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Solution-phase parallel synthesis of substituted 1,2-ethyl and 1,3-propyl diamines

Ido D. Dagan and Christopher T. Lowden*

PPD Discovery, 3500 Paramount Parkway, Morrisville, NC 27560, USA

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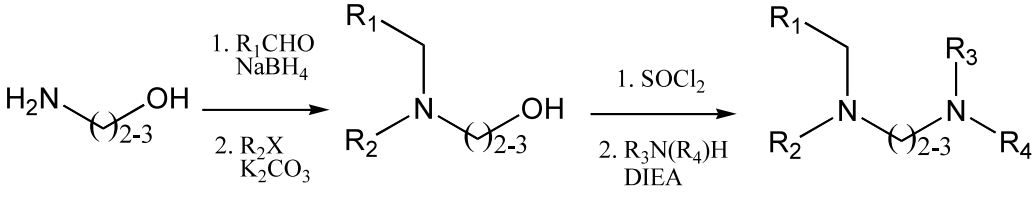
Abstract—A solution-phase synthesis for the preparation of substituted 1,2-ethyl and 1,3-propyl diamines has been developed for the purpose of producing diverse lead generation libraries with a minimal scaffold. Crude products were obtained in high purity and further purified through mass guided preparative HPLC.

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 synthetic sequences that facilitate the expedient production of large numbers of pure compounds with a high degree of structural diversity and drug-like features. The following parallel synthesis allows for variable substitution at both ends of the diamine scaffold, and sources of diversity include aldehydes, alkyl halides and secondary amines. The 1,2-ethyl- and 1,3-propyl-diamine substructure provides an excellent core for a drug-like lead generation library, without introducing a bulky scaffold that limits the diversity of the library. Minimization of the scaffold allows the library's diversity to be defined by its source reagents rather than the scaffold. Additionally, the reagents and equipment necessary for library synthesis are relatively inexpensive, making the cost per compound minimal. Finally, substituted diamines such as these have proven to possess biological activities, making them interesting targets for a general diversity library.[2]

In this procedure (Scheme 1), aldehydes were subjected to reductive amination with ethanolamine, or 1-amino-3-propyl alcohol. Resulting secondary amines were alkylated with alkyl halides. Primary alcohols were converted to chlorides, and used to alkylate various secondary amines, giving the final products up to 4 sites of diversity. The first two steps were performed on relatively large scale with minimal work-up and purification. The final alkylation was carried out on a 160 μmol scale in a commercially available 96-well array of glass vials.[3] Over 600 final products were prepared.

Chloride intermediates were analyzed through proton NMR,[4] and low resolution mass spectroscopy. Final products were purified through mass guided preparative HPLC and analyzed through HPLC (UV detection, 210 nm, 254 nm, ELSD), and low resolution mass spectroscopy. Figure 1 shows row and column reagents from a selected library plate. Table 1 shows the results of this analysis based on a theoretical yield of 160 μmol. Figure 2 shows example products from the library.



Scheme 1. Synthesis of diamines.

Keywords: solution-phase parallel synthesis; 1,2-ethyldiamines; 1,3-propyldiamines.
* Corresponding author. E-mail: christopher.lowden@rtp.ppdi.com

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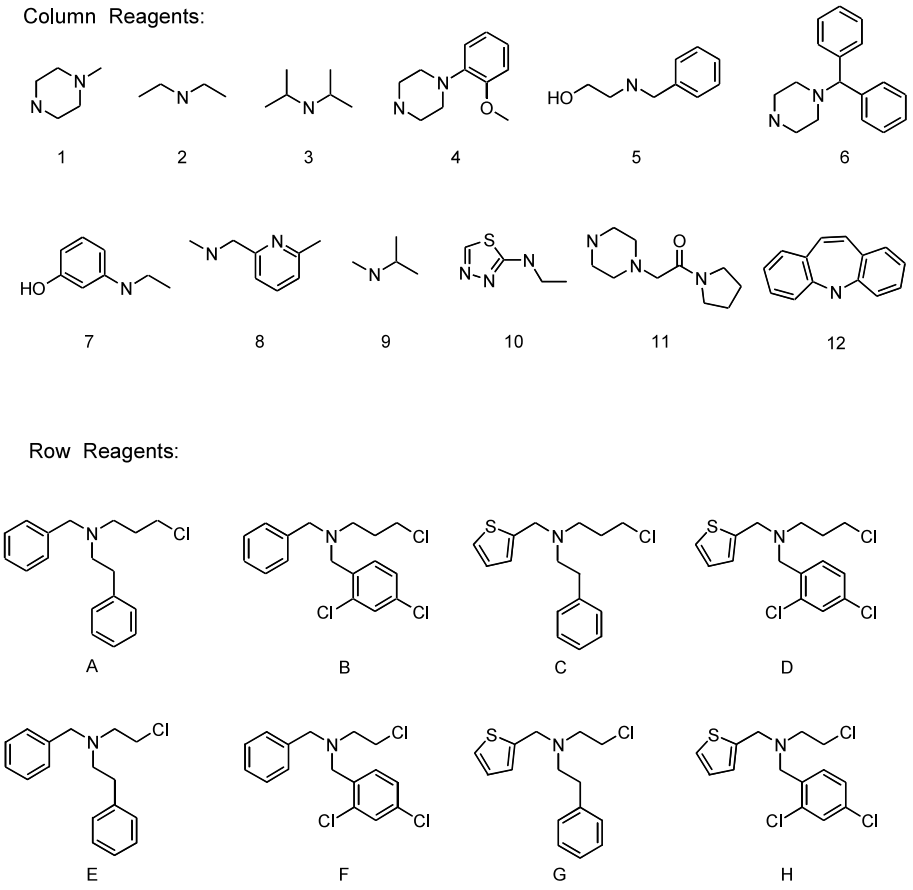

Figure 1. Example column and row reagents.

Table 1. Yield and purity of selected final products from example plate

Well location[a]	Weight (mg)	Mol. wt.	Amount (μmol)	% Purity[b]	% Yield[c]
A1	32.0	351.54	91.03	81.1	46.1
A11	49.7	448.66	110.77	90.0	62.3
B9	19.0	379.38	50.08	97.4	30.5
C5	21.3	408.61	52.13	94.6	30.8
C8	21.2	393.60	53.86	94.0	31.6
D10	38.6	441.44	87.44	92.8	50.7
E4	35.3	429.61	82.17	82.8	42.5
E5	35.6	388.56	91.62	89.2	51.1
F2	17.5	365.35	47.90	94.2	28.2
G4	29.6	435.63	67.95	81.3	34.5
G11	45.5	440.65	103.26	87.8	56.6
H2	23.1	371.38	62.20	96.9	37.7
Averages:	30.7	404.53	75.03	90.2	41.9

[a] Well locations in 96 well plate. A–H refer to rows, 1–12 refer to columns.
[b] % Purity based on HPLC analysis (lower value of either ELSD or UV detection is reported).
[c] % Yield calculated based on the following formula: (amount/160 μmol)×% purity.

1. General procedure for the synthesis of intermediates

To a stirring solution of 1-amino-2-ethyl alcohol or 1-amino-3-propyl alcohol (100 mmol) in methyl alcohol (50 mL) was added aldehyde (100 mmol). The reaction was cooled to 0°C in an ice bath, and sodium borohydride (100 mmol) was then added portion-wise over a period of 15 min, and stirred at 0°C for an additional 15 min. Water (100 mL) was added to the reaction. Most of the methanol was removed in vacuo. The resulting aqueous solution was extracted with chloroform and or ethyl acetate, dried over sodium sulfate, filtered, and concentrated in vacuo to yield the secondary amine product. Secondary amine products were

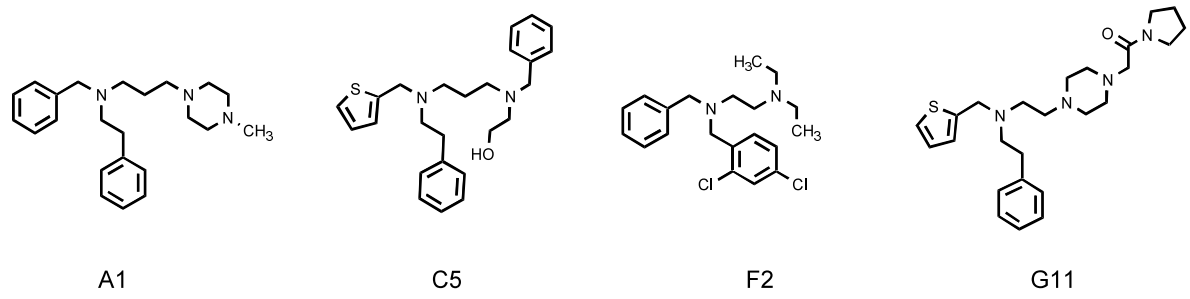

Figure 2. Example products.

dissolved in DMF (30 mL), and potassium carbonate (1.2 equiv.) was added. Alkyl halides (1.1 equiv.) were then added. The reaction was stirred at rt for 2–24 h. Water (200 mL) was added, the aqueous solution was extracted with ethyl acetate (200 mL), and the organic phase was washed with water (3×300 mL). The organic phase was dried with sodium sulfate, filtered, and concentrated in vacuo. Amino alcohol products were dissolved in chloroform (50 mL), and thionyl chloride (2.0 equiv.) was added. The reaction was stirred at rt for 2–24 h, diluted with chloroform (100 mL) and washed with saturated aqueous sodium bicarbonate (2×100 mL). The organic phase was dried with sodium sulfate, filtered, and concentrated in vacuo to yield the desired alkyl chloride intermediate for plate synthesis. In most cases, the products required purification by flash chromatography.

2. General procedure for plate synthesis and purification

Solutions of alkyl chlorides A–H (0.8 M in DMF), secondary amines 1–12 (0.8 M in DMF) and diisopropylethylamine (2.0 M in DMF) were prepared. Alkyl chloride solutions A–H (200 μL/well) were added to their corresponding rows in 96-well plates. Diisopropylethylamine solution (100 μL/well) was then added to each well. Next, amines 1–12 (200 μL/well) were added to their corresponding columns. The resulting solutions were capped securely with strip caps and heated to 70°C in aluminum blocks for 3 days. Strip caps were then removed, and solvent was evaporated to dryness with a nitrogen stream. Crude products were evaluated through mass spectroscopy and HPLC. Over 90% of the reaction wells yielded the desired molecular weight. Final products were purified through mass-guided preparative HPLC. Product containing fractions were transferred to tared vials, concentrated in vacuo, and evaluated through HPLC with UV (254 nm), and ELS detection.

Acknowledgements

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3. A 96-position microtiter plate formatted aluminum heating block obtained from Kontes was loaded with 1 mL glass vials from Wheaton.
4. Example ^{1}H NMR data for plate B3 row reagents; compound **A**: (250 MHz, $CDCl_3$) δ 7.30–7.12 (10H, m), 3.63 (2H, s), 3.50 (2H, t, $J=6.5$ Hz), 2.77–2.67 (4H, m), 2.64 (2H, t, $J=7.0$ Hz), 1.93–1.83 (2H, m); compound **C**: (250 MHz, $CDCl_3$) δ 7.28–7.15 (6H, m), 6.96–6.87 (2H, m), 3.86 (2H, d, $J=0.8$ Hz), 3.53 (2H, t, $J=6.5$ Hz), 2.80–2.70 (4H, m), 2.66 (2H, t, $J=7.0$ Hz), 1.94–1.83 (2H, m); compound **D**: (250 MHz, $CDCl_3$) δ 7.55 (1H, d, $J=8.3$ Hz), 7.35 (1H, d, $J=2.3$ Hz), 7.26–7.22 (2H, m), 6.96–6.90 (2H, m), 3.81 (2H, d, $J=0.8$ Hz), 3.68 (2H, s), 3.57 (2H, t, $J=6.8$ Hz), 2.64 (2H, t, $J=6.8$ Hz), 2.00–1.90 (2H, m); compound **H**: (250 MHz, $CDCl_3$) δ 7.62 (1H, d, $J=8.3$ Hz), 7.36 (1H, d, $J=2.3$ Hz), 7.27–7.23 (2H, m), 6.95–6.92 (2H, m), 3.90 (2H, s), 3.79 (2H, s), 3.54 (2H, t, $J=6.8$ Hz), 2.90 (2H, t, $J=7.3$ Hz).