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SOLID-PHASE PYRROLIDINE SYNTHESIS *VIA* 1,3-DIPOLAR CYCLOADDITION OF AZOMETHINE YLIDES GENERATED BY THE DECARBOXYLATIVE ROUTE

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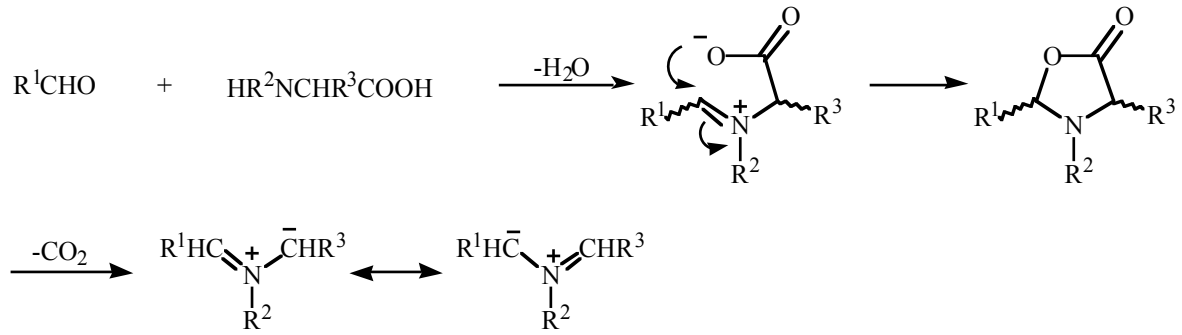
Abstract – Although solid-phase pyrrolidine synthesis *via* dipolar cycloaddition of ester-stabilized azomethine ylides has been demonstrated on several occasions, this reaction with nonstabilized azomethine ylides, generated on solid support by a decarboxylative pathway, has never been reported. Herein we present the first solid-phase synthesis of pyrrolidines *via* this route and demonstrate that the reacting azomethine ylide can be generated both from a resin-bound aldehyde or amino acid. Using cyclic and acyclic dipolarophiles, bi- and monocyclic resin-bound pyrrolidines were obtained. The modest to high degree of regio- and diastereoselectivity observed in the reaction can be tuned by the substituents of the partners of this three-component process.

Pyrrolidine heterocycle-containing alkaloids are known for their biological activities,[1,2] and accordingly, a number of combinatorial libraries of pyrrolidines were prepared over the last few years. High throughput screening techniques revealed bioactive leads for future drug development in these libraries.[3] Solid-Phase Organic Synthesis (SPOS) is one of the core techniques for the preparation of combinatorial libraries due to its ability to create arrays of diverse polyfunctional molecules in an easy, clean and fast fashion.

One of the major routes to pyrrolidines proceeds through 1,3-dipolar cycloaddition, based on the formation of an azomethine ylide (e.g. from an aldehyde and amino acid *in situ*) followed by reaction with an olefin.[4] This one-pot reaction enables the preparation of diverse poly- and mono-cyclic

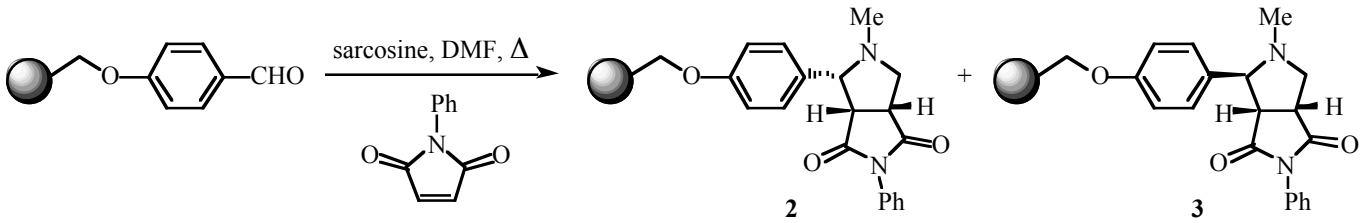
pyrrolidines. 1,3-Dipolar cycloaddition of stabilized azomethine ylides, generated from the esters of amino acids was established as the main method for the preparation of functionalized pyrrolidines bearing an ester group, both in solution and on solid support.[1,3,5,6] The use of α-amino acids, which generate azomethine ylides through a decarboxylative mechanism introduced by Grigg (Scheme 1), was applied only in solution synthesis.[2,7] Herein we present the first use of this method for the general synthesis of a number of pyrrolidine compounds using SPOS techniques.



Scheme 1 The decarboxylative mechanism of azomethine ylide formation

Three components are required to generate pyrrolidines in this type of dipolar cycloaddition. Amine (amino acid) and aldehyde form the imine, which is activated *via* decarboxylation, forming the transient azomethine ylide – the 1,3-dipole element. An olefin, usually containing an electron-withdrawing group, plays the role of the dipolarophile. In this work we examine general methods for the full conversion of each of these components, linked to solid support (Wang resin in this study), to the corresponding pyrrolidine. The reaction products were analyzed on the resin by a gel-phase ^{13}C NMR spectroscopic technique and in solution, following trifluoroacetic acid-induced cleavage, by a variety of techniques.

The model reaction of resin-bound aldehyde,[8] sarcosine and *N*-phenylmaleimide was used to determine the optimized conditions required (Scheme 2).[9] We used DMF as the solvent and refluxed the reaction overnight in the presence of trimethyl orthoformate which, from our experience, improves the formation of the imine expected as an intermediate.[10] Two diastereomers (**2**) and (**3**) were produced in equal amounts (combined yield >98%, purity 95%) and fully characterized by NMR and MS spectrometry, following their cleavage.[11]



Scheme 2 The model reaction[9]

Optimization screening of the solvent, temperature and time parameters, revealed that the best results were achieved at 90 ^{0}C in DMF after 24 h. Trimethyl orthoformate was found to be unnecessary for this solid-phase reaction. A base was needed, however, when hydrochlorides of additional *N*-methylated amino acids (Ala and Val) were used, in order to generate the active reacting component. In both cases, bicyclic pyrrolidine products (**4** and **5** for alanine, **6** and **7** for valine) were formed, in 95% and 85% combined yields respectively (Figure 1).

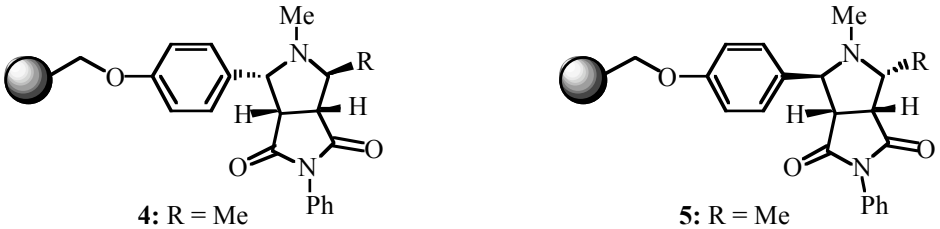


Figure 1

Although four diastereomeric products are possible, only two were formed in the case of alanine in a 1:0.8 ratio. Interestingly, mostly one diastereomer (**6**) was formed in the case of valine, and only traces of one of its diastereomeric counterparts was observed in the ^{1}H NMR spectrum of the crude mixture in cleavage solution.

The relative configuration of the products (**2**-**6**) was established, following their cleavage from the support. 1,3-Dipolar cycloaddition is a concerted process. Accordingly, the addition is *syn*, and the two hydrogens of the common edge of the two cycles are always mutually *cis*-positioned. The NOESY experiments and the coupling constants of the pyrrolidine hydrogens demonstrated that the aryl and carbonyls of **2**, **4** and **6** are cofacial, and *trans* to the alkyl substituent in **4** and **6**.[12] The opposite configuration of the aryl and alkyl substituents relative to the carbonyls was revealed in **5** and **7**.[13] The aryl group is also positioned trans to the carbonyls in **3**.

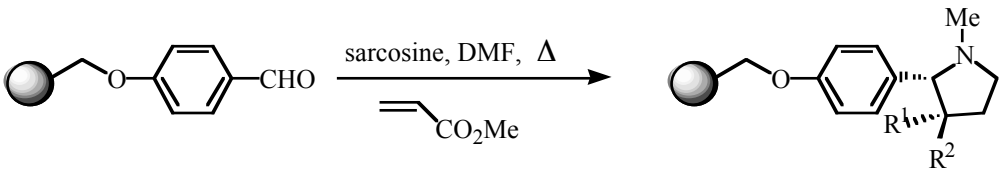
Figure 2 Four possible azomethine ylide configurations

From these findings, it is clear that the products originate from the anti-dipoles **I** and **II** rather than from *syn*-dipoles, as also frequently observed in solution (Figure 2).[14] Since **I**-*exo* and **II**-*endo* reaction modes form the same product (e.g. **5**) as well as **II**-*exo* and **I**-*endo* reaction modes (e.g. **4**), it is difficult to

distinguish at this stage between the three possibilities. Either only one of the *anti*-dipoles is involved and the two products are the outcome of the *endo*/*exo* approach, or both dipoles are formed and one of the approaches (either *endo* or *exo*) dominates the reaction pathway. It is also possible, of course, that both dipoles (**I** and **II**) are formed and each reacts through both *endo* and *exo* modes.

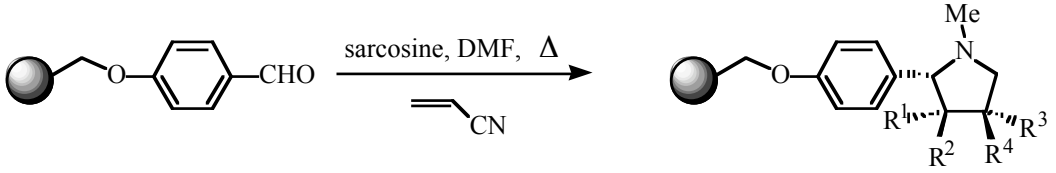
Two acyclic olefins were tested in the reaction: acrylonitrile and methyl acrylate. In the presence of sarcosine, the same reaction conditions led to the full conversion of the resin-bound aldehyde to the corresponding pyrrolidine products.

In the case of these monosubstituted dipolarophiles, the issue of regioselectivity adds to that of stereoselectivity. Fortunately, in the case of methyl acrylate, the regioselectivity was high and only two diastereomeric products (**8**) and (**9**) with the methoxycarbonyl vicinal to the aryl substituent were formed in a 6:1 ratio (combined yield 97%, purity 90%, Scheme 3). It is surprising that the two most bulky substituents of the pyrrolidine ring in these products are vicinal. It is even more surprising that, in the major product, they are in the *cis* configuration. Although the exact source of the regioselectivity is not clear, it must be an electronic effect.



8: $R^1 = CO_2Me$, $R^2 = H$
9: $R^1 = H$, $R^2 = CO_2Me$

Scheme 3



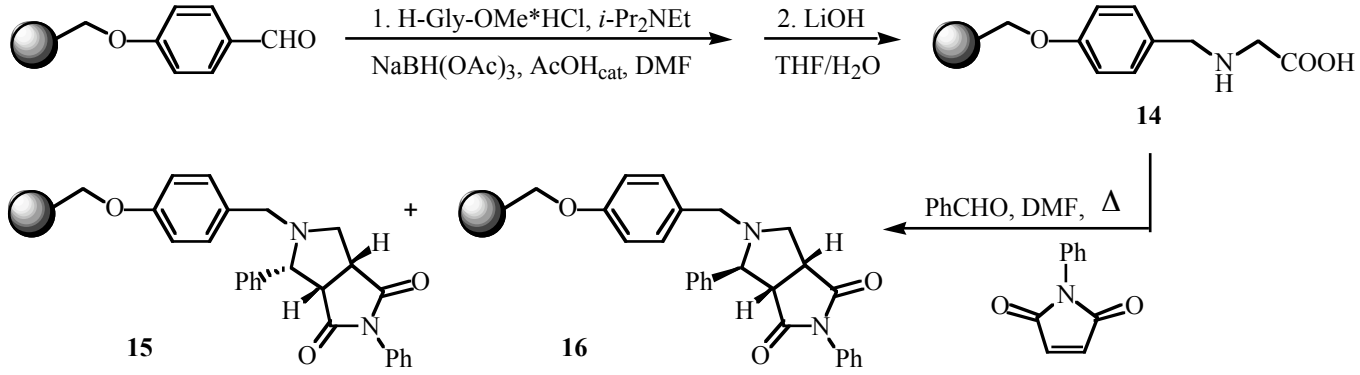
10: $R^1 = CN$, $R^2 = R^3 = R^4 = H$ (major)
11: $R^2 = CN$, $R^1 = R^3 = R^4 = H$
12: $R^3 = CN$, $R^1 = R^2 = R^4 = H$ (traces)
13: $R^4 = CN$, $R^1 = R^2 = R^3 = H$ (traces)

Scheme 4

In the case of acrylonitrile, the regioselectivity is diminished. Although two dominant products (**10** and **11**) were formed, displaying a vicinal aryl and cyano group, traces of two minor products resulting from

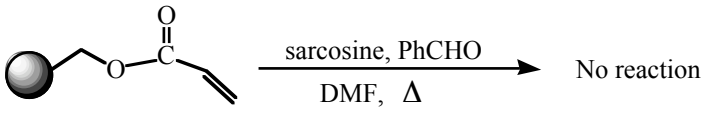
the opposite regioselectivity of the addition are visible in the gel-phase ^{13}C NMR spectrum as well as the ^{13}C NMR spectrum of the cleavage solution (combined yield 95%, purity 90%, Scheme 4). The configuration of the major isomer (**10**) is similar to that of **8**.

A different type of bicyclic pyrrolidines was prepared *via* a resin-bound amino acid instead of an aldehyde.[15] To prepare this resin-bound building block of the dipolar cycloaddition, the resin-bound aldehyde (**1**) was reductively aminated with the methyl ester of glycine, and the product of the amination was hydrolized to form resin-bound *N*-benzylglycine (**14**) (Scheme 5). The reaction of **14** in the presence of benzaldehyde and *N*-phenylmaleimide cleanly converted the resin into two bicyclic diastereomeric products (**15** and **16**) formed in equivalent amounts (combined yield 80%, purity 80%).



Scheme 5 1,3-Dipolar cycloaddition *via* resin-bound aminoacid

Thus, both the aldehyde and amino acid components of the three-component 1,3-dipolar cycloaddition can be used as resin-bound building blocks. On the other hand, all attempts to perform the reaction with the resin-bound dipolarophile (e.g. acrylate) and soluble aldehyde and amino acid (or a preformed imine derivative of an amino acid) failed, for a reason yet to be discovered (Scheme 6).



Scheme 6 Attempted dipolar cycloaddition *via* a resin-bound olefin

In conclusion, we were able, for the first time, to carry out on solid support 1,3-dipolar cycloaddition *via* nonstabilized azomethine ylides, generated by a decarboxylative route. We demonstrated that this transformation can be accomplished starting both from a resin-bound aldehyde or resin-bound amino acid. We discovered that, for some substrates, high regio- and diastereoselectivity can be achieved. Further studies, exploiting these first results and directed to increase the selectivity of the transformation, are underway.

ACKNOWLEDGEMENTS

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9. General procedure for 1,3-DC using anchored aldehyde: *N*-Me-amino acid (5 equiv.) and an olefin (7 equiv.) dissolved in DMF (5 mL/g resin) were added to a vial containing a resin-bound aldehyde swollen in DMF (5 mL/g resin). When hydrochloride salts of amino acids were used, triethylamine (7 equiv.) was added. The vial was closed under a nitrogen atmosphere and gently stirred overnight at 90ºC. After cooling, the resin was filtered and washed with DMF×2, DMF/H_2O×2, H_2O×2, DMF×2 and DCM×3. The resin was dried on vacuum. For characterization, the resin was subjected to gel-phase ^{13}C NMR or cleaved by TFA:$CDCl_3$ solution (1:1 with 11mM benzene as internal standard, 1 mL/100 mg resin). Following the cleavage, the filtrate was collected and diluted in EtOAc. The organic layer was neutralized through extensive washing by saturated aqueous $NaHCO_3$, until no reaction was observed, washed with brine, dried over magnesium sulfate and concentrated by evaporation yielding the crude as an yellowish oil. The residue was purified by flash chromatography (EtOAc/hexanes, silica gel), to give the pure products.

   Typical characterization, compound (**8**): Partial gel-phase ^{13}C NMR (100.8 MHz, C_6D_6): δ 174.3, 158.4, 144.9, 73.4, 55.3, 52.4, 50.5, 49.4, 26.8. Following acidolytic cleavage, ^1H NMR (400 MHz, CD_3COCD_3): δ 7.03 (d, *J* = 8.4 Hz, 2H), 6.64 (d, *J* = 8.4 Hz, 2H), 3.48 (s, 3H), 3.10 (d, *J* = 9.6 Hz, 1H), 3.09 (m, 1H), 2.83 (q, *J* = 9.6 Hz, 1H), 2.32 (t, *J* = 9.6 Hz, 1H), 2.13 (t, *J* = 9.6 Hz, 1H), 2.01 (s, 3H), 1.93 (m, 1H). ^{13}C NMR (100.8 MHz, CD_3COCD_3): δ 176.9, 158.9, 130.9, 130.6, 116.8, 76.3, 57.3, 55.4, 52.8, 40.7, 28.3. HRMS (EI): m/z calcd for $C_{13}H_{17}NO_3$ (M^+) 235.1208; found 235.1211.
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11. **2** and **3** are not two separate resins, but rather two diastereomers, obtained as a mixture on the same support beads. For clarity reasons they are drawn as two separate structures, but only after cleavage is their separation possible. The same is true for pairs **4** and **5**, **6** and **7**, **8** and **9**, **15** and **16** as well as for the four isomers (**10**-**13**).
12. Larger coupling constants (8-10 Hz) were attributed to mutually *cis* vicinal hydrogens, while smaller constants (usually 1-3 Hz, at most 6.5 Hz) were attributed to *trans* hydrogens.
13. Compound (**7**) exhibiting a spectral pattern similar to that of **5**, was identified in the cleavage solution of the reaction product, but not isolated due to the very low yield.
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15. Procedure for the preparation of *N*-anchored glycine: H-Gly-OMe hydrochloride (0.5 g, 4 mmol, 5 equiv.) was dissolved in 1% AcOH in DMF (10 mL/ g resin) and then $NaBH(OAc)_3$ (2.5 g, 12 mmol,

15 equiv.) was added. Resin-bound aldehyde (1 g, 0.8 mmol/g, 0.8 mmol) was immediately added to the mixture. The reaction was complete in 1 h. The resin was then rinsed with MeOH ×2, 10% DIPEA in DMF ×2, DMF ×3, DCM ×5 and dried on vacuum. A solution of LiOH (58 mg, 2.4 mmol, 3 equiv.) in 10% H_2O in THF (5 mL) was added to the amino acid ester resin, swollen in the same solvent mixture (5 mL). The reaction was gently stirred overnight at rt. The resin was then rinsed with 10% H_2O in THF ×5, THF ×5, DCM ×5 and dried on vacuum. Yield 97%. Following acidolytic cleavage: ^{1}H NMR (200 MHz, $CDCl_3$/TFA 1:1): δ 7.93 (br s), 7.32 (d, J = 7.3 Hz, 2H), 6.68 (d, J = 7.3 Hz, 2H), 4.37 (t, J = 4.3 Hz, 2H), 4.08 (t, J = 5.1 Hz, 2H). ^{13}C NMR (50.4 MHz, $CDCl_3$/TFA 1:1): δ 170.5, 156.3, 132.9, 132.0, 116.9, 52.6, 46.7.

The dipolar cycloaddition procedure is the same as in footnote 9, but the resin-bound glycine is used instead of the resin-bound aldehyde, and benzaldehyde (10 equiv.) is used in solution instead of the *N*-Me-amino acid.