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Solid-Phase Synthesis of Pyrrolidines *Via* 2-Azaallyl Anion Cycloadditions with Alkenes

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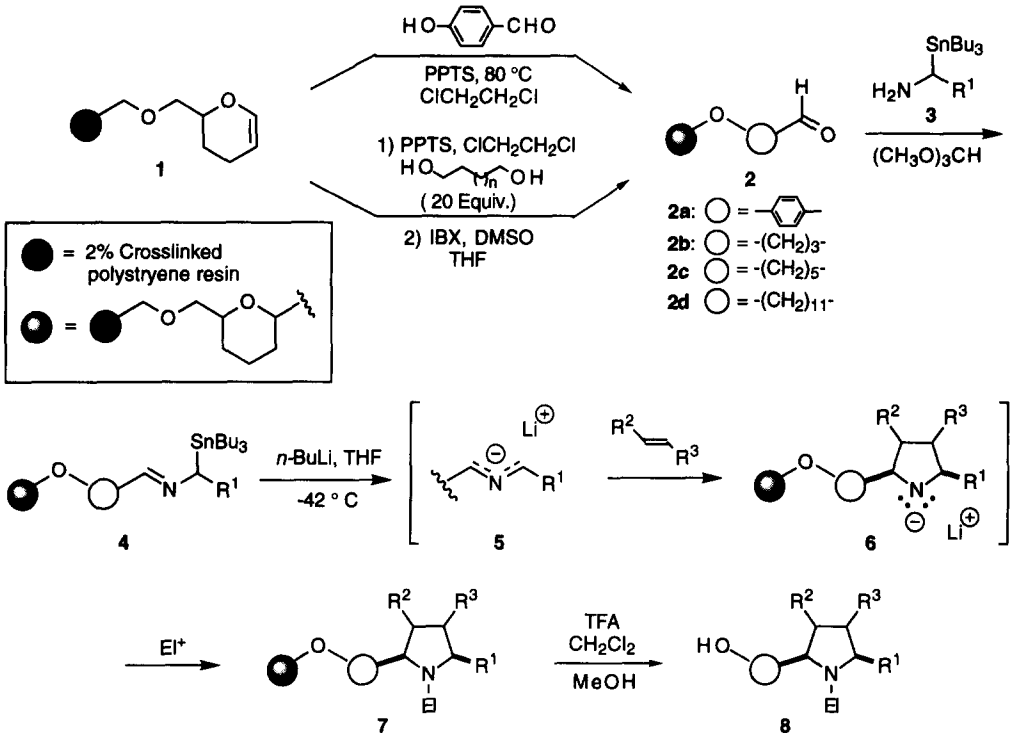
Abstract: The preparation of a variety of highly substituted pyrrolidines was achieved by solid-phase synthesis through the [2πs + 4πs] cycloaddition of 2-azaallyl anions with alkenes. Resin-bound aldehydes **2** were condensed with α-amino stannanes **3** to afford (2-azaallyl)stannanes **4**. Transmetalation of **4** with *n*-BuLi in the presence of electron-rich alkenes followed by the addition of an electrophile provided the polymer-bound pyrrolidines **7**. The free pyrrolidines **9-23** were obtained upon cleavage from the solid support. © 1997 Elsevier Science Ltd.

Solid-phase organic synthesis has become an important tool for the rapid preparation of compound libraries for lead generation and optimization.[1] Consequently, a great deal of effort has been directed toward extending the range of reactions available for use on solid supports. The wide occurrence of heterocycles in biologically active compounds makes them attractive targets for library generation. The syntheses of heterocyclic compounds *via* cycloaddition reactions on the solid phase are of especially high potential. Indeed, several reports of the use of 1,3-dipolar cycloaddition reactions on the solid phase have appeared.[2] We report herein the adaptation of our 2-azaallyl anion cycloaddition methodology to the solid phase, resulting in a new method that may be useful for the generation of libraries of pyrrolidines.

We have reported the solution-phase synthesis of pyrrolidines by the cycloaddition of non-stabilized 2-azaallyl anions with electron rich alkenes.[3,4] Application of the 2-azaallyl anion method to the solid phase may result in the assembly of diverse libraries of pyrrolidines, since the use of different 2-azaallyl anions, alkenes, and quenching reagents would allow variation of all five positions of the pyrrolidine ring in one key operation. This method would complement the related azomethine ylide cycloadditions,[5] which have already been adapted to the solid phase,[2] since azomethine ylides generally require electron-poor (rather than electron-rich) alkenes, and variation of the *N*-substituent of the pyrrolidine is more difficult in the ylide method.

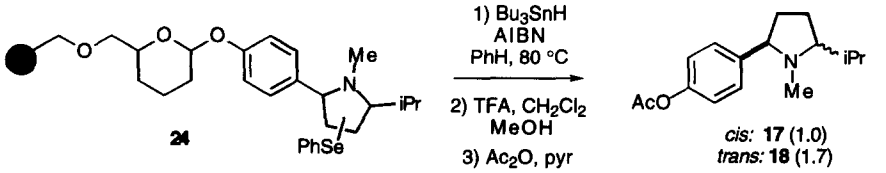
Our initial work centered on the attachment of the 2-azaallyl anions, rather than the alkenes, to the polymer support (Scheme 1). The resin was used either loose or contained in IRORI MicroKans™, both in a round-bottomed flask. Agitation was accomplished with either a shaker table or by rotating the flask with a rotary evaporator motor. *p*-Hydroxybenzaldehyde was attached to Thompson and Ellman's dihydropyran resin **1**,[6] prepared from (chloromethyl)polystyrene), to give the aldehyde **2a**. Three different 1,n-diols were also loaded, producing the aldehydes **2b-2d** after oxidation of the intermediate alcohol with 2-iodoxybenzoic acid (IBX) in DMSO/THF.[7] Twenty equivalents of the diol were used to avoid crosslinking. Condensation of the aldehydes **2** with an α-amino stannane **3**[4] in the presence of trimethylorthoformate[8] gave the imines **4**, which were mixed with an alkene and treated with *n*-butyllithium at an optimal temperature of -42 °C to produce the 2-azaallyl anions **5** and thus the *N*-lithiopyrrolidines **6**. Quenching **6** with an electrophile produced the support-bound pyrrolidines **7**. In general, it is thought that these cycloadditions proceed in a concerted fashion through the "W"-conformation of the anion **5** as shown, leading to *cis*-2,5-disubstituted pyrrolidines.[3,4] Cleavage from the support was accomplished with a 5:1:1 mixture of CH_2Cl_2/TFA/MeOH to yield the free pyrrolidines **8** after basic workup.



Scheme 1. Solid-phase synthesis of pyrrolidines using the support-bound 2-azaallyl anions 5.

Table 1 summarizes the specific cycloadditions that were carried out in order to show that polymer-supported 2-azaallyl anion chemistry is possible. Overall yields of 32-50% based on the the loading of (chloromethyl)polystyrene are excellent for such a multi-step process. As expected from earlier work,[3] mixtures of regio- and stereoisomers were obtained,[9] adding to the diversity of the products. Symmetrical diols with four, six, and twelve carbons were used to explore the effect of tether length on the cycloadditions (Entries 1-4). Similar yields and product ratios of pyrrolidines **9-16** were obtained, indicating that the tether length had no appreciable influence on the outcome of the reaction.

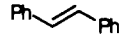
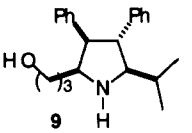
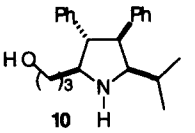
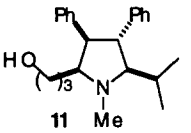
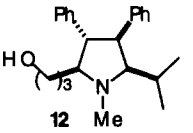
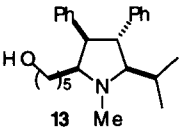
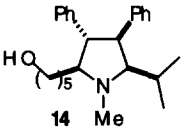
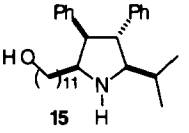
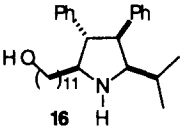
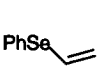
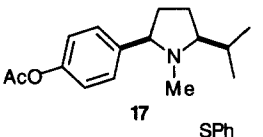
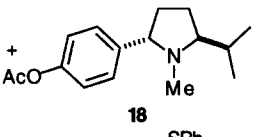
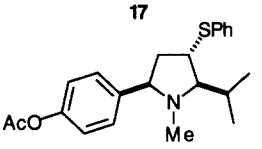
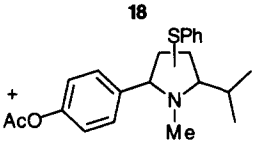
Entries 5 and 6 show both the use of an unsymmetrical tether and the use of anionophiles that are known to be useful for further transformations (i.e., reductive cleavage or elimination).[3] For example, equation 1 shows the removal of the selenide from the initial resin-bound pyrrolidine **24**, producing **17** and **18** (see also Table 1, entry 5).[10] While the *cis*-pyrrolidine **17** was expected based on a stereospecific cycloaddition of the "W"-form of the 2-azaallyl anion,[3] the presence of the *trans*-pyrrolidine **18** was surprising, though not unprecedented,[3,4] perhaps arising from a stepwise reaction pathway.



(eq. 1)

Although all of the examples in Table 1 were carried out using the same stannyl amine **3** (R^1=iPr), resulting in an isopropyl group at C(5), future work will employ other stannyl amines bearing H, alkyl, aryl, and alkenyl groups, all known from our earlier studies.[3,4,11]

Table 1. Pyrrolidines prepared using the solid-phase method.

Entry	Aldehyde	Alkene	El^+	Products	Yield[a] (ratio)
1	**2b**		H_2O	 **9** +  **10**	48%[b] (2:1)
2	**2b**		MeI	 **11** +  **12**	44%[c,d] (2:1)
3	**2c**		MeI	 **13** +  **14**	45%[c,d] (2:1)
4	**2d**		H_2O	 **15** +  **16**	50%[b] (2:1)
5	**2a**		MeI	 **17** +  **18**	32%[b,e,f] (1:1.7)
6	**2a**		MeI	 +  **19** **19-21 + 22,23**	39%[b,f,g]

[a] Purified yields, determined by mass balance based on the initial loading level of the resin. [b] Loose resin used. [c]Reaction run with resin contained in IRORI MicroKan™ reactors. [d] Isomers were not separated. [e]Pyrrolidines **17** and **18** were isolated after removal of the phenylseleno group with Bu_3SnH, AIBN followed by cleavage from the resin (TFA) and acetylation. See eq. 1. [f]Acetylation after cleavage from the resin was carried out to avoid problems with the isolation of these water-soluble phenolic amines. [g]Isolated as two chromatographic fractions. The first fraction gave a 27% yield of three compounds (**19-21**) as a 3.4:1.4:1.0 mixture, from which **19** was isolated upon crystallization from hexane. The second fraction gave a 12% yield of a 1.2:1 ratio of **22** and **23**.

In conclusion, we have developed a solid-phase synthesis of pyrrolidines using 2-azaallyl anion cycloadditions with electron-rich alkenes. This method is complementary to azomethine ylide routes which involve electron-poor alkenes. Substitution at all five ring positions can be varied, potentially generating a diverse array of pyrrolidines. Our recent extension of this method to the synthesis of libraries of pyrrolidines will be described in a full account of this work.

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