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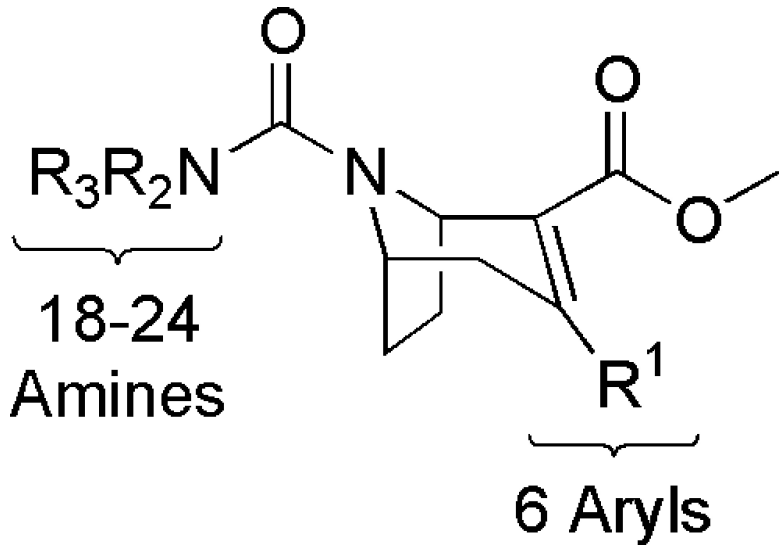

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Preparation of a Library of Unsymmetrical Ureas Based on 8-Azabicyclo[3.2.1]Octane Scaffold

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This paper reports the preparation of a library of unsymmetrical ureas based on 8-azabicyclo[3.2.1]octane scaffold. The reported synthetic route uses nortropane-8-carbonyl chlorides as key intermediates that, when treated with a slight excess of amine, give the corresponding ureas in high yield (129 examples).

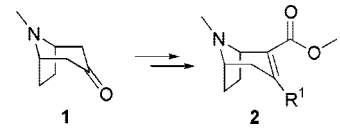
The biological importance of compounds containing 8-azabicyclo[3.2.1]octane is well-known and documented. The majority of these compounds, for example, tropane alkaloids, contain a methyl group on the nitrogen atom and are known for their central nervous system activity.[1] In part because of their known activity, the nortropane scaffold was selected as the centerpiece of a moderate-sized library with the intention of converting the basic nitrogen into a different pharmacophore. The goal was to synthesize libraries of compounds with acceptable solubility and a relatively rigid frame upon which a variety of pharmacophores could be displayed. Following hits from the initial screen, a focused library of enantiomerically pure compounds with different substituents and an altered spatial orientation should be easily accessible.

Although many advanced intermediates and synthetic routes are reported for the preparation of compounds based on the tropane ring system, including the classical Robinson tropinone synthesis,[2] for our purposes an approach to advanced intermediate **2** (Scheme 1) similar to Carroll's stood out.[3] The route employs commercially available starting materials and provides access to a class of compounds that can be modified further and also be prepared in an enantiomerically pure form. Demethylation, followed by urea formation, provides the desired library where the carbonyl of the tropinone ketone has been converted to an aromatic ring and the amine is now a urea.

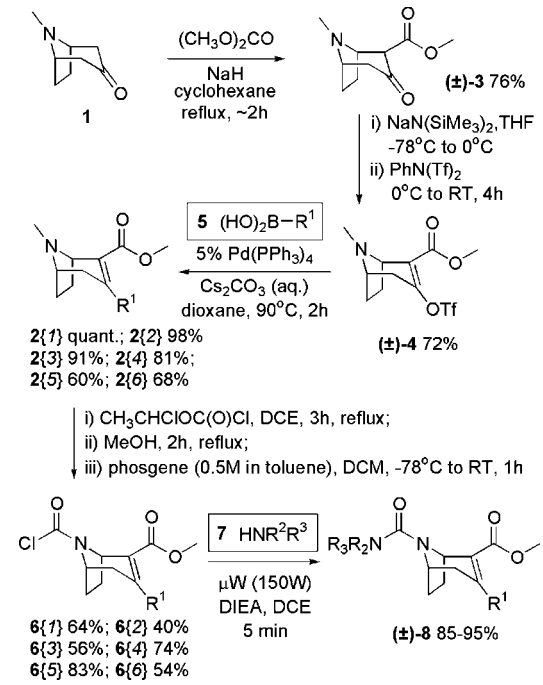
The synthesis started with conversion of tropinone **1** into (±)-2-carbomethoxy-3-tropinone **3** (Scheme 2). (At this point an optical resolution of the enantiomers is possible with tartaric acid as reported by Peter Meltzer.)[4] The crude material was converted into triflate **4**, which was subjected to the reported conditions, with CsF as a base, tetrakistriphenylphosphine palladium as the catalyst, and dimethoxymethane as a solvent, for the Suzuki reaction.[3] We found that although these conditions worked for the reported examples, they were not general enough for our aims. With some boronic acids, no product was observed after 2 h at 60 °C. However, upon addition of water, the reaction proceeded to completion. Eventually, the conditions shown in Scheme 2 became our established method for this step with all boronic acids examined giving good yields. The triflate **4** can be stored at −5 °C as a 0.5−0.6 M frozen solution in dioxane for an extended period of time, and so dioxane became the preferred solvent.

Demethylation of the nitrogen[5] was performed using α-chloroethyl chloroformate, followed by treatment with methanol.[6] Typically, after flash chromatography, the product was obtained in average to good yield. The original plan had been to treat the demethylated substrate with 1 equiv of phosgene at low temperature, followed by addition of an

Scheme 1. Reported Advanced Intermediate



Scheme 2. General Protocol for Library Synthesis



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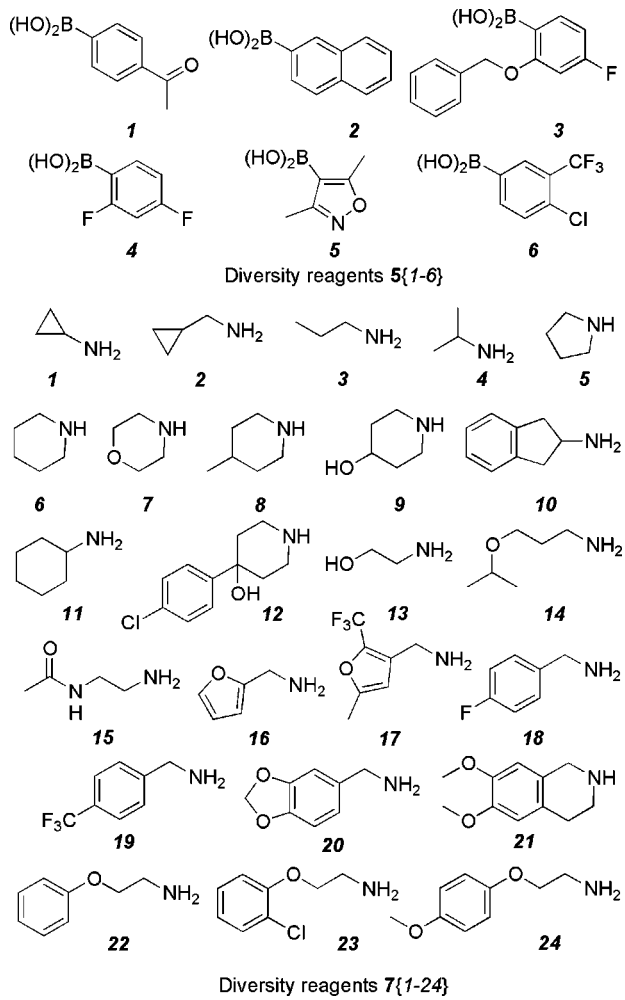

Figure 1. Diversity reagents used in production of the library.

amine. Although this approach provided the desired ureas in some cases, the major product after column chromatography was the corresponding carbamoyl chloride **6**. After some experimentation it was found that these compounds are useful intermediates on the route toward unsymmetrical ureas. They are sufficiently stable to survive an aqueous workup and very nonpolar compared to the demethylated starting material, thus facilitating purification by column chromatography. Because of the low polarity, it was possible to directly convert **2** to **6** in a similar or slightly higher yield than for the stepwise procedure (demethylation−purification−treatment with phosgene−purification).

The final reaction of amines with the corresponding carbamoyl chlorides proceeds in good yield but requires elevated temperature or microwave irradiation. In the case of amines with low boiling points (**7**{*1*−*4*}, Figure 1), the microwave-assisted reaction provides higher yields with the same amount of amine. This is probably the result of the reduced evaporation with the sealed microwave vial. Shorter reaction time (5 min for microwave assisted reaction vs 1 h for the thermal reaction) was another plus for the microwave system. Ultimately, a constant microwave power of 150 W was used as the temperature ramped from ambient to ∼100 °C in 30 s, where it was then held for 5 min. A wide range of mono- and dialkyl amines except anilines (Figure 1) react under these conditions. If after 5 min, starting material was still present (as determined by TLC), another portion (typically 0.3 equiv) of amine was added, and the reaction was placed in the microwave unit for additional 5 min. The use of 1.2 equiv of an amine, followed by extraction of its excess with 0.5 M citric acid, produced the final compounds in good yields and purity (Table 1). The majority of the compounds were prepared on a 45−55 mg scale.

Table 1. LC-MS Analysis of the Library[a]

crude purity	number of compounds	fraction of the library
<80	1	1%
80−84	1	1%
85−89	7	5%
90−94	11	9%
≥95	109	84%

[a] The purity of the library was established independently by University of Kansas Chemical Methodologies and Library Development Center of Excellence (see the Acknowledgments).

Through the reaction of the six different boronic acid adducts (Figure 1) with 24 different amines, a library of 144 compounds could be prepared. Because the final purity depended on the amine used, the last synthetic step has been carried out in batches of six compounds using one amine and six nortropane-8-carbonyl chlorides. Depending on the amount of the starting chlorides available, from 18 to 24 amines were employed with 129 compounds synthesized in total.[7] The compounds possess 2−4 pharmacophore points essential for specific drug-target interactions. The average molecular weight for the library is 444 (median 437, range 345−605); the average number of hydrogen acceptors is 4.6 (median 5, range 2−9),[8] and the average number of hydrogen donors is 0.9 (median 1, range 0−2).[9] This library has been submitted to the NIH Molecular Libraries-Small Molecule Repository and, as such, has been evaluated for its members' solubility and stability.[10] They have all been found to have adequate solubility (at least 10 mg in 2 mL of 90:10 chloroform/methanol). In addition, these molecules have been screened for activity in a hepatitis C replicon system.[11]

In summary, utilizing carbonyl chlorides **6**{*1*−*6*} as the key intermediates, a library of unsymmetrical ureas was prepared in good yield and purities. The scaffold this library is based on has three sites of diversity, the amine and ketone of the compound **1**, as well as the carboxyl group.

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Supporting Information Available. General procedures for library synthesis and ^{1}H NMR data for the compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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(7) These 15 compounds have not been prepared: **8**{*1*,*17*}, **8**{*1*,*22*}, **8**{*1*,*24*}, **8**{*2*,*12*}, **8**{*2*,*17*}, **8**{*2*,*20*}, **8**{*2*,*22*}, **8**{*2*,*23*}, **8**{*2*,*24*}, **8**{*6*,*6*}, **8**{*6*,*9*}, **8**{*6*,*10*}, **8**{*6*,*18*}, **8**{*6*,*19*}, **8**{*6*,*21*}.
(8) A function CHEM.NUM.HBACCEPTORS(structure) of ChemDraw for Excel from ChemDraw Ultra 10.0 package by CambridgeSoft was used.
(9) A function CHEM.NUM.HBDONORS(structure) of ChemDraw for Excel from ChemDraw Ultra 10.0 package by CambridgeSoft was used.
(10) Thiazolidine and 2-(methylthio)ethylamine were excluded from the library synthesis because of oxidation of the sulfur (+16 peak in LC-MS).
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