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Chemoselective 1,3-dipolar cycloadditions of azomethine ylide with conjugated dienes

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ABSTRACT

Methods are described of synthesizing various 3-carboxy-4-vinyl pyrrolidines, versatile building blocks for our drug discovery efforts. The 1,3-dipolar cycloaddition between activated olefins and nonstabilized azomethine ylide is a known method for synthesizing pyrrolidines in a stereospecific manner. Steric and electronic effects on the chemoselectivity of the 1,3-dipolar cycloaddition between azomethine ylide and α,β,γ,δ-unsaturated carboxylates have been explored.

Pyrrolidines are common fragments found in various biologically active small molecules, and as a result new synthetic methods to prepare highly functionalized pyrrolidines are of great interest in the field of medicinal chemistry. The 1,3-dipolar cycloaddition between activated olefins and nonstabilized azomethine ylides is a known method for synthesizing pyrrolidines in a stereospecific manner.[1] The utility of this cycloaddition has been expanded with developments of enantioselective dipolar cycloadditions by introducing chirality to the dipolarophile,[2] the azo methine ylide,[3] or chiral catalysts.[4]

We envisioned the preparation of 3-carboxy-4-vinyl pyrrolidines **1** through a chemoselective dipolar cycloaddition of an azomethine ylide **2** with simple α,β,δ,γ–unsaturated esters **3** (Fig. 1). In addition to the carboxylic acid and deprotected amine as handles for diversification, the vinyl side chain may be converted to amines, ethers, esters, and amides through an aldehyde or ketone intermediate.

The dipolar cycloaddition between the azomethine ylide derived from *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine **2** and the terminal olefins of 4-vinyl furanones **4** and **6** is the only account to date of a chemoselective dipolar cycloaddition between azomethine ylide and a diene[5] (Scheme 1). The author proposed that despite the stronger electronic effect the ester has on the α,β-olefin, the terminal olefin is more reactive due to the reduced steric hinderance.

We set out to study steric effects on this chemoselectivity with simplified dienes **3a–e**, where R2, R3, R4, and R5 are hydrogen or methyl groups. As shown in Scheme 2, there are two possible cycloaddition products, the desired **1** that results from the dipole addition to the α,β-positions of the diene, as well as the product

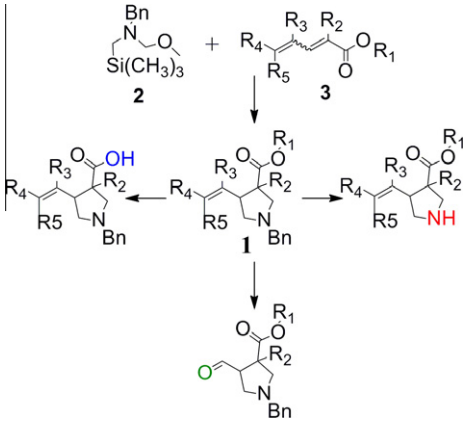
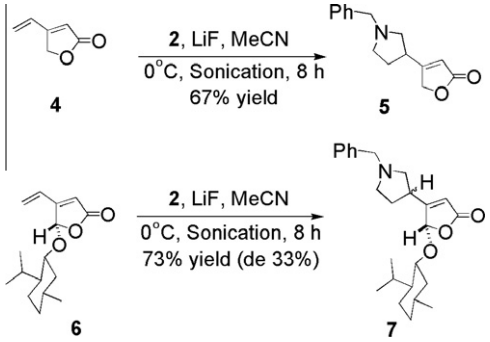


Figure 1. Versatility of building block **1.**



Scheme 1. The chemoselective cycloaddition with 4-vinyl furanones.

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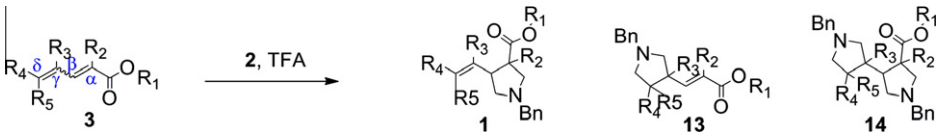
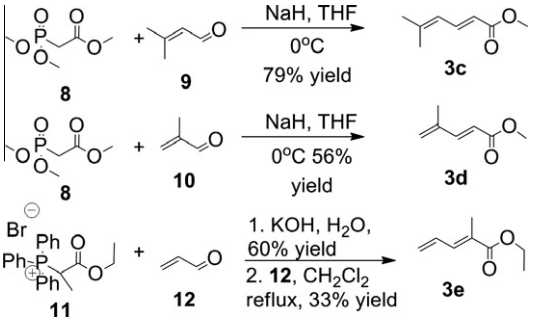


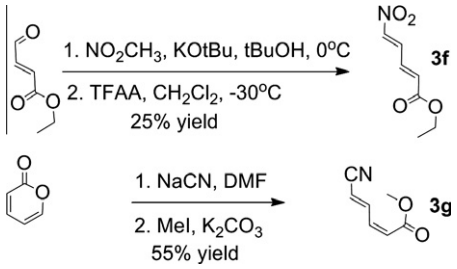
Scheme 2. 1,3 Dipolar cycloaddition between **1** and **3** provides three possible products.



Scheme 3. The synthesis of dienes **3c**–**e**.

13 formed when the methine ylide dipole adds to the γ,δ-positions of the diene. According to the calculated LUMO energies and orbital coefficients for the dienes **3a–e** and products **1a–e** and **13a–e**,[6] we expected preferential dipole cycloaddition to the α,β olefin to form product **1**, which is predicted to be unreactive in the reaction conditions, since its LUMO energy is quite high. On the other hand based on its calculated low energy LUMO we expected the undesired product **13** to react further to form the bis adduct **14**. Dienes **3a** and **3b** are commercially available; dienes **3c**, **3d**, and **3e** were synthesized as shown in Scheme 3.[7–9]

We designed dienes **3f** and **3g** to explore the electronic effects on the chemoselectivity of this reaction.[10] The calculated LUMO, the orbital coefficients for **3f** are largest at the γ,δ positions; therefore, **13f** is expected to be the major product. In the case of **3g**, the cyano and ester groups have similar electron withdrawing effects,



Scheme 4. The synthesis of dienes **3f** and **3g.**

which are reflected in the even distribution of LUMO orbital size across both double bonds; therefore, both products **1g** and **13g** are expected. Since the LUMO energies are relatively low for all of the products, **1f–g** and **13f–g**, the bis adducts **14f–g** are also expected. (2*E*,4*E*)-Methyl 5-nitropenta-2,4-dienoate **3f** was synthesized according to Cote's two step method for the condensation of ethyl-trans-4-oxo-2-butenoate and nitromethane.[11] The cyano containing (2*Z*,4*E*)-methyl 5-cyanopenta-2,4-dienoate **3g** was prepared by modifying Vogel's published synthesis.[12] (Caution: this procedure will release hydrogen cyanide.) In order to avoid release of cyanide gas, we treated the cyanide containing mixture directly with excess potassium carbonate and methyl iodide, and isolated the methyl ester with a basic aqueous work up (Scheme 4).

We coupled these dienes **3a–g** with *N*-benzyl-*N*-(methoxymethyl)trimethylsilylmethylamine **2** in the presence of TFA. The general procedure for these 1,3-dipolar cycloadditions is as follows: Trifluoroacetic acid (1 M in THF, 0.1 equivalent) is slowly added to a 0 °C solution of diene (1 equivalent) and dipole (1 equivalent) in toluene. The reaction is slowly warmed to 25 °C over 18 h, and then quenched with saturated aqueous sodium bicarbonate. The distribution of products was established through integration of the crude ^{1}H NMR spectra. The observed product distributions in these reactions are all consistent with the predictions made with the analysis of frontier molecular orbital energies and coefficients.[6] In our simplest case, (*E*)-methyl penta-2,4-dienoate **3a**, the major product **1a** is formed by the dipole coupling to the α,β-olefin. However, the crude material contains <10% of what is proposed to be **13a**. Evidence for this side product as well as bis adduct **14a**, is also found in the GCMS and ^{1}H NMR of the crude reaction mixture.[13] In the cases of dienes **3b**, **3c**, and **3d** the additional steric hinderance around the γ,δ-olefin coupled with the stronger electronic effects on the α,β-olefin results in selective formation of products **1b–d**. However, this selectivity is reversed in the case of **3e**, where the methyl substituent at the alpha position sterically blocks the dipole addition to the α,β-olefin. This ratio of products is degraded with longer reaction times, when **13e** further reacts to form the bisadduct **14e**. In fact, the bis-adduct **14e** is the major product when this reaction is allowed to run overnight. In the case of nitro containing **3f**, we only observe product **13f**, and bis adduct **14f**. We were unable to prevent this second addition from taking place even in conditions of lower temperature and shorter reaction times. Since the calculated LUMO energy for product **1f** is still quite

Table 1
1,3 Dipolar cycloaddition run under general conditions.

Diene ID	R_1	R_2	R_3	R_4	R_5	Reaction time/temperature	Crude yield (%)	Ratio of products 1:13:14[a]	Isolated yield
3a	CH_3	H	H	H	H	1 h/0 °C then 15 h/rt	148	5/1/4[b]	37% **1a**
3b	CH_3	H	H	CH_3	H	1 h/0 °C then 15 h/rt	167	1/0/0	38% **1b**
3c	CH_3	H	H	CH_3	CH_3	1 h/0 °C then 15 h/rt	97	1/0/0	60% **1c**
3d	CH_3	H	CH_3	H	H	1 h/0 °C then 15 h/rt	100	1/0/0	64% **1d**
3e	CH_2 CH_3	CH_3	H	H	H	1 h/0 °C then 15 h/rt	152	1/4/12	31% **13e** 6% **1e**
3e	CH_2 CH_3	CH_3	H	H	H	1 h/0 °C then 5 h/rt	72	1/5.8/2	—
3f	CH_2 CH_3	H	H	NO_2	H	1 h/0 °C then 1.5 h/rt	69	0/1/4.4	—[c]
3f	CH_2 CH_3	H	H	NO_2	H	4 h/0 °C	50	0/1/2.7	—[c]
3g	CH_3	H	H	CN	H	1 h/0 °C then 15 h/rt	184	1/1/1	22% **13g** 22% **1g**

[a] The ratio of products **1**/**13**/**14** was determined by integration of the crude ^{1}H NMR spectrum.
[b] This product distribution has been determined by GC-MS.
[c] The product **13f** of this reaction was isolated and characterized from a reaction run under different stoichiometry.

low, if formed this product would quickly react further to form the bisadduct **14f**. Therefore, we cannot eliminate the possibility that the methine ylide also reacts with the α,β-olefin of the starting diene **3f**. In the case of the cyano substituted diene **3g**, a 1:1 ratio of mono addition products **1g** and **13g** is produced. In addition, since both products are still reactive, as predicted by their low LUMO energies, a significant amount of bis adduct **14g** is observed in the crude ^{1}H NMR.

Our results are consistent with those reported by Gerlach et al. As observed in our reaction with **3e**, the steric effects can outweigh the electronic effects, resulting in preferred cycloaddition on the less hindered terminal olefin. However, based on our experience it is somewhat surprising that Gerlach did not report any bis adduct formation as a result of the dipole reacting with the still activated olefin in the products **5** and **7**. While it may be possible that further reaction with product **7** is prevented by the steric bulk of the chiral center on the furanone, we would expect that cycloaddition to **5** would be possible under our reaction conditions. It is important to note that the activation of the dipole with LiF, basic conditions, could also result in a difference in the reactivity.

Our study demonstrates that the 1,3-dipolar cycloaddition of unactivated azomethine ylide to activated 1,4-dienes is a powerful method to synthesize highly versatile building blocks. With the introduction of a simple methyl substitution on either the γ or δ positions of these dienes the chemoselectivity can be ensured, to provide a single product in synthetically useful yields (Table 1).

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Supplementary data

Supplementary data (the ^{1}H NMR and GS-MS spectra of the crude reaction mixtures produced from all of the dipolar cycloadditions, the experimental and characterization data for all isolated products, and calculated HOMO and LUMO energies and coefficients, have been included in the supplementary data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.042.

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