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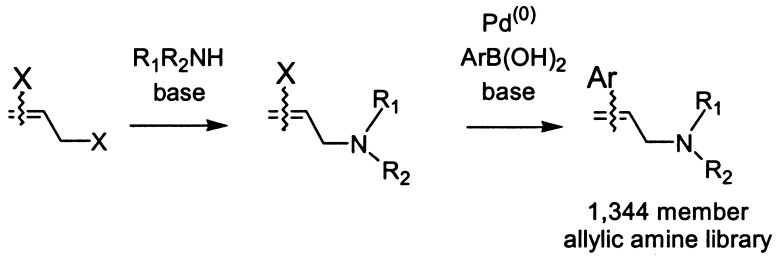

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Solution Phase Synthesis of Libraries of Variably Substituted Olefin Scaffolds: A Library of Allylic Amines

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The synthesis of allylic amine libraries derived from olefin templates is described. The two-step, solution phase reaction sequence consists of amination of the template followed by Suzuki coupling and expedited purification via ion exchange chromatography. The methodology has been used to synthesize a 1344-member allylic amine library.

Introduction

The synthesis of small molecule libraries has received a considerable amount of attention in the last several years.[1] Many of these libraries are directed toward a particular biological target or platform, while others are constructed in an effort to explore uncharted areas of molecular diversity. In designing libraries of the latter type, several criteria are of particular importance. First, the scaffold should be readily available, either from commercial sources or via a short synthetic sequence. Second, the scaffold should be derivatizable with a variety of inputs. Third, if possible, the scaffold should be capable of a variety of distinct, complementary, and well-defined substitution patterns. Finally, the scaffold should preferably bear at least some resemblance to known biologically active compounds. We felt that olefin derived scaffolds could meet all these criteria.[2,3] One can envision that a differentially substituted olefin could act as a template for selective, sequential functionalization. This leads to products with up to four substituents which are geometrically well defined and potentially trivially mutated relative to each other by simple variations in either order of reagent addition or initial scaffold substitution (Figure 1). In addition, olefins are present as central motifs in molecules with diverse pharmacological properties such as Acrivastine (Semprex),[4,5] Flunarizine (Sibelium, Ca channel blocker),[6,7] and several GABA uptake inhibitors (Figure 2).[8]

In an effort to explore the possibility of constructing libraries from olefin scaffolds, we chose as initial templates the commercially available 2,3-dibromopropene (**1**) and the readily prepared (*E*)-1-iodo-3-bromopropene[9−11] (**2**, Scheme 1). For each template, the two halide functionalities can be distinguished easily to allow for selective sequential reactions, while the substitution patterns of the final products **5** and **6** are complementary.

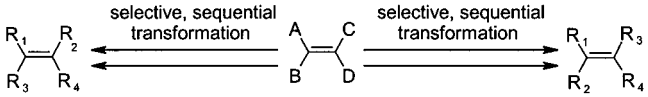


Figure 1. Functionalization of olefin scaffolds.

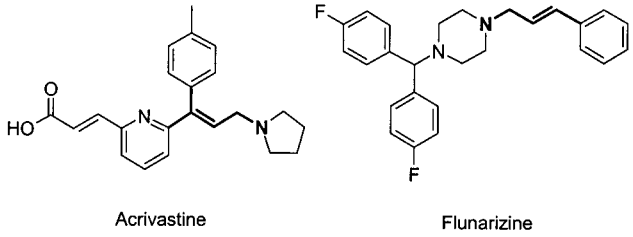
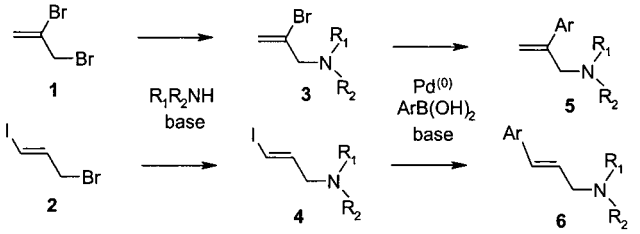


Figure 2. Pharmaceutical products containing allylic amines.

Scheme 1



In light of the short synthetic sequence and presence of the ion-forming amine handle for ion exchange chromatography, this library is well suited to solution phase preparation. Further, the apparent lack of solid phase attachment points on the sparsely functionalized initial scaffolds makes solid phase organic synthesis (SPOS) less attractive. We[12,13] and others[14−23] have previously described the use of ion exchange chromatography and solid phase scavenging reagents for the expedited purification of solution phase small molecule amine libraries, and we felt these techniques could be applied readily to the construction of this library as well.

Results and Discussion

Model Studies. We began library preparation by first examining the alkylation of secondary amines with 2,3-

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Scheme 2

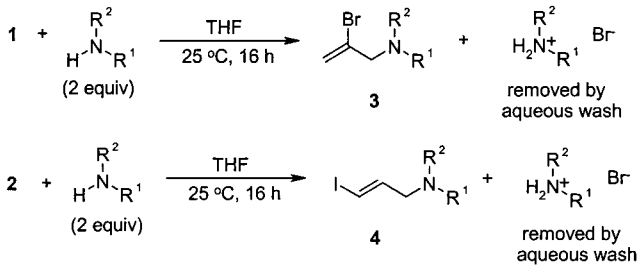
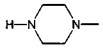
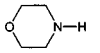
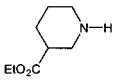
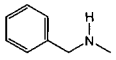
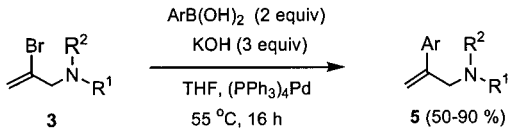


Table 1. Amination of 2,3-Dibromopropene with Representative Secondary Amines

Secondary Amine	Yield[a]	Secondary Amine	Yield[a]
	85		90
	80		80
	80		70

[a] The yield reported is approximate and is based on nonpurified material. It is estimated based on the ^{1}H NMR spectrum of the crude mixture and the mass balance.

Scheme 3



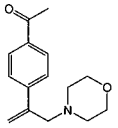
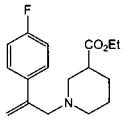
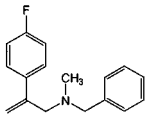
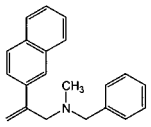
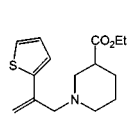
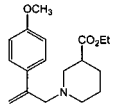
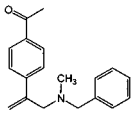
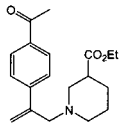
dibromopropene. Initially, it was found that the alkylation proceeded as anticipated in high yield and purity with polystyrene 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PTBD) resin as base.[24] However, it proved operationally simpler to react the bromide with excess secondary amine, then remove the HBr salt of the excess secondary amine by either filtration or aqueous extraction (Scheme 2). This alkylation also proceeded smoothly on (*E*)-1-iodo-3-bromopropene (Scheme 2).

To establish the scope of the alkylation, several amines were tested (Table 1). Generally, the yields were satisfactory, and importantly, no additional purification of the products was necessary (compounds appeared >90% pure by ^{1}H NMR spectroscopic analysis). Unsuitable amines included aromatic amines (e.g., *N*-methylaniline, diphenylamine), which were too sluggish in their reactivity to be useful. Steric factors only caused problems in the most severe cases (e.g., dicyclohexylamine). We used these preliminary studies as a guide in selecting amines for eventual library production.

With a reliable method established for the preparation of the sub-library of haloalkenes (**3** and **4**), attention was turned to the transition metal-mediated cross coupling. The method of choice was to use boronic acid partners because of their low toxicity, stability to air and moisture, and commercial availability.[25] The optimized conditions for the Suzuki reaction are indicated in Scheme 3. The yields were acceptable in the majority of cases (50−90%).

Some selected individual results from the cross coupling are shown in Table 2. In all, 20 Suzuki reactions were done individually in order to establish some guidelines as to what

Table 2. Suzuki Reaction Products

Secondary Amine	Product Number	Yield[a] (Purity)[b]	Secondary Amine	Product Number	Yield[a] (Purity)[b]
	**5i**	55 (78%)		**5v**	76 (86%)
	**5ii**	70 (88%)		**5vi**	65 (95%)
	**5iii**	75 (89%)		**5vii**	73 (91%)
	**5iv**	54 (95%)		**5viii**	73 (78%)

[a] Yields are based on isolated material following SCX chromatography. [b] Purity was assessed by LCMS (λ = 254 and 280 nm). See Experimental Section for full details.

types of substrates would be suitable for library production. The results given in Tables 1 and 2, for the 2,3-dibromopropene template (**1**), mirror those results later found when using (*E*)-1-iodo-3-bromopropene (**2**). Subsequently, both scaffolds were used to produce the allylic amine libraries.

Library Production. With the scope studies completed and the two-step sequence optimized, we then proceeded with library production. In general, each alkylated amine was coupled with 16 different boronic acids. Eight plates of compounds originating from the 2,3-dibromopropene template (**1**) were produced. We also obtained six plates of allylic amines using (*E*)-1-iodo-3-bromopropene (**2**) as the starting material. All final compounds were purified using ion exchange chromatography (see Experimental Section) and were analyzed by HPLC and mass spectrometry. The correct mass was obtained for over 90% of all wells, and the average purity as determined by HPLC for all plates was >80% (as determined by UV detection at 254 and 280 nm). In all, a total of 14 96-well plates (1344 compounds) of general structures **5** and **6** were synthesized, in an average overall yield of 35%.

Conclusion

We have demonstrated the use of functionalized olefins as templates for diverse library synthesis. These templates have been obtained from readily available starting materials, and molecular libraries of aryl-substituted allylic amines have been prepared from them. The preparation of new templates is underway as is the production of libraries from them. Further, the preparation of olefin-derived libraries, i.e., libraries from libraries, [26] are in progress and will be reported in future communications.

Experimental Section

Mass spectra (150−650 amu) were obtained using a PE Sciex API 2000 triple quadrupole mass spectrometer using

turboionspray as the method of ionization. Chromatographs were obtained using a Shimadzu LC possessing a dual LC-8A pumping system in conjunction with a SPD10^{VP} UV-detector (λ = 254 and 280 nm) and a Gilson 215 autosampler. The UV detector and mass spectrometer were used in parallel with a near 50:50 split of the mobile phase postcolumn. Separations were achieved using a Zorbax C_{18} (30 × 4.6 mm, 3.5 μm) analytical column and a linear gradient (from 80% A to 10% A, where A = H_2O + 1% AcOH and B = ACN + 1% AcOH).

Proton NMR spectra were obtained on a Bruker 400 MHz Avance spectrometer. All samples were dissolved in $CDCl_3$, and the spectra were referenced to residual $CHCl_3$ at 7.26 ppm.

The following general procedure is representative of our procedure for amine alkylations: Morpholine (0.75 g, 8.61 mmol) was added to a stirred solution of 2,3-dibromopropene (0.86 g, 4.31 mmol) in THF (15 mL). After 14 h, water (5 mL) and ether (2 mL) were added. The aqueous layer was separated and discarded. The organic layer was dried (anhydrous $MgSO_4$), and the solvent was removed in vacuo to obtain the amine-alkylated product (818 mg, 92% yield). The product was used in subsequent Suzuki reactions without purification.

The following general procedure is representative for Suzuki couplings (nonplate reactions). Aqueous KOH (1 M, 0.7 mL, 0.7 mmol) was added to a solution of phenylboronic acid (59 mg, 0.48 mmol) in THF (3 mL). A solution of the vinyl bromide from the above procedure (50 mg, 0.24 mmol) in THF (1 mL) was then added. Finally, $(PPh_3)_4Pd$ (14 mg, 12 μmol) was added, and the resulting solution was stirred at 55 °C for 14 h. Upon cooling to room temperature, water (2 mL) and CH_2Cl_2 (5 mL) were added. The organic layer was collected and the solvent removed in vacuo. The residue was taken up in 10% AcOH/MeOH and loaded onto a strong cation exchange (SCX) column (Varian BondElut, 500 mg SCX resin/3 mL column). The impurities were eluted with MeOH (3 × 2 mL). Then, the desired tertiary amine product was collected by eluting the SCX column with 2 M NH_3/MeOH (3 × 2 mL). After removal of the solvent, the final product was obtained (39.5 mg, 81% yield).

The following general procedure is representative for Suzuki reactions performed in Robbins FlexChem Reactor Blocks. All procedures were conducted in a semi-automated fashion. The procedure given was repeated for each well of the 96-well plate. Aqueous KOH (1M, 0.3 mmol, 0.3 mL) was added to a solution of a boronic acid (0.2 mmol) in THF (0.2 mL). A solution of tertiary amine **3** or **4** (0.1 mmol) in THF (0.1 mL) was added. Finally, a solution of $(PPh_3)_4Pd$ (5 μmol) in THF (0.2 mL) was added. The mixture was agitated (Robbins oven) at 55 °C for 14 h. Upon cooling to room temperature, water (0.2 mL) and CH_2Cl_2 (0.7 mL) were added. The two-phase solution was filtered through a 96-well plate filled with Varian Hydromatrix, and the plate was rinsed with CH_2Cl_2 to ensure complete elution. The residue was concentrated and taken up in 10% AcOH/MeOH, and the resulting solutions were filtered through a 96-well plate with 500 mg SCX per well, using a 96-well plate vacuum manifold available from Varian. Product was eluted with 2 M NH_3/MeOH. In general, no signals corresponding to reagents or intermediates were observed in the subset of ^{1}H NMR examined. For representative NMR and LCMS data, see the Supporting Information.

Representative proton NMR and mass spectral data for compounds in Table 2:

Compound **5i**: 7.93 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 5.61 (br s, 1H), 5.37 (br s, 1H), 3.67 (m, 4H), 3.21 (s, 2H), 2.62 (s, 3H), 2.48 (m, 4H). ESI-MS m/z 246 (M^+ + 1).

Compound **5ii**: 7.45 (m, 2H), 7.28 (m, 5H), 7.02 (t, J = 7.8 Hz, 2H), 5.43 (s, 1H), 5.28 (s, 1H), 3.53 (s, 2H), 3.36 (s, 2H), 2.20 (s, 3H). ESI-MS m/z 256 (M^+ + 1).

Compound **5iii**: 7.58 (s, 1H), 7.32 (d, J = 4.0 Hz, 1H), 7.24 (m, 1H), 5.50 (s, 1H), 5.19 (s, 1H), 4.13 (m, 2H), 3.29 (s, 2H), 2.96 (m, 1H), 2.74 (m, 1H), 2.58 (m, 1H), 2.31 (m, 1H), 2.10 (m, 1H), 1.89 (m, 1H), 1.73 (m, 1H), 1.59 (m, 2H), 1.24 (m, 3H). Note: the ethyl ester is diasterotopic, hence overlapping signals. ESI-MS m/z 280 (M^+ + 1).

Compound **5iv**: 7.93 (d, J = 8.0 Hz, 2H), 7.56 (d, J = 8.0 Hz, 2H), 7.47 (m, 1H), 7.27 (m, 4H), 5.58 (s, 1H), 5.41 (s, 1H), 3.53 (s, 2H), 3.23 (s, 2H), 2.63 (s, 3H), 2.20 (s, 3H). ESI-MS m/z 280 (M^+ + 1).

Compound **5v**: 7.52 (m, 2H), 7.00 (m, 2H), 5.44 (s, 1H), 5.22 (s, 1H), 4.10 (m, 2H), 3.31 (br s, 2H), 2.95 (m, 1H), 2.73 (m, 1H), 2.53 (m, 1H), 2.30 (m, 1H), 2.08 (m, 1H), 1.89 (m, 1H), 1.73 (m, 1H), 1.53 (m, 2H), 1.25 (m, 3H). Note: the ethyl ester is diasterotopic, hence overlapping signals. ESI-MS m/z 292 (M^+ + 1).

Compound **5vi**: 7.92 (br s, 1H), 7.83 (m, 2H), 7.63 (d, J = 7.5 Hz, 1H), 7.48 (m, 2H), 7.32 (m, 6H), 5.64 (s, 1H), 5.41 (s, 1H), 3.60 (s, 2H), 3.50 (s, 2H), 2.25 (s, 3H). ESI-MS m/z 288 (M^+ + 1).

Compound **5vii**: 7.56 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 5.43 (s, 1H), 5.16 (s, 1H), 4.10 (t, J = 6.8 Hz, 2H), 3.82 (s, 3H), 3.34 (br s, 2H), 3.01 (m, 1H), 2.78 (m, 1H), 2.55 (m, 1H), 2.27 (m, 1H), 2.08 (m, 1H), 1.90 (m, 1H), 1.71 (m, 1H), 1.52 (m, 2H), 1.24 (t, J = 6.8 Hz, 3H). ESI-MS m/z 304 (M^+ + 1).

Compound **5viii**: 7.79 (d, J = 7.7 Hz, 2H), 7.65 (d, J = 7.7 Hz, 2H), 5.81 (s, 1H), 5.61 (s, 1H), 4.24 (m, 2H), 3.24 (s, 2H), 2.90 (m, 1H), 2.71 (m, 1H), 2.61 (s, 3H), 2.51 (m, 1H), 2.32 (m, 1H), 2.15 (m, 1H), 1.85 (m, 1H), 1.71 (m, 1H), 1.50 (m, 2H), 1.32 (t, J = 6.6 Hz, 3H). ESI-MS m/z 316 (M^+ + 1)

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Supporting Information Available. ^{1}H NMR and HPLC on 20 random samples from the library, and MS data for 10 of the 14 plates. This material is available free of charge via the Internet at http://pubs.acs.org.

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