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Solid Support Synthesis of Tetrahydroquinolines via the Grieco Three Component Condensation

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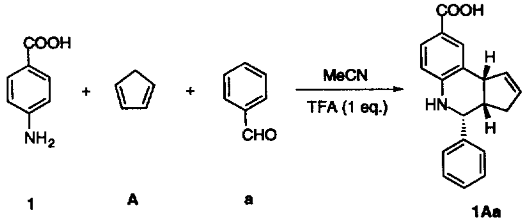
Summary: A three component condensation involving aromatic amines, aldehydes, alkenes and TFA as a catalyst affords the desired tetrahydroquinolines in good yields. A variety of structures for the olefin and aldehyde inputs in the library were investigated. © 1997 Elsevier Science Ltd.

A subset of libraries generated by combinatorial chemistry methods is represented by multiple component condensations (MCC). Unlike linear libraries, the number of structural analogs which can be generated is dependent only on the number of inputs in the MCC reaction and the availability of each of these inputs. The library is synthesized in a single chemical transformation, and is thus typically generated in a parallel fashion. In our continuing efforts at identifying new reaction templates to investigate by solid support methods,[1] we were intrigued by the possibility of utilizing the condensation shown in equation 1 introduced by Grieco.[2] Attempts have been made to expand the scope of this chemistry as well as to apply polymer supported Sc catalyst.[3] This paper describes the first solid support version of the Grieco three component condensation (3CC) to afford tetrahydroquinolines, an important class of biologically active compounds.[4]

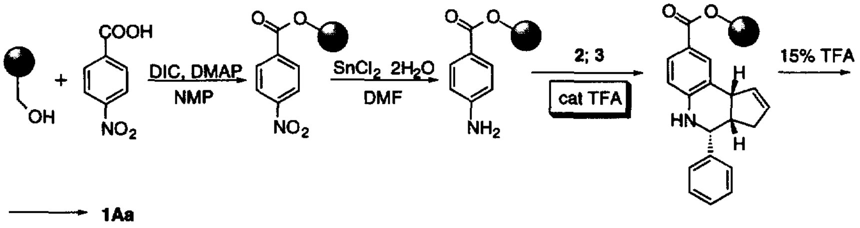


(1)

The aromatic amine input 1 served as the anchoring site, where we could utilize the carboxylate to tether directly to the resin or introduce further diversity sites with other bifunctional inputs (i.e. amino acids). The availability of aldehydes was not expected to be a problem, but the number of alkenes which might participate in the cycloadditon was not clear at the onset of this study.[5] Furthermore, the use of stoichiometric TFA[1] was not a viable reaction condition, and we thus investigated the reaction profile using catalytic acids.

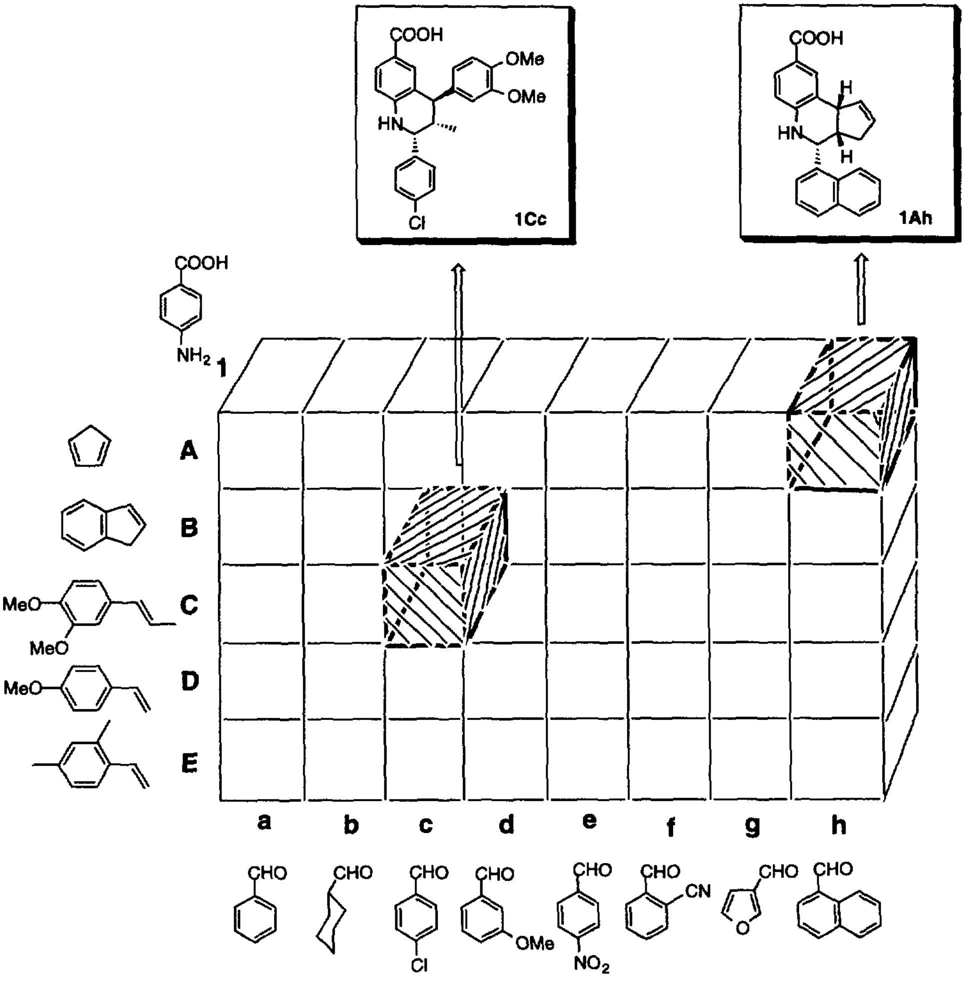
Loading of p-nitrobenzoic acid onto Wang resin afforded the corresponding aromatic amine after reduction with $SnCl_2$ H_2O in DMF (1 M solution).[6] The yield in this transformation was determined to be 75 to 86% depending upon quality of the starting Wang resin. Application of dioxane for the resin wash was found to be necessary to remove the residual traces of DMF. The three-component condensation of the amine with benzaldehyde and cyclopentadiene at room temperature in acetonitrile with catalytic TFA and subsequent removal from resin afforded 1Aa in 76 % yield. The reaction proceeded for 12 hours and did not appear to afford any other by-products.[1]

Scheme 1.



To evaluate the scope of this MCC reaction, we synthesized a library of 80 members consisting of amine input (**1**), five alkenes (**A-E**) and eight aldehydes (**a-h**). This library was synthesized in parallel under the following reaction conditions: the polymer bound aniline **1** (100 mg of the resin per reaction vessel [a], standard loading 0.6-0.8 mM/g) was treated with 500 μL of 1M solution of aldehyde and 500 μL of 1M solution of alkene in MeCN, 50μL of 1% TFA in MeCN was introduced, and the mixture was agitated by bubbling N_2. After 12 hrs. the resulting resin was filtered, washed with DMF, MeOH, CH_2Cl_2, dried and treated with 15% TFA (2 mL per vessel) to cleave the target tetrahydroquinoline product. The resulting solution was collected, concentrated under reduced pressure (attention! efficient liquid N_2 trap), and the residue was triturated with Et_2O to afford the desired solid product (90-95% purity by HPLC and ^1H NMR analysis).[7] The yields of the tetrahydroquinolines varied from 53 to 92% (based upon 0.8 mm/g loading). The best yields (about 80-90%) were achieved with the aldehydes containing electron-withdrawing group (**1Ac**, 89%; **1Bc**, 85%; **1Cc**, 91%; **1Dc**, 87%; **1Ec**, 84%; **1Ae**, 88%; **1Be**, 89%; **1Ce**, 93%; **1De**, 86%; **1Ee**, 80%; **1Af**, 91%; **1Bf**, 88%; **1Cf**, 91%; **1Df**, 83%; **1Ef**, 81%). Similar reactions with more electron-rich aldehydes afforded lower yield of the product (**1Aa**, 76%; **1Ba**, 64%; **1Ca**, 61%; **1Da**, 66%; **1Ea**, 53%; **1Ab**, 70%; **1Bb**, 67%; **1Cb**, 73%; **1Db**, 64%; **1Eb**, 64%; **1Ad**, 57%; **1Bd**, 54%; **1Cd**, 58%; **1Dd**, 59%; **1Ed**, 60%; **1Ag**, 59%; **1Bg**, 53%; **1Cg**, 66%; **1Dg**, 57%; **1Eg**, 53%; **1Ah**, 56%; **1Bh**, 53%; **1Ch**, 71%; **1Dh**, 67%; **1Eh**, 52%). The single major impurity detected in the reaction mixtures (LC MS) was the corresponding Schiff base, the postulated intermediate in the Grieco 3CC. Acetaldehyde and valeraldehyde did not afford the desired tetrahydroquinolines.) A number of catalysts were found to be efficient in the described synthesis, namely camphorsulphonic acid, BF_3 Et_2O, $FeCl_3$,[3d] $TiCl_4$, the yield of the target compounds however was somewhat inferior to that using 1% TFA. Acetonitrile was found to be the best solvent for the reaction.[1] Application of DMF, MeOH, dioxane or CH_2Cl_2 as a reaction media led to lower yields of tetrahydroquinolines. Cyclopentadiene was found to be the most efficient olefin input for the Grieco 3CC reaction, whereas the lowest yields of products were observed with 2,4-dimethylstyrene, probably due to its polymerization. Thus, considerable polymer formation was detected by ^1H NMR analysis of the crude reaction mixture resulting from the reaction of **1**, **a**, and **E** in solution. Attempts to improve the yields by changing the reaction conditions (temperature, reaction time, concentration of TFA) were only marginally successful.

Scheme 2.



In conclusion, a solid-support version of the 3CC reaction to generate tetrahydroquinolines based on Grieco's protocol has been developed. A combinatorial approach to this chemistry allowed fast and efficient entry into a diverse array of the target compounds. A number of electron-rich alkenes were developed as new olefin inputs for the tetrahydroquinoline library.

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7. Satisfactory analytical data (^{1}H NMR, MS/HRMS, and HPLC) were obtained for all the compounds described.

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