

# Generation and Cycloaddition of Polymer-Supported Azomethine Ylide via a 1,2-Silatropic Shift of $\alpha$ -Silylimines: Traceless Synthesis of Pyrrolidine Derivatives

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## ABSTRACT



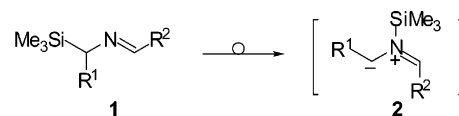
The 1,3-dipolar cycloaddition of polymer-supported azomethine ylides to dipolarophiles gave pyrrolidine derivatives in good yields. The azomethine ylides were generated from resin-bound  $\alpha$ -silylimines via a 1,2-silatropic shift. The features of this method are not only a traceless synthesis but also a unique solid-phase route to pyrrolidines with extensive diversity.

Solid-phase organic synthesis (SPOS)<sup>1</sup> is, at this time, a well-respected tool for the production of combinatorial libraries.<sup>2</sup> One of the most useful approaches to the synthesis of diverse heterocyclic compounds involves 1,3-dipolar cycloaddition,<sup>3</sup> and in the past few years, a considerable number of procedures for the solid-phase synthesis of heterocycles using 1,3-dipolar cycloaddition have been reported,<sup>4</sup> including our recent procedure.<sup>5</sup>

In a series of studies in our laboratories<sup>6</sup> on the generation of 1,3-dipoles in solution phase, we discovered a unique method for the generation of azomethine ylides from

$\alpha$ -silylimines via a 1,2-silatropic shift of the silyl group onto the nitrogen of the imino group (Scheme 1).<sup>6d,f</sup> It is

**Scheme 1.** Generation of Azomethine Ylides from  $\alpha$ -Silylimines via 1,2-Silatropy



noteworthy that this method does not require any additives and can be performed under completely neutral conditions. Moreover, after cycloaddition, the migrated silyl group can be readily detached by simple treatment to afford N-substituted or unsubstituted five-membered heterocycles.

If a polymer is attached to the silyl group of **1**, this would greatly enhance the versatility of the reaction. Not only could the target pyrrolidines be easily separated from the resin,

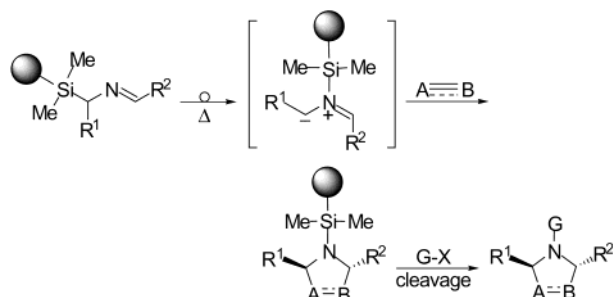
(1) (a) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137. (b) Hall, D. G.; Manku, S.; Wang, F. J. *Comb. Chem.* **2001**, *3*, 125. (c) Wang, J.; Ramnarayan, K. J. *Comb. Chem.* **1999**, *1*, 524. (d) Lorschach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549. (e) Bunin, B. A. In *The Combinatorial Index*; Academic Press: San Diego, 1998. (f) Ellman, J. A. *Acc. Chem. Res.* **1996**, *29*, 132.

(2) (a) Dolle, R. E. J. *Comb. Chem.* **2000**, *2*, 383. (b) Dolle, R. E.; Nelson, K. H. J. *Comb. Chem.* **1999**, *1*, 235. (c) Kobayashi, S. *Chem. Soc. Rev.* **1999**, *28*, 1.

(3) *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vols. 1 and 2.

but diverse pyrrolidines could be obtained, even at the cleavage step by the introduction of an electrophilic group (G) onto the nitrogen (Scheme 2). On the basis of this

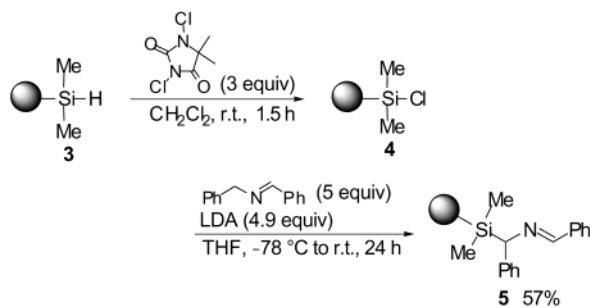
**Scheme 2.** Protocol for Generation and Cycloaddition of Polymer-Supported Azomethine Ylides



scenario, we report here on the solid-phase synthesis of pyrrolidines from polymer-supported  $\alpha$ -silylimines.

The polymer-supported  $\alpha$ -silylimine **5** was prepared according to Scheme 3. The starting resin **3** was converted to

**Scheme 3.** Preparation of Polymer-Supported  $\alpha$ -Silylimine **5**



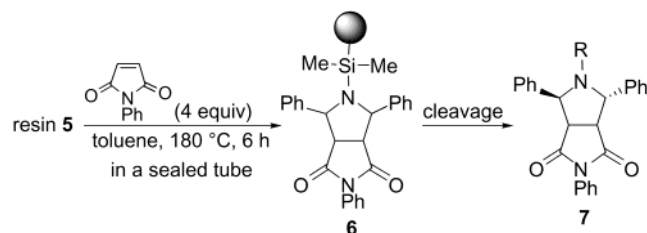
an activated silyl chloride resin **4** immediately prior to use, thus avoiding the need to store this highly reactive, moisture-sensitive intermediate. Chlorination was accomplished by treatment of **3** with 1,3-dichloro-5,5-dimethylhydantoin.<sup>7</sup>

(4) See, for example: (a) Cheng, W.-C.; Wong, M.; Olmstead, M. M.; Kurth, M. J. *Org. Lett.* **2002**, *4*, 741. (b) Shang, Y.-J.; Wang, Y.-G. *Tetrahedron Lett.* **2002**, *43*, 2247. (c) Faita, G.; Mella, M.; Mortoni, A.; Paio, A.; Quadrelli, P.; Seneci, P. *Eur. J. Org. Chem.* **2002**, 1175. (d) Barrett, A. G. M.; Boffey, R. J.; Frederiksen, M. U.; Newton, C. G.; Roberts, R. S. *Tetrahedron Lett.* **2001**, *42*, 5579. (e) Hoveyda, H. R.; Hall, D. G. *Org. Lett.* **2001**, *3*, 3491. (f) Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron Lett.* **2000**, *41*, 1265. (g) Dondas, H. A.; Grigg, R.; MacLachlan, W. S.; MacPherson, D. T.; Markandu, J.; Sridharan, V.; Suganthan, S. *Tetrahedron Lett.* **2000**, *41*, 967. (h) Park, K.-H.; Kurth, M. J. *Tetrahedron Lett.* **1999**, *40*, 5841. (i) Gong, Y.-D.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 3081. (j) Bilodeau, M. T.; Cunningham, A. M. *J. Org. Chem.* **1998**, *63*, 2800. (k) Kobayashi, S.; Akiyama, R. *Tetrahedron Lett.* **1998**, *39*, 9211. (l) Whitehouse, D. L.; Nelson, K. H.; Savinov, S. N.; Löwe, R. S.; Austin, D. J. *Bioorg. Med. Chem.* **1998**, *6*, 1273. (m) Whitehouse, D. L.; Nelson, K. H.; Savinov, S. N.; Austin, D. J. *Tetrahedron Lett.* **1997**, *38*, 7139. (n) Gowravaram, M. R.; Gallop, M. A. *Tetrahedron Lett.* **1997**, *38*, 6973. (o) Kurth, M. J.; Randall, L. A. A.; Takenouchi, K. *J. Org. Chem.* **1996**, *61*, 8755. (p) Murphy, M. M.; Schullek, J. R.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 7029. (q) Beebe, X.; Chiappari, C. L.; Olmstead, M. M.; Kurth, M. J.; Schore, N. E. *J. Org. Chem.* **1995**, *60*, 4204.

Freshly prepared resin **4** was treated with an azaallyl anion, generated in situ from *N*-benzylidene-*N*-benzylamine and LDA, to afford the desired  $\alpha$ -silylimine **5** bound to the resin. The progress of the reactions was directly monitored by FT-IR while the product was attached to the resin. The yield of resin **5** based on the loading of resin **3** was determined by elemental analysis.

The prepared polymer-supported  $\alpha$ -silylimine **5** was reacted with *N*-phenylmaleimide in toluene at 180 °C for 6 h. After the reaction, the polymer was filtered off and washed repeatedly with several organic solvents. No residue was recovered from the filtrate, indicating that the Si–N bond in the polymer was not easily cleaved by moisture, in contrast to that in the product from the corresponding solution-phase cycloaddition. The fact led us to examine the conditions of the final cleavage step (Table 1). Although cleavage using

**Table 1.** Cycloaddition of Resin **5** with *N*-Phenylmaleimide and Successive Cleavage Conditions



entry	cleavage reagent	solvent	temp	time (h)	R	yield <sup>a</sup> (%)
1	H <sub>2</sub> O (excess)	THF	rt	48	H	( <b>7a</b> ) 49 <sup>b</sup>
2	HCl (excess)	THF	rt	3	H	( <b>7a</b> ) 90
3	TFA (excess)	CH <sub>2</sub> Cl <sub>2</sub>	rt	0.1	H	( <b>7a</b> ) 90
4	PhCOCl (3 equiv)	CH <sub>2</sub> Cl <sub>2</sub>	rt	12	PhCO	( <b>7b</b> ) 70
5	CH <sub>2</sub> =CHCH <sub>2</sub> I (6 equiv)	DMF	90 °C	5	CH <sub>2</sub> =CHCH <sub>2</sub> ( <b>7c</b> )	45

<sup>a</sup> Based on the loading of resin **5**. <sup>b</sup> Resin **6** was recovered.

aqueous THF was not effective under mild conditions (entry 1), a stereoselective cycloaddition proceeded to give the sole product **7a** resulting in a solid-phase synthesis without leaving a linker trace. When acids were employed in the cleavage reaction, the *N*-unsubstituted cycloadduct was obtained in high yields (entries 2 and 3). Other electrophiles were also tested to evaluate the utility of this simple operation. The successful introduction of a benzoyl or an

(5) Washizuka, K.-I.; Nagai, K.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **2000**, *41*, 691.

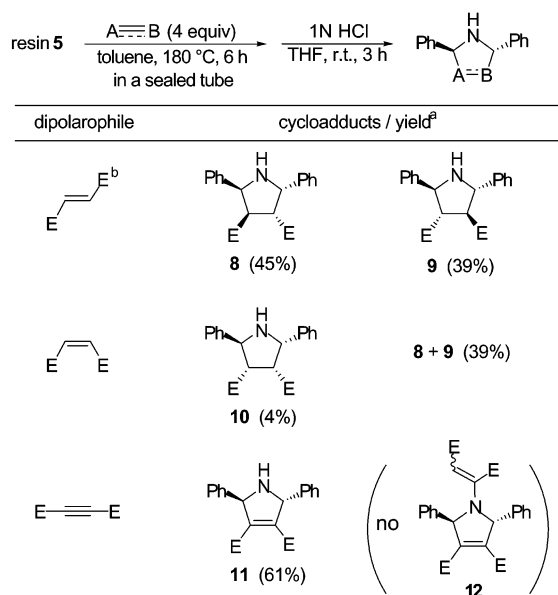
(6) (a) Komatsu, M.; Choi, J.; Oderaotoshi, Y.; Minakata, S. *Tetrahedron Lett.* **2001**, *42*, 9221. (b) Washizuka, K.-I.; Nagai, K.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1999**, *40*, 8849. (c) Washizuka, K.-I.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1999**, *55*, 12969. (d) Iyoda, M.; Sultana, F.; Komatsu, M. *Chem. Lett.* **1995**, 1133. (e) Ohno, M.; Komatsu, M.; Miyata, H.; Ohshiro, Y. *Tetrahedron Lett.* **1991**, *32*, 5813. (f) Komatsu, M.; Ohno, M.; Tsuno, S.; Ohshiro, Y. *Chem. Lett.* **1990**, 575. Although refs 6d and 6f are the preliminary reports on generation and cycloaddition of azomethine ylides via thermal 1,2-silylropy, details of this chemistry will be published elsewhere.

(7) Hu, Y.; Porco, J. A., Jr.; Labadie, J. W.; Gooding, O. W. *J. Org. Chem.* **1998**, *63*, 4518.

allyl group on the nitrogen of the cycloadduct was achieved when benzoyl chloride or allyl iodide was used as the cleavage reagents (entries 4 and 5).

The present method can also be applied to solid-phase 1,3-dipolar cycloadditions with other olefinic and acetylenic dipolarophiles (Table 2). Treatment of resin **5** with dimethyl

**Table 2.** Cycloaddition of Resin **5** with Dipolarophiles



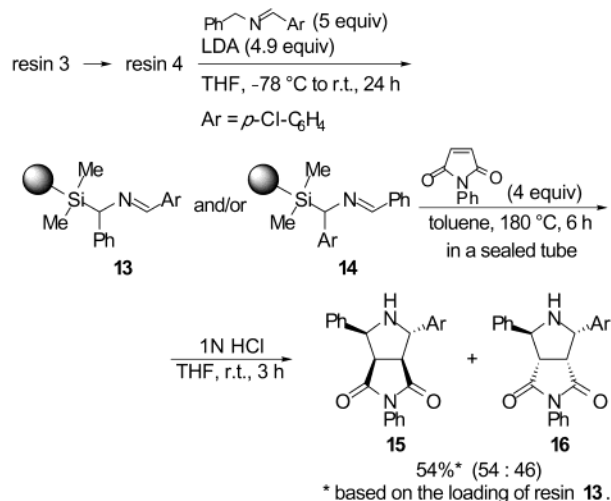
<sup>a</sup> Based on the loading of resin **5**. <sup>b</sup> E = -COOMe.

fumarate in toluene under standard conditions, followed by cleavage with 1 N HCl, gave pyrrolidine derivatives in 84% yield. When dimethyl maleate was employed in the reaction, pyrrolidines **8** and **9** were obtained as major products, along with a small amount of pyrrolidine **10**. The stereochemistry in the case where dimethyl maleate is used can be explained as follows. An in situ isomerization of the starting olefin (dimethyl maleate) to the fumarate derivative induced the formation of compounds **8** and **9**, because dimethyl fumarate was detected in the resulting reaction mixtures, even when the maleate derivative was used. In our preliminary experiment, isomerization of dimethyl maleate to dimethyl fumarate was observed in the presence of a catalytic amount of an imine at 180 °C. Moreover, when pyrrolidine **10** was treated under the reaction conditions, no isomerization to **8** and/or **9** took place and the starting material **10** was recovered quantitatively. A reaction using an acetylenic dipolarophile such as dimethyl acetylenedicarboxylate (DMAD) also proceeded smoothly to afford an *N*-unsubstituted 3-pyrroline derivative **11** in good yield. While the corresponding cycloaddition in solution phase<sup>6c</sup> produced compound **12** as the sole product, formed by the insertion of excessive DMAD to the Si-N bond of the initial cycloadduct, the solid-phase permitted the formation of undesired insertion product to be completely controlled.

To obtain further diverse cycloadducts, an unsymmetrical azallyl anion was employed in the solid-phase synthesis.

Although the same procedure as shown in Scheme 3 would permit the production of two regioisomers at the step of silylation, the structure of an active species (an azomethine ylide) generated from the each isomers would be expected to be the same. This is one of the characteristic advantages of the present method.  $\alpha$ -Silylimines (**13** and/or **14**) were prepared according to Scheme 4. The polymer was treated

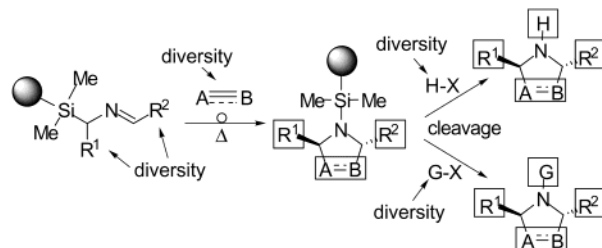
**Scheme 4.** Solid-Phase Synthesis of an Unsymmetrical Pyrrolidine



with *N*-phenylmaleimide under thermal conditions, and the subsequent cleavage operation gave unsymmetrical pyrrolidines in good yields.

In summary, we report on the development of a novel traceless synthesis of pyrrolidine derivatives using polymer-supported  $\alpha$ -silylimines. An intramolecular 1,2-silatropic shift of the  $\alpha$ -silylimines gave the polymer-supported azomethine ylides, which underwent 1,3-dipolar cycloaddition with dipolarophiles. As reported here, we have also demonstrated reagent versatility in (i) the formation of  $\alpha$ -silylimines, (ii) cycloaddition, and (iii) cleavage, suggesting that this methodology has great potential for use in constructing libraries (Scheme 5). The introduction of a functional group as well as hydrogen in a cleavage step is particularly unique and promises to be useful from the synthetic point of view.

**Scheme 5.** Solid-Phase Synthesis of Highly Diverse Pyrrolidines



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**Supporting Information Available:** Experimental procedures and characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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