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Solid-Phase Synthesis of Proline Analogs *via* a Three Component 1,3-Dipolar Cycloaddition

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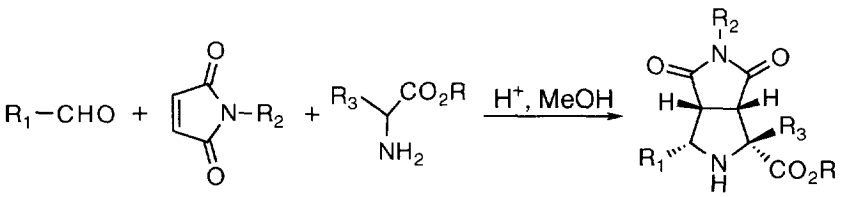
Abstract: Preparation of highly substituted pyrrolidines (proline analogs) was achieved by solid-phase organic synthesis using a three component 1,3-dipolar cycloaddition of a resin bound azomethine ylide. The synthesis utilizes a series of hydroxybenzaldehydes attached to Wang's resin *via* a Mitsunobu coupling followed by reaction with an alpha-amino ester and a maleimide. The solid phase reaction is utilized to obtain **3a** as a single component. Alternatively, the reaction may be performed using an equimolar mixture of resins to afford a defined product mixture **4a-i** as determined by LC-MS analysis.

Combinatorial libraries have been recognized as a valuable new tool for the discovery of biologically active compounds.[1] Solid phase organic synthesis (SPOS) provides a rapid means for preparation of such libraries and has been used for the construction of oligomeric compounds and small organic molecules.[2,3] SPOS dipolar cycloadditions of nitrile oxides have been reported for modification of the side chains of an oligomeric peptoid library[4] and for the preparation of isoxazolines.[5] Recently, an inhibitor of angiotensin converting enzyme has been identified from a combinatorial mercaptoacyl proline library of functionalized pyrrolidines[6] using a two step synthesis *via* a 1,3-dipolar cycloaddition of an azomethine ylide from resin bound amino acids. We required a straightforward method for the preparation of a combinatorial library of highly substituted pyrrolidines as potential biologically active agents.

Multicomponent reactions continue to be of interest for the construction of small molecules and have advantages for the preparation of combinatorial libraries since three or more subgroups can be combined in one step.[7] Bicyclic proline analogs **1** (R = H) have been prepared by solution chemistry using the three-component strategy.[8] Our attempts to prepare mixtures of components for testing using this synthetic method, however, were unsuccessful. The presence of more than one amine, maleimide, or aldehyde led to side reactions between the various components. We reasoned that by attaching one of the components to a solid support, a mixture of



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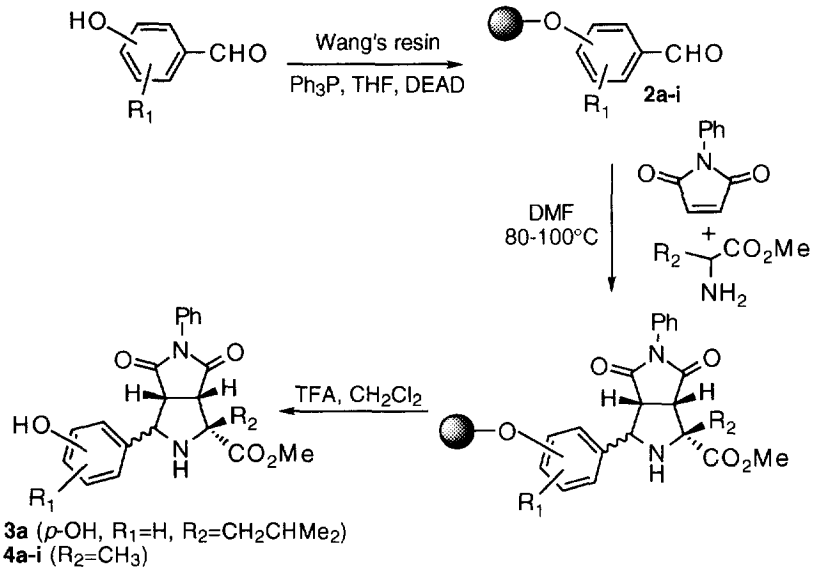
support bound materials could be employed to obtain a defined mixture of products. The resin bound components, in our case substituted benzaldehydes, would each be exposed to a single amino ester and *N*-substituted maleimide. Thus, the mixture reaction should proceed in an analogous manner to the single product, three-component reaction. We have investigated a one-step, three component synthesis of pyrrolidines or bicyclic proline analogs **1** (R = alkyl) on a solid phase from a resin bound aryl aldehyde, an alpha-amino ester, and a maleimide, which proceeds through a 1,3-dipolar cycloaddition of an azomethine ylide.[9] The method is currently being used to prepare a combinatorial library of **1** using a resin mixture strategy.[10]

In order to carry out the SPOS of the bicyclic pyrrolidines, substituted benzaldehydes were attached to Wang's resin by an alkylaryl ether linkage (Scheme). Mitsunobu coupling[11] of the hydroxybenzaldehydes to the benzyl alcohol of Wang's resin afforded aldehyde resin **2.** Polymer supported Mitsunobu coupling has been reported for the formation of ethers,[12] but has not been previously employed to directly prepare a TFA cleavable link to the resin.[13] The loading of the resin was determined by cleavage of a resin sample of known weight with TFA in methylene chloride and either GC or HPLC analysis of a volumetric solution of the recovered filtrate. By comparison of the recovered benzaldehyde with known standards, the loading of the resin was determined. Nine substituted benzaldehydes were attached to Wang's resin using Mitsunobu coupling with loadings ranging from 0.24 to 0.89 meq/g (Table).[14]

Scheme



3a (*p*-OH, R_1=H, R_2=CH_2CHMe_2)
4a-i (R_2=CH_3)

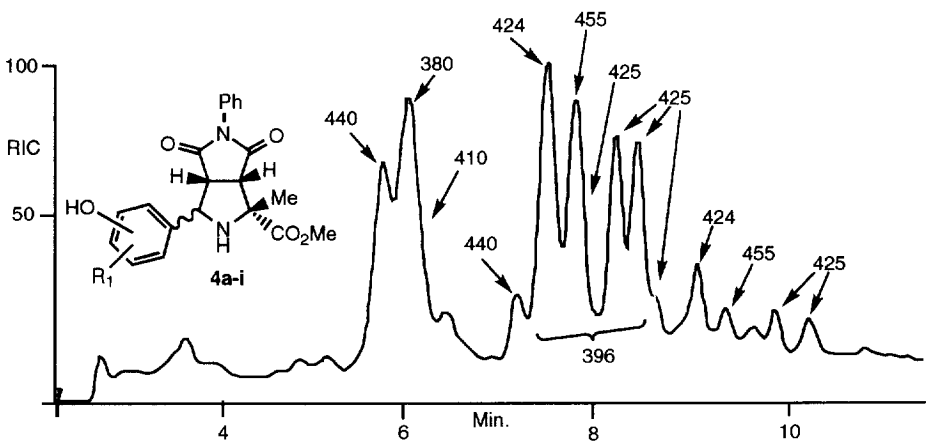
Table. Preparation of Substituted Benzaldehyde Resins 2.

Run	Benzaldehyde	Loading (meq/g)
a	4-hydroxybenzaldehyde	0.78[a]
b	4-hydroxy-3-methoxybenzaldehyde	0.67
c	3,5-dimethoxy-4-hydroxybenzaldehyde	0.89
d	4-hydroxy-3-nitrobenzaldehyde	0.58
e	2,4-dihydroxybenzaldehyde	0.28[a]
f	4-ethoxy-3-hydroxybenzaldehyde	0.69
g	5-hydroxy-2-nitrobenzaldehyde	0.24[a]
h	3-hydroxy-4-nitrobenzaldehyde	0.30[a]
i	4-hydroxy-3-methoxy-5-nitrobenzaldehyde	0.58
j	salicylaldehyde	0.00

a) Resin was treated twice with the Mitsunobu reaction conditions to provide higher loadings.

Solid phase synthesis was carried out by treatment of **2a** with leucine methyl ester and *N*-phenylmaleimide in DMF in a sealed vial at 100 °C. The product was cleaved from the resin with TFA and characterized without purification as a mixture of diastereomers **3a**.[15] Amino acids did not react with the resin under these reaction conditions most likely due to a lack of solubility or permeability in the resin. A magnetic stirrer was required in the vial and all the reagents must be anhydrous in order to obtain complete reaction. In solution phase studies, it was noted that the reactants were not very soluble in DMF or methanol. Thus, the stirring assists in dissolving the reagents as the reaction proceeds. We also prepared a mixture of products in a single run in which nine different aldehyde resins **2a-i** (resins from runs a-i) were mixed in equimolar amounts and treated with alanine methyl ester and *N*-phenylmaleimide. Since each aldehyde is exposed to a single amino ester and maleimide, this is analogous to a single component run. After the three component reaction and cleavage, the mixture of products **4a-i** was analyzed by LC-MS (Figure). The dipolar cycloaddition provides mixtures of diastereomers which for some of the expected products were separated by HPLC. Thus, more than one component was obtained of identical molecular weight for some of the expected products. Using this mixture approach, each expected MW from the nine resin bound aldehydes was observed based on the mass spectral identification of the molecular ions of the chromatographic peaks.

Figure. LC-MS Obtained from the Mixture Synthesis of Pyrrolidines 4 from Aldehyde Resins 2a-i.[a,b]



a) Chromatographic separation was achieved by reverse phase chromatography (C18; acetonitrile/water; 2 mL/min.) and the peaks displayed as a reconstructed ion chromatogram (RIC). b) For MW 425 (**4d,g,h**), 6/6 possible diastereomers were observed. For MW 424 (**4f**), 2/2 possible diastereomers were observed. For MW 440 (**4c**), 2/2 possible diastereomers were observed. For MW 455 (**4i**), 2/2 possible diastereomers were observed. For MW 396 (**4e**), 1/2 possible diastereomers were observed. For MW 410 (**4b**), 1/2 possible diastereomers were observed. For MW 380 (**4a**), 1/2 possible diastereomers were observed.

We have demonstrated a three component reaction on a solid support for the preparation of highly functionalized pyrrolidines **3**. These proline analogs can be prepared as single components or as an equimolar mixture of products by control of the starting benzaldehyde resin.

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14. Preparation of 4-hydroxybenzaldehyde linked to wang's resin (**2a**). To a dry, solid phase reactor flask was added (15 g, 15 mmol) of Wang's resin which was washed sequentially with CH_2Cl_2 and three times with anhydrous THF. The filtered resin was treated with 100 mL of anhydrous THF, 5.90 g (22.5 mmol) of triphenylphosphine, and 6.11 g (50 mmol) of 4-hydroxybenzaldehyde. To the stirred slurry was added 3.95 mL (25 mmol) diethylazodicarboxylate dropwise over a period of 15 min. After allowing the mixture to stir overnight, the reaction solvent was removed and the resin washed three times each with THF, DMF, methanol, CH_2Cl_2, and ether. The resin was collected and washed with diethyl ether and dried *in vacuo* to afford 15.25 g of **2a**. A loading of 0.70 meq/g was determined by quantitative measurement of the cleaved material.

15. Solid phase synthesis of **3a.** In a dry 15 mL vial equipped with a magnetic stirrer was placed 0.25 g (0.13 mmol) of **2a**, 75 mg (0.42 mmol) of leucine methyl ester hydrochloride, 71 mg (0.42 mmol) of *N*-phenylmaleimide and 8 mL of dry DMF. The mixture was treated with 60 μL (0.42 mL) of triethylamine followed by two drops of acetic acid. The vial was capped, magnetically stirred, and treated at 100 °C for 18 h. After allowing the mixture to cool, the resin was filtered, washed three times each with DMF, methanol, CH_2Cl_2 and diethyl ether and the resultant polymer dried *in vacuo*. The product was obtained by cleavage of the resin twice with trifluoroacetic acid/CH_2Cl_2 (1:1) for one h. Combined filtrates were concd to afford 63 mg of **3** as a mixture of isomers: ^{1}H NMR (DMSO) δ 1.61 (s, 3H), 2.83 (s, 3H), 3.48 (d, 1H), 3.75 (t, 1H), 4.28 (b, 2H), 4.89 (d, 1H), 6.82 (d, 1H), 6.90 (t, 1H), 7.24 (m, 1H), 7.30 (d, 1H). HRMS (FAB+): Calculated, 379.1505; Observed, 379.1522.

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