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Construction of Combinatorial Chemical Libraries Using a Rapid and Efficient Solid Phase Synthesis Based on a Multicomponent Condensation Reaction

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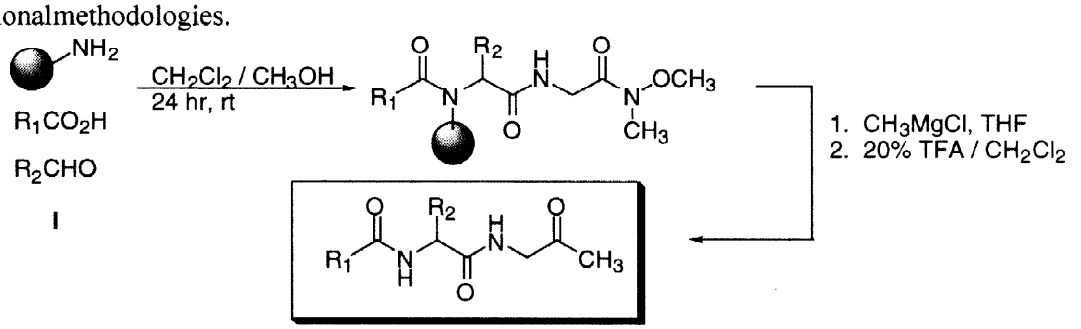
Abstract: A 96 member library of acylated dipeptides based on a known anticonvulsant was synthesized utilizing an Ugi four component condensation followed by derivitization through nucleophilic displacement of a Weinreb type amide. The library afforded compounds in reasonable yield and high purity after cleavage from solid support.

Recently, combinatorial chemistry has received a good deal of attention as a tool for drug discovery.[3] This consideration is based on the ability to synthesize a large library of therapeutically important compounds based on a common core structure with a minimum of time and effort.[4] Although early work on combinatorial libraries has focused on peptides[5] and oligonucleotides,[6] more recently, small organic molecules have attracted widespread consideration.[7] In this paper, we describe the solid phase synthesis of a library based on a known acylated dipeptide which shows anticonvulsant activity.[8] For the construction of the polyamide skeleton of the molecule we used an Ugi four component condensation[9] (4CC) reaction. This strategy--unlike mult-step reaction strategies--permits the creation of a functionally complex organic molecule with a single synthetic transformation which would otherwise take numerous linear steps to construct using conventionalmethodologies.



Scheme 1

The overall synthetic plan for the library relies on a 4CC for construction of the diamide backbone of the molecule followed by subsequent derivitization by displacement of a Weinreb amide[10] with a Grignard reagent. Although it is theoretically possible to use the solid support as any one of the four components in the 4CC, we chose to attach the molecule through the secondary amide generated in the reaction. The reason for this is twofold, cleavage of amides from solid support is a well known transformation and thus should pose no difficulty to our synthetic plan and also, by generating a tertiary amide in the initial step, there will

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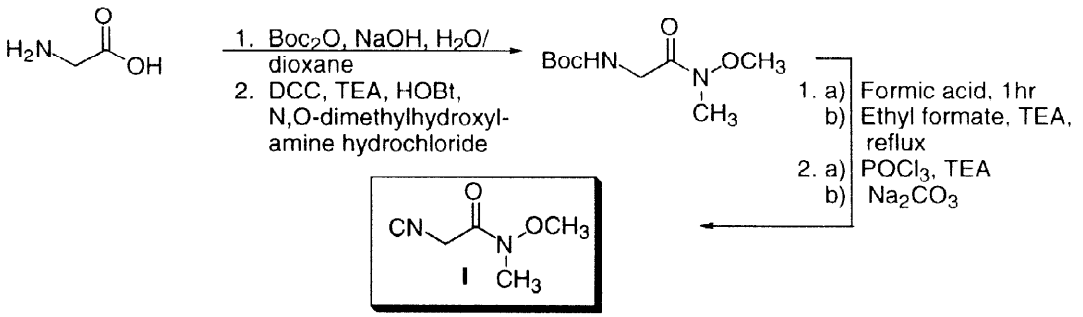
be no acidic amide proton present during the nucleophilic displacement. Thus, the linker acts as a protecting group for one of the amides as well as an attachment site for the solid support. (Scheme 1).

While isocyanide **I** was known prior to this work,[11] we attempted to devise a synthesis that afforded the material in higher yield (Scheme 2). Thus, from *t*-butoxycarbonyl (Boc) protected glycine the Weinreb amide was generated using N,O-dimethylhydroxylamine hydrochloride under standard dicyclohexylcarbodiimide (DCC) coupling conditions. Treatment of the protected amine with formic acid for 1 hr followed by removal of the solvent *in vacuo* gave the free amine. This was then converted to the formamide using refluxing ethyl formate and triethyl amine (TEA) and finally to isocyanide **I** by dehydration of the formamide with phosphorus oxychloride and TEA at 0 °C.



Scheme 2

The 96-member library was generated by treating Rink amine resin[12] (1 eq), with equimolar (5 eq) amounts of isocyanide **I**, carboxylic acids **1 - 12,** and **A - H** (Scheme 3) in methanol / CH_2Cl_2 (1:4). The mixture was stirred overnight, then excess reagents were removed by filtration, and the resulting polymer supported tripeptide treated with methyl Grignard (5 eq) overnight. After workup and filtraton the resulting ketone was cleaved from the solid support affording 2 - 4 mg of the desired product after evaporation of solvent.[13]

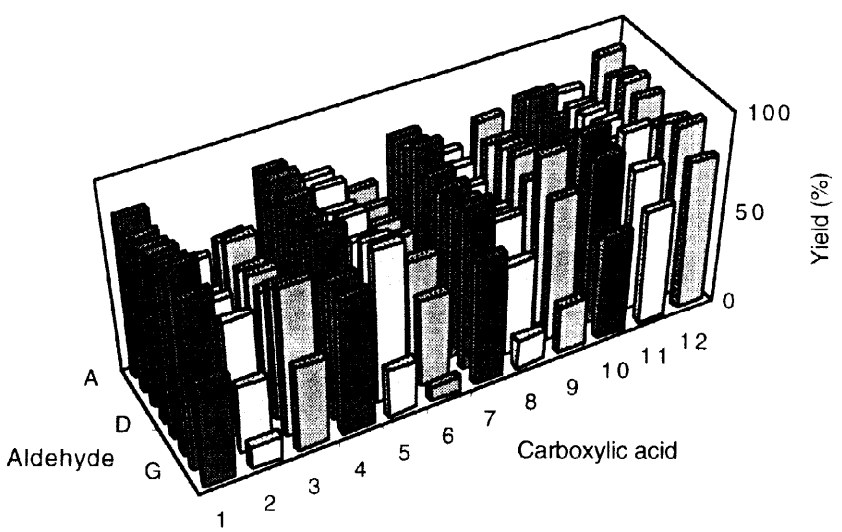
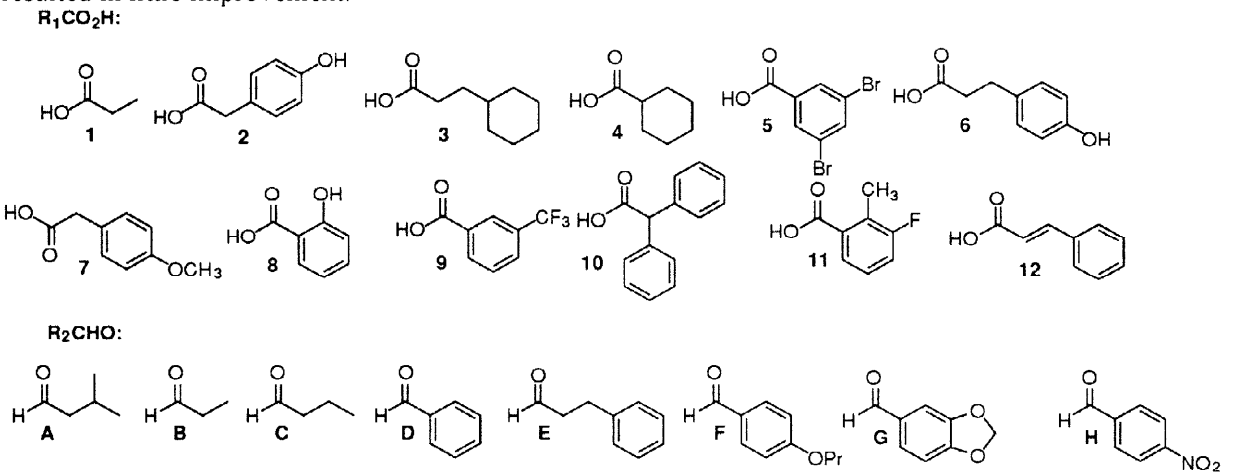


Figure 1

From the variety of inputs used (Scheme 3) it was possible to observe substituent effects on yield. A sensitivity of the product yields to the structure of the aldehyde input was noted (Figure 1): aliphatic aldehydes (**A**, **B**, **C**) or those bearing electron-donating groups (**F**, **G**) gave good overall yields, in contrast to the case which contained an electron withdrawing group (**H**) which furnished products in relatively low yield. Attempts to increase yields by using a large excess of the aldehyde or the repeated addition of fresh reagents resulted in little improvement.



Scheme 3

Turning our attention to the effect of carboxylic acid on yield we found that the reactions involving phenolic derivatives **2**, **6** and **8** generally gave low yields. This is likely due to their precipitation from solution over the 24 h reaction period. This case aside, the remainder of the carboxylic acids tried--including electron rich and electron poor--gave good yields. To further investigate the reproducibility of the results five reactions were carried out on a larger scale (0.1 mmol) and afforded products in the following yields:[14] **1A** (17 mg, 71 %); **2C** (17 mg, 55 %); **9B** (25 mg, 75 %); **10E** (36 mg, 83%); **11D** (27 mg, 80%), which gave good agreement with the library yields. Analysis by ^{13}C and ^{1}H NMR revealed >90% purity in all cases.

We have described the parallel synthesis of a combinatorial library on solid support based on an Ugi 4CC with further modification via Grignard displacement of a Weinreb type amide. The isocyanide input was prepared in high overall yield. The synthesis resulted in a library of compounds in reasonable yields and purity suitable for biological testing. Further results from this research will be forthcoming.

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13 Analytical data for compound **C9**: ^{1}H NMR (400 MHz,, CD_3OD) δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.48 (m, 2H), 1.80 (dddd, *j* = 4.5, 9.5, 13.7, 19.0 Hz, 1H), 1.89 (m, 1H), 2.13 (s, 3H), 4.00 (d, *J* = 18.6 Hz, 1H), 4.07 (d, *J* = 18.6 Hz, 1H), 4.58 (dd, *J* = 5.5, 9.2 Hz, 1H), 7.66 (t, *j* = 7.9 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 8.12 (d, *J* = 7.9 Hz, 1H) 8.19 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 14.0, 20.4, 27.0, 35.0, 50.3, 55.4, 125.5, 129.3, 130.5, 132.3, 136.3, 168.9, 174.9, 205.7; IR (NaBr, thin film) 2963, 1733, 1636, 1327 cm^{-1}. Analytical data for compound **E9**: ^{1}H NMR (400 MHz,, CD_3OD) δ 2.13 (s, 3H), 2.14 (m, 1H), 2.22 (m, 1H), 2.78 (m, 2H), 4.00 (d, *J* = 18.6 Hz, 1H), 4.08 (d, *J* = 18.6 Hz, 1H), 4.59 (dd, *J* = 5.3, 14.4 Hz, 1H), 7.12 (m, 1H), 7.24 (m, 4H), 7.66 (t, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 8.08 (d, *J* = 7.9 Hz, 1H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 27.0, 33.4, 34.7, 55.3, 125.5, 127.1, 129.3, 129.6, 130.5, 131.9 (q, *J* = 32.4 Hz), 132.3, 136.3, 142.5, 168.7, 174.6, 205.6; IR (NaBr, thin film) 2930, 1732, 1660, 1327 cm^{-1}.
14. Yields based on eq of FMOC amine on Rink resin.