# A Versatile Cycloaddition for the Generation of Pyrrolidine Derivatives *via* C–N–C 1,3-Dipoles

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The condensation of *N*-(trimethylsilylmethyl)benzylamine and aldehydes spontaneously gave azomethine ylides, which react with electron deficient olefins to yield cycloadducts under mild conditions.

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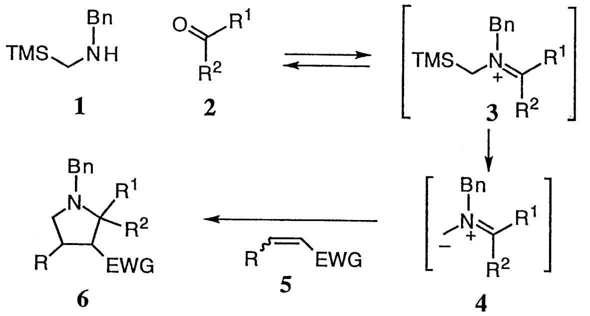
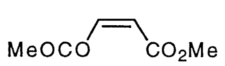
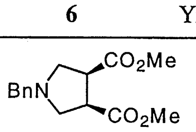
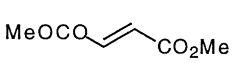
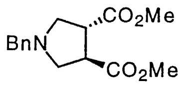
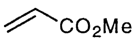
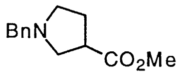
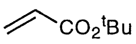
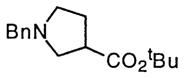
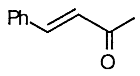
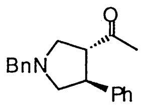
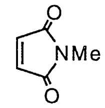
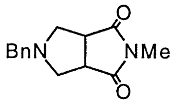
Among a variety of 1,3-dipoles, the cycloaddition of azomethine ylides and olefins offers a straightforward way for the construction of a pyrrolidine framework.[1] In the context of our research directed toward the facile generation of such a 1,3-dipole, we have investigated the utilization of bis(trimethylsilylmethyl)amine as a dipole source.[2] Recently, trimethylsilylmethylamine homologues have been employed as versatile reactive substrates,[3] by which precursors for the C-N-C 1,3-dipoles were exploited.[4] A most reliable method to generate azomethine ylides **4** is a desilylation of an *N,O*-acetal prepared by the condensation of *N*-(trimethylsilylmethyl)benzylamine **1** and formaldehyde in MeOH.[5] Diverse approaches to iminium ions **3** are conceivable. For example, silylmethylation[6] of an imine with $TMSCH_2OTf$ and quaternarization[7] or 1,2-silicon shift[8] of a silylmethylimine have been reported. They have often used an activating agent such as LiF, CsF or TMSOTf releasing the azomethine ylide **4**. The potentiality of the 1,3-dipolar cycloaddition has intrigued us to examine a direct way leading to azomethine ylide **4**. Although Padwa[5] reported that the reaction of **1** and formaldehyde predominantly afforded an inactive self-condensation product, we found that the simple mixing of the silylmethylamine **1** and carbonyl compounds **2** in the presence of dipolarophiles **5**, smoothly led to the formation of the cycloadduct without use of any promoting reagents. Herein, we wish to disclose a very practical and convenient process to produce pyrrolidine derivatives **6** (Scheme 1).



**Scheme 1.**

Table 1 shows the results of the condensation of the silylmethylamine **1** and aq. 35% formalin. The reaction can be carried out in the presence of water to give the desired products in high yields. Neither catalyst such as acid and base nor activating reagent such as CsF is required. Simple stirring of the reactants, *i.e.*, the amine **1**, formaldehyde, and the dipolarophile **5** in THF gave pyrrolidine **6**. For the convenience, the reaction was carried out under reflux, while the cycloaddition proceeds at room temperature. In place of formalin, paraformaldehyde can also be used. As can be seen in Table 1, usual dipolarophiles reacted to give the corresponding pyrrolidine compounds **6** in good yields.

**Table 1.** 1,3-Dipolar cycloaddition by the condensation of silylmethylamine **1** and formaldehyde[a]

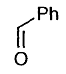
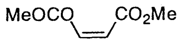
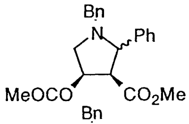
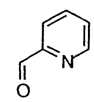
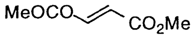
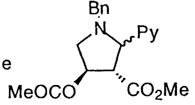
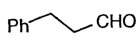
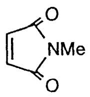
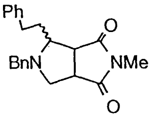
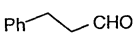
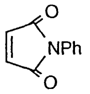
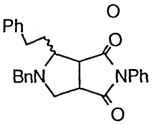
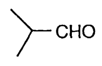
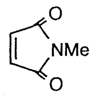
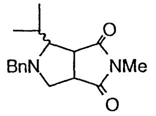
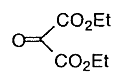
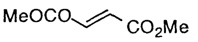
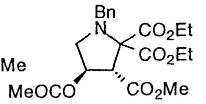
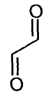
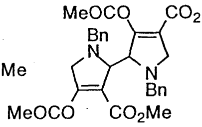
| Run | 5 | 6 | Yield /% |
|---|---|---|---|
| 1 |  |  | 71[b] |
| 2 |  |  | 87 |
| 3 |  |  | 75 |
| 4 |  |  | 78 |
| 5 |  |  | 80 |
| 6 |  |  | 87 |

[a] Carried out using **1**, **5** (2 eq.), and 35% $CH_2O$ (2 eq.) under refluxing in THF for 7 h. [b] A *trans* isomer was obtained in 3%.

Besides formaldehyde as a condensing partner, other carbonyl compounds **2** can also participate in the cycloaddition. The results by the reaction with various aldehydes and ketone are summarized in Table 2. The cycloaddition is stereospecific, as usual, with regard to the geometry of the dipolarophile. On the other hand, stereoselectivity was very poor and an unseparable mixture of two stereoisomers was obtained. The low selectivity was partially attributed to rather high temperature, and hence sometimes isomerization of the dipolarophiles would take place (Runs 1–5). The advantages to be noticed are the easiness of the procedure and the wide applicability for the synthesis of diamines (Runs 2 and 7). In the case of glyoxal, the bispyrrolidine compound was obtained from aqueous glyoxal. Interestingly, the $^1H$ and $^{13}C$ NMR spectra showed that the product consisted of a single isomer (Run 7).

The condensation of a silylmethylamine and an aldehyde would provide a very practical method by virtue of its potent flexibility to accommodate a wide range of substituents on

**Table 2.** Cycloaddition by the condensation with carbonyl compounds[a]

| Run | 2 | 5 | 6 | Yield/% |
|---|---|---|---|---|
| 1 |  |  |  | 81[b] |
| 2 |  |  |  | 46[b] |
| 3 |  |  |  | 42[b] |
| 4 |  |  |  | 46[b] |
| 5 |  |  |  | 58[b] |
| 6 |  |  |  | 23 |
| 7[c] |  | MeOCO—≡—CO$_2$Me |  | 94[d] |

[a]Carried out using **1**, **2** (2 eq.), and **5** (2 eq.) under refluxing in THF for 7 h. [b]1:1 mixture. [c]Aq. 40% glyoxal was used. [d]Single isomer by NMR.

pyrrolidine skeleton.[9] As a similar method, the condensation of *N*-benzylglycine and paraformaldehyde has been shown to accompany a decarboxylation generating an azomethine ylide.[10] The silyl group as a latent anion is highly superior to the carboxyl functionality, since it releases a negative charge under mild conditions immediately after the iminium formation.

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9 A general procedure is as follows. A mixture of amine **1** (0.6 mmol), aldehyde **2** (1.2 mmol), and dipolarophile **5** (1.2 mmol) dissolved in THF (5 mL) was heated to reflux for 7 h. The reaction mixture was poured into water and extracted with AcOEt. The concentrated extracts were chromatographed on SiO$_2$ to give pyrrolidine **6**.

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