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SYNTHESIS OF A HIGHLY FUNCTIONALIZED RIGID TEMPLATE BY SOLID PHASE AZOMETHINE YLIDE CYCLOADDITION

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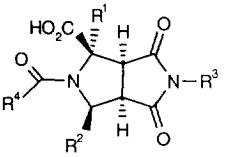
Abstract: A series of 1,5-diazabicyclo[3.3.0]octane-2-carboxylic acids have been synthesized in good yields and purities via cycloaddition of maleimides to polymer supported azomethine ylides. N-Acylation of the resulting cycloadduct enables the synthesis of diverse molecules based on a highly functionalized rigid template.

The potential for rapid lead generation by use of combinatorial libraries has recently revolutionized the drug discovery process[1] and the preparation of these libraries has prompted intense interest in solid-phase synthesis. To date the majority of libraries synthesized have been of an oligomeric peptidic nature and the requirement for small molecule non-oligomeric libraries necessitates expans1ion of the range of organic chemistry that can be carried out on polymeric supports. This, while rapidly growing, remains limited[2]. There is also a desire to construct highly diverse molecules based on rigid templates to discover ligands with improved selectivity for their biological targets. As part of our continuing effort to develop novel solid phase reactions we have examined polymer supported azomethine ylide cycloaddition chemistry to construct such a rigid template, and a recent report[3] prompts us to disclose our results.



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Our interest in this area was stimulated by work of Costero *et al*[4] who reported the use of a solid phase azomethine ylide as a trapping agent to establish the identity of a reactive intermediate. More recently solid phase azomethine ylide cycloaddition chemistry has been used preparatively to synthesize libraries of pyrrolidines from which an angiotensin converting enzyme inhibitor lead was obtained[5]. Herein we report the

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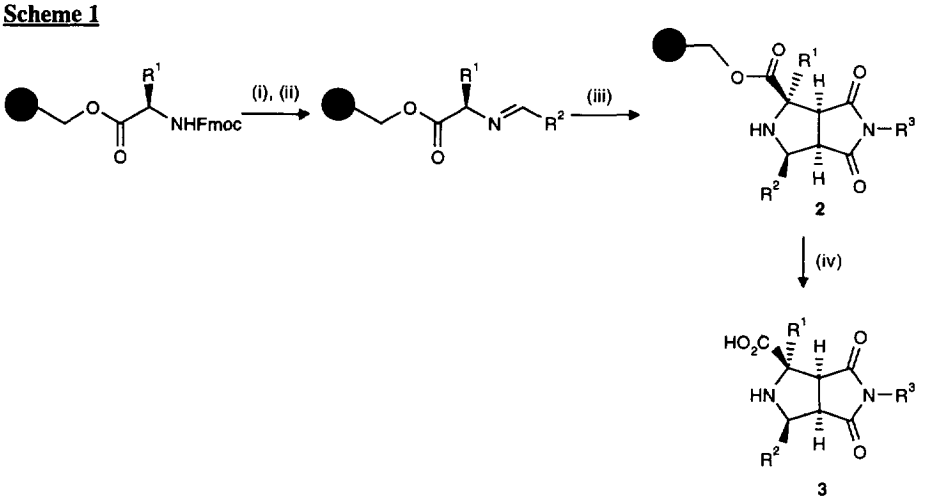
extension of this reaction to maleimides to give highly functionalized bicyclic pyrrolidines **1** in good yield and purity. Since the completion of this work Hamper et al[3] have reported the solid phase synthesis of this template via a multi-component cascade reaction with a resin-bound aldehyde.

Our strategy allows the synthesis of diverse non-oligomeric libraries with four points of variation around a rigid template from readily available starting materials. Wang resin linked Fmoc amino acid is deprotected and reacted with aldehyde to give the imine (scheme 1). For alanine and phenylalanine complete reaction occurred at room temperature in dichloromethane[6], but for leucine reaction required refluxing in toluene[7]. In our hands more efficient condensations were obtained in the absence of dehydrating agents[5]. Cycloadditon was carried out under anhydrous conditions by heating imine resin with maleimide for 24h under reflux in toluene[8]. Lower reaction temperatures gave incomplete cycloaddition.

Scheme 1



Conditions: (i) Piperidine, DMF, 30min. (ii) R^2CHO, CH_2Cl_2, room temperature or toluene, reflux, 16h (iii) N-R^3maleimide, toluene, reflux, 24h (iv) TFA/CH_2Cl_2 (1:1) 1h

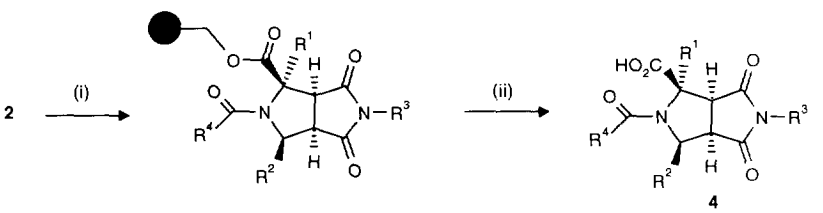
Compound	R^1	R^2	R^3	Yield (%)	HPLC purity (%)
3a	CH_3	4-MeOPh	Ph	81	89
3b	CH_3	4-NO_2Ph	Ph	90	84
3c	CH_2Ph	4-MeOPh	Ph	85	90
3d	CH_2Ph	4-NO_2Ph	Ph	84	86
3e	$CH_2CH(CH_3)_2$	4-MeOPh	CH_3	78	72
3f	$CH_2CH(CH_3)_2$	4-NO_2Ph	CH_3	75	84
3g	CH_3	4-MeOPh	CH_3	78	85
3h	CH_3	4-NO_2Ph	CH_3	83	82

The cycloadducts were obtained in high yield and good purity after cleavage (by NMR and HPLC) which was not significantly affected by the nature of the dipolarophile or aldehyde. ^{1}H NMR of the product indicated that predominantly a single diastereomer had been synthesized, with only trace amounts of the other diastereomer. NOE measurement of **3a** confirmed the stereochemistry shown, and addition of the chiral shift

reagent R-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol indicated the presence of a 1:1 mixture of enantiomers. This is consistent with the analogous solution chemistry[9], in which a single diastereomer was obtained by endo addition to the ylide in the "W"-configuration. Interestingly the multicomponent synthesis in which the azomethine ylide is tethered to the resin via the aldehyde component was reported to give a mixture of diastereomers[3].

A further point of diversity could be introduced by N-acylation of the synthesized template. Thus treatment of **2** with a large excess of an acid chloride in pyridine at room temperature gave **4** after TFA cleavage (scheme 2).[10] A double coupling protocol was needed to drive the reaction to completion, and the reaction did not proceed as well with lower concentrations of acylating agent, presumably due to the steric constraints of this system.

Scheme 2



Conditions: (i) R^4COCl, CH_2Cl_2, pyridine (ii) TFA/CH_2Cl_2 (1:1)

Compound	R^1	R^2	R^3	R^4	Yield (%)	HPLC purity (%)
4a	CH_3	4-MeOPh	Ph	Ph	95	86
4b	CH_3	4-NO_2Ph	CH_3	Ph	97	91
4c	CH_2Ph	4-MeOPh	CH_3	CH_2Ph	86	94
4d	$CH_2CH(CH_3)$	4-MeOPh	CH_3	CH_3	90	71
4e	CH_3	4-MeOPh	CH_3	CH_3	99	89

In conclusion we have developed conditions for the solid phase synthesis of several bicyclic pyrrolidines in high yields and in good purity. This strategy provides an alternative to the multicomponent procedure[3] and allows the synthesis of libraries based on a highly functionalized rigid template where substituent diversity can be introduced from readily available starting materials. Additionally the carboxyl linkage of the template to the polymeric support offers potential for the introduction of another point of diversity by nucleophilic cleavage with amines[11] which avoids the presence of a constant functional group on the template.

Acknowledgement

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References and Notes

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4. A. M. Costero, M. Pitarch and M. Luz Cano, *J. Chem Res (S)*, **1994**, 316
5. Murphy, M.M.; Schullek, J.R.; Gordon, E.M.; Gallop, M.A. *J. Am. Chem. Soc.*, **1995**, *117*, 7029
6. Typical Procedure: To 0.3mmol deprotected Fmoc Ala Wang resin(0.52mmol/g) (dried in vacuo) suspended in dry dichloromethane (10ml) in a round bottom flask under argon was added 4-nitrobenzaldehyde (3mmol) and the mixture shaken overnight. The resin was removed by filtration and washed with 3x20ml dry dichloromethane and dried in vacuo.
7. As 6 except resin was suspended in dry toluene (10ml) in a round bottom flask under argon, to which was added aldehyde (3mmol) and the mixture was heated to reflux overnight.
8. Typical Procedure: 0.16mmol resin was suspended in dry toluene (10ml) in a round bottom flask under argon and N-phenylmaleimide (1.6mmol) was added. The mixture was refluxed for 24h after which the resin was filtered and washed successively with toluene, dioxane and ether (each 3x10ml) and dried under high vacuum. The resin was cleaved by suspension in trifluoroacetic acid/ dichloromethane (1:1) for 1h, followed by washing with dichloromethane.
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10. Typical Procedure: 0.1mmol resin was suspended in 1:1 (v/v) phenylacetylchloride in dichloromethane (1ml) to which 1eq of pyridine was added, and the mixture was shaken for 16h. The resin was removed by filtration and washed successively with dichloromethane, methanol, methanol-water (3:1), methanol and dioxane (each 3x10ml). The coupling procedure was repeated, and the resin was cleaved as described above.
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