2 equiv. MsCl, Et_2O, 30 min; (iii) 2 equiv. Et_3N, $R3NH_2$, H_2O, 16 h. Parallel synthesis procedure: *Reagents and conditions*: (i) secondary amine, neat, 90°C; (ii) 3 equiv. Et_3N, 1.2 equiv. MsCl, THF, 30 min; (iii) 2 equiv. Et_3N, $R3NH_2$, H_2O, 3 days.

Keywords: solution phase parallel synthesis; 1,2-phenethyldiamines.

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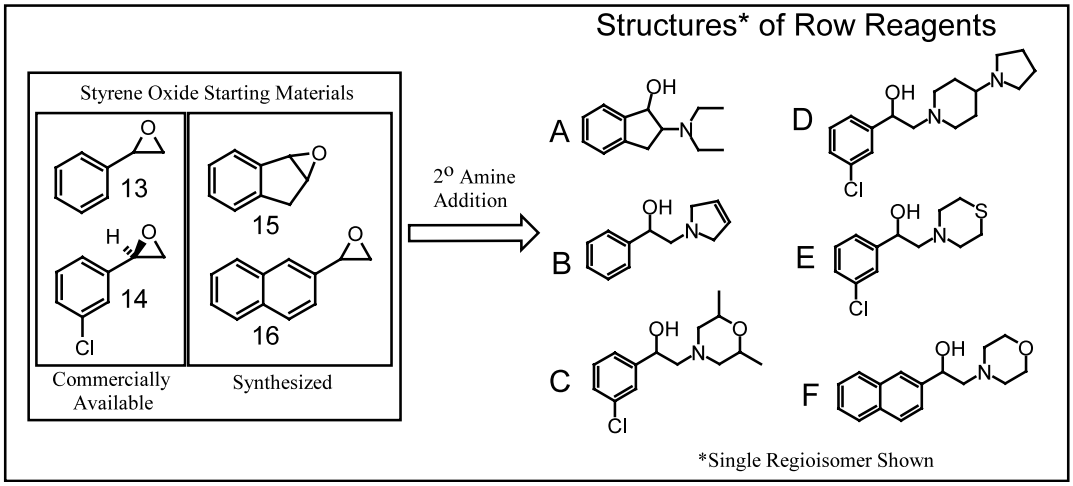

Figure 1. Styrene oxides starting materials and products after addition of secondary amine (**A**–**F** refer to row designations).

nucleophiles (Fig. 2, **1**–**12**) was performed in 96-well plates. The original procedure called for the aziridinium ring to be formed at 0°C, but experiments revealed the yields were rarely affected adversely by running the reaction at room temperature. Since cooling to 0°C is often difficult to accomplish in a 96-deep well plate format, the decision was made to initiate the reaction at room temperature for library production. As a result, THF was used in place of ethyl ether because of the exothermic nature of the mesylation. Reagent concentrations were also increased to accommodate the formation of enough product for sustained biological testing. Finally, the reaction time of the final step was increased from 16 h to 3 days to ensure that hindered nucleophiles reacted completely. The final products were purified in a two step process involving liquid/liquid extraction followed by solid phase extraction facilitated by robotic solution transfer.[7] Crude products were washed with aqueous sodium bicarbonate and extracted with ethyl acetate. Final products were obtained by filtration over silica gel to remove baseline material.

Amino alcohol intermediates were analyzed through TLC, NMR, low and high resolution mass spectroscopy.[8] Final products were analyzed through TLC, HPLC (UV detection, 210 nm), and low resolution mass spectroscopy. TLCs were visualized in an iodine chamber due to the fact that many of the products did not absorb UV light at 254 nm. Average plate purity was estimated to be 90%, and the average yield was estimated to be 50%. A more rigorous examination of yield and purity was carried out on 12 of the 72 samples. These products were weighed individually and examined through proton NMR. Table 1 shows the results of this analysis based on a theoretical yield of 75 μmol.

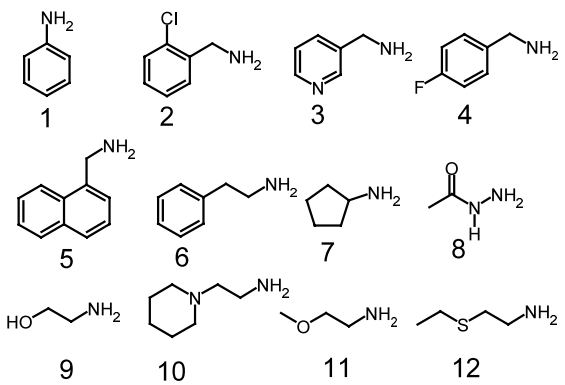

Figure 2. Nucleophile reagent set (numbers **1**–**12** refer to column designations).

1. General procedure for the synthesis of amino alcohols

Styrene oxides (10 mmol) and secondary amines (10 mmol) were combined in a 20 mL vial. The vial was capped and heated to 90°C in a sand bath for 3 h. The resulting residue was triturated in ethyl acetate and filtered to yield a white or beige powder consisting of different ratios of amino alcohol regioisomers depending on the starting materials.

2. General procedure for plate synthesis and purification

Amino alcohol solutions labeled **A**–**F** (0.30 M in 0.90 M triethylamine in THF, 250 μL, 75 μmol/well) were added in rows to a 96-well deep well plate. A solution of methylsulfonylchloride (2.0 M in THF, 50 μL, 100 μmol/well) was added to each well. The reactions were capped and shaken on an orbital shaker for 30 min. A solution of triethylamine (2.0 M in THF, 50 μL, 100 μmol/well) was then added to each well, and the plate was capped and shaken for 10 min. Solutions of nucleophiles labeled **1**–**12** (1.2 M in THF, 75 μL, 90 μmol/well) were then added in columns to the plate. Shortly thereafter, water (100 μL/well) was added to each well. The plate was capped and shaken sideways (to ensure adequate mixing of aqueous and organic layers) for a period of 3 days. To each well was added ethyl acetate

Table 1. Yield and purity of randomly selected final products

Well location [a]	Weight (mg)	Mol. wt.	Amount (μmol)	% purity [b]	% yield [c]
A4	12.1	312.43	38.7	90	46
A7	7.3	272.44	26.8	85	30
B6	11.2	293.42	38.2	85	43
C5	20.9	408.98	51.1	95	65
D2	17.3	432.44	40.0	87	46
D12	10.6	396.04	26.8	100	36
E4	18.4	364.92	50.4	95	64
E5	21.5	396.99	54.2	91	66
E11	14.6	314.88	46.4	90	56
F1	14.9	332.45	44.8	98	59
F3	8.7	346.48	25.1	87	29
F10	12.1	367.54	32.9	93	41
Averages	14.1	353.25	39.6	91	48

[a] Well locations in 96 well plate. **A**–**F** refer to rows, **1**–**12** refer to columns.
[b] % purity based on HPLC and NMR analysis.
[c] % yield calculated based on the following formula: (amount/75)×%purity.

(200 μL/well) and saturated aqueous sodium bicarbonate (100 μL/well). The plates were capped and shaken vigorously. The organic phase in each well was separated via robotic transfer, and the plate extracted again with ethyl acetate (250 μL/well). The combined organic phases were then evaporated to dryness. The crude products were dissolved in dichloromethane (300 μL/well) and filtered over a 96-well filter plate loaded with silica gel (150 mg/well). Ethyl acetate (1.4 mL/well) was used to elute the product. The resulting filtrates were evaporated to dryness to yield the final products (example products shown in Fig. 3).[9]

Acknowledgements

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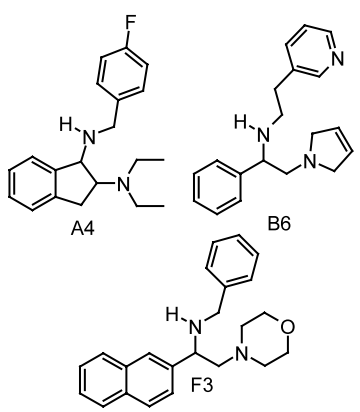

Figure 3. Example product structures.

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5. For the preparation of 6,6a-dihydro-1a*H*-1-oxa-cyclopropa[*a*]indene, see: (a) Gagnieu, C. H.; Grouiller, A. V. *J. Chem. Soc., Perkins Trans. 1* **1982**, *4*, 1009–1011; (b) Majetich, G.; Hicks, R. *Synlett* **1996**, *7*, 649–651.
6. 2-Vinylnaphthalene was oxidized to the corresponding oxirane with 2 equiv. MCPBA in dichoromethane. The reaction was stirred for 1 h, and quenched with aqueous sodium bicarbonate. The organic phase was isolated and dried with sodium sulfate, and filtered over a pad of silica gel. The filtrate was concentrated and dissolved in ethyl alcohol. A white solid precipitated, and was filtered. The filtrate was concentrated to yield the desired epoxide.
7. For a review of solid phase extraction in solution phase parallel synthesis, see Nilsson, U. J. *J. Chromatogr. A* **2000**, *885*, 305–319.

8. High resolution mass spectroscopy was performed by Analytical Instrument Group, Inc., Raleigh, NC.
9. Example ^{1}H NMR data; compound **A4**: (400 MHz, $CDCl_3$) δ 7.36–7.32 (3H, m), 7.19–7.17 (3H, m), 7.01–6.96 (2H, m), 4.23 (1H, d, $J=7.0$), 3.93 (2H, d, $J=8.4$), 3.57 (1H, d, $J=7.0$), 2.95 (1H, dd, $J=15.7$, $J=8.1$), 2.81 (1H, dd, $J=15.0$, $J=7.7$), 2.67–2.60 (2H, m), 2.53–2.46 (2H, m), 1.06 (6H, t, $J=7.0$); compound **B6**: (400 MHz, $CDCl_3$) δ 7.34–7.12 (10H, m), 5.73 (s, 2H), 3.67 (dd, 1H, $J=10.7$, $J=3.3$), 3.47 (broad s, 4H), 2.85–2.57 (m, 6H); compound **F3**: (400 MHz, $CDCl_3$) δ 8.49 (2H, s), 7.82 (4H, s), 7.60–7.46 (5H, m), 3.83 (1H, d, $J=8.1$), 3.75–3.46 (6H, m), 2.60 (1H, t, $J=6.6$), 2.47 (2H, s), 2.38–2.35 (3H, m).