Thermal Hetero [3 + 2] Cycloaddition of Dipolar Trimethylenemethane to *N*-Sulfonyl and *N*-Acyl Imines. Synthesis of γ-Amino Acid Derivatives

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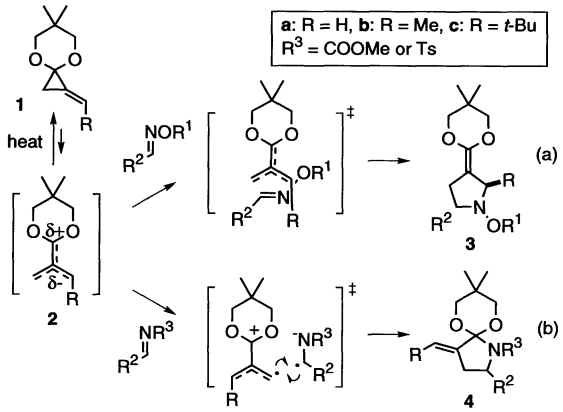
Thermal hetero [3 + 2] cycloaddition reaction of a dipolar trimethylenemethane **2** with an *N*-acyl or *N*-tosyl imine gives an α-methylene-γ-pyrrolidone acetal **4** in high yield, which upon hydrolysis affords a γ-amino acid derivative.

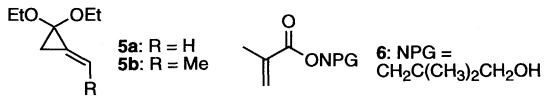
Mild thermolysis of methylenecyclopropane **1** reversibly generates dipolar trimethylenemethane (TMM) **2**,[1,2] which undergoes [3 +2] cycloaddition to electron-deficient olefin,[3] acetylene,[4] carbonyl group[5] and *O*-alkyloxime (Scheme 1a).[6] The high reactivity to the last compound illustrated the uniqueness of **2** among other TMM species, which are unreactive to C=N bonds. We report herein further examples of smooth cycloaddition of **2** to C=N compounds, *N*-methoxycarbonyl and *N*-tosyl imines (Scheme 1b). In contrast to the *O*-alkyloxime reaction, however, the reaction took place with such regioselectivity that it gives a lactam acetal **4** rather than a pyrrolidine ketene acetal **3**. The cycloadducts serve as synthetically useful precursors to γ-amino acid derivatives.



Scheme 1.

The cycloaddition reaction is effected simply by heating an equimolar mixture of an alkylidenecyclopropane **1** and an *N*-tosyl or *N*-acyl imine at 50-80 °C for a few hours in acetonitrile. This reaction proceeded much faster than the cycloaddition to *O*-alkyloximes, which are less electrophilic than *N*-tosyl and *N*-acyl imines. The reaction took place cleanly to give the [3 + 2] cycloadduct in high yield without appreciable amounts of side products. Removal of the solvent from the reaction mixture afforded the desired cycloadduct pure enough for further synthetic use. The product was an acetal of α-methylene-γ-lactam **4**, which is rather sensitive to acid (e.g., silica gel), and may be isolated as the corresponding α-alkylidene-γ-amino esters as listed in Table 1. The preferential hydrolytic cleavage of C-N bond over C-O bond in **4** is due to strong electron donation from the lone pairs of two oxygen atoms. The ester recyclizes to the corresponding lactam after prolonged acid treatment.

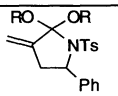
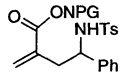
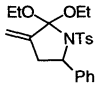
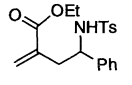
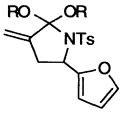
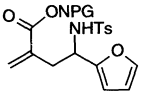
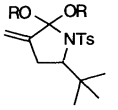
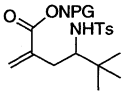
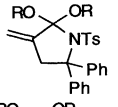
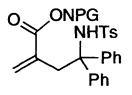
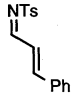
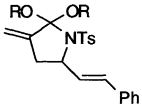
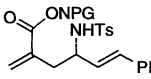
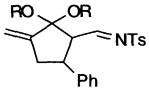
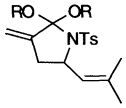
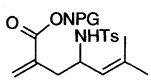
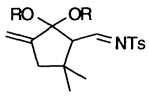
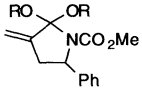
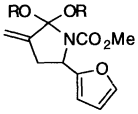
The cycloaddition of the parent methylenecyclopropane **1a** and the diethoxy substituted one **5a** with various *N*-tosyl imines was investigated first (Table 1). The lactam acetal adduct was obtained exclusively in a nearly quantitative at 80 °C (entries 1 and 2). The reaction with 2-furaldehyde tosylimine was faster and was complete after 3 h at 60 °C (entry 3). The reaction was found to be rather insensitive to steric hinderance. Thus, pivalaldehyde tosylimine reacted smoothly (86% yield, entry 4), and the cycloaddition with benzophenone tosylimine proceeded in high yield albeit more sluggishly (88% yield, entry 5). On the other hand, the reaction cannot be applied to the tosylimine of an enolizable aldehyde (e.g., a C_{22}-steroidal aldehyde), and the hydrorazone was recovered quatitatively together with neopentyl glycol mono-methacrylate **6** formed by protonation of the TMM.



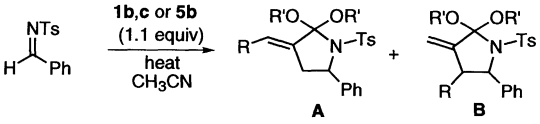
The tosylimines of α,β–unsaturated aldehydes also took part in the cycloaddition reaction. The reaction of an equimolar mixture of **1a** and the tosyl imine of cinnamaldehyde gave the desired lactam acetal (entry 6), which was isolated as the corresponding γ-amino ester in 81% yield. Interestingly, [3 + 2] cycloaddition to the olefinic moiety also proceeded in 12% yield. This side reaction occurs even for 3-methyl-2-butenal tosylimine, whose olefin may be deactivated sterically and electronically (entry 7). *N*-Methoxycarbonyl imines also took part in the cycloaddition, giving the cycloadduct cleanly and in high yield (entries 8 and 9).

An issue of regioselectivity occurs when a higher homolog of methylenecyclopropane is used as a TMM precursor (Scheme 2). Ethylidenecyclopropanes **1b** and **5b** reacted with benzaldehyde tosylimine to give a regioisomeric mixture of **A** and **B** in a ratio of 63:37 and 62:38, respectively (entries 1 and 2). Increasing the steric demand on the alkylidene group through installation of a tert-butyl group reactant (**1c**) afforded the cycloadduct as a single isomer **A** (entry 3). In all these experiments, the alkylidene group in the products was exclusively in an *E* geometry, probably reflecting the geometry of the TMM species.[2]

Table 1. Cycloaddition of **1a** and **5a** with N-tosyl and N-methoxycarbonyl imines[a]

Entry	Imine	Conditions °C/h	Cycloadduct[b]	Hydrolyzed product	Yield/%
1		80/2			92[c]
2		80/3			90[c]
3		60/3			89[c]
4		80/5.5			86[c]
5		60/12			85[c]
6		60/3.5			81[c]
					12
7		60/4.5			72[c]
					14
8		80/11			77[d]
9		50/12			78[e]

[a] The reactions were carried out by using 1.1 equiv. of **1a** (except in entry 2 where **5c** was used) with an *N*-tosylimine or an *N*-acylimine in CH_3CN (1.5 M solution). In all experiments, we used a single geometric isomer, which is believed to be anti-isomer. [b] R, R = $CH_2C(CH_3)_2CH_2$, and NPG = $CH_2C(CH_3)_2CH_2OH$. [c] The pyrrolidine cycloadducts were characterized after removal of the solvent and the yields were determined after mild hydrolysis to the ring opened esters. [d] A small amount (13%) of ketene acetal product was formed. [e] A small amount (3%) of ketene acetal product was formed.

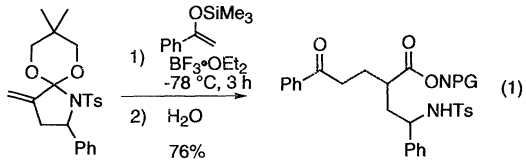


entry	(%*E*)	R	Yield/% (**A**:**B**)
1	**1b** (90)	Me	98 (63:37)
2	**5b** (76)	Me	47[a] (62:38)
3	**1c** (>98)	*t*-Bu	35 (100:0)

[a] 50% of the imine was recovered.

Scheme 2.

The exo-methylene group serves as a useful group for the synthesis of various γ-amino acid derivatives. For instance, treatment of an equimolar mixture of the adduct and an enol silyl ether with $BF_3 \cdot Et_2O$[7] (1.1 equiv) at -78 °C in CH_2Cl_2 for 3 h afforded a Michael adduct product as a single diastereomer (eq 1).



Several features of the present cycloaddition are notable. First, the reaction does not necessitate rigorous exclusion of oxygen or moisture, since the singlet TMM **2** is rather inert to triplet molecular oxygen and to a proton source. Second, because the TMM generation is reversible, we encounter much fewer side reactions that one may find in an irreversible TMM generation method. In light of the previous mechanistic studies for olefin cycloadditions[2] as well as the characteristics of the reaction described above, the present reaction likely takes place in a stepwise manner involving a TMM radical cation and an imine radical anion (cf. Scheme 1b). This stands in contrast to the reaction of **2** with *O*-alkyloximes that takes place in a concerted manner (Scheme 1a),[4] and has some mechanistic similarity to the cycloaddition of dithio TMM species that we recently reported.[8,9]

References and Notes

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9 Representative procedure: A solution of **1a** (102 mg, 0.66 mmol) and benzaldehyde *p*-toluenesulfonylimine (159 mg, 0.60 mmol) in CH_3CN (0.4 mL) was stirred for 2 h at 80 °C. The NMR-pure [3+2] cycloadduct was obtained quantitatively after removal of solvent. ^1H NMR (δ, $CDCl_3$) 1.07 (s, 3H), 1.23 (s, 3H), 2.41 (s, 3H), 2.35-2.40 (m, 1H), 2.88-2.94 (m, 1H), 3.61 (d, *J* = 11.4 Hz, 1H), 3.66 (d, *J* = 11.0 Hz, 1H), 3.97 (d, *J* = 11.4 Hz, 1H), 4.26 (d, *J* = 11.4 Hz, 1H), 4.91 (d, *J* = 1.9 Hz, 1H), 4.98 (dd, *J* = 9.1, 3.4 Hz, 1H), 5.31 (d, *J* = 1.9 Hz, 1H), 7.14-7.57 (m, 7H), 7.64 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 21.42, 21.59, 21.64, 36.40, 40.33, 57.83, 68.00, 69.90, 126.32 (2C), 127.00 (2C), 127.46, 128.43 (2C), 129.21 (3C), 136.14, 137.39, 140.42, 142.97, 167.54
The crude mixture was treated for 30 min with H_2O (0.2 mL) and Amberlyst 15•2,6-di -*tert*-butylpyridine complex (10 mg), and purified on silica to obtain the ring opened ester in 92% yield (238 mg, 0.55 mmol). IR (neat) 3525, 3280, 2970, 1715, 1330, 1165, 1060, 810, 705, 670, 510; ^1H NMR (δ, $CDCl_3$) 0.97 (s, 6H), 1.71 (br s, 1H), 2.34 (s, 3H), 2.65-2.75 (m, 2H), 3.37 (s, 2H), 4.03 (s, 2H), 4.54 (q, *J* = 7.6 Hz, 1H), 5.40 (d, *J* = 7.6 Hz, 1H), 5.57 (d, *J* = 1.0 Hz, 1H), 6.20 (d, *J* = 1.0 Hz, 1H), 7.03-7.26 (m, 7H), 7.51 (d, *J* = 8.6 Hz, 2H); ^{13}C (100 MHz, $CDCl_3$) 21.40, 21.59, 21.64, 36.40, 40.35, 57.81, 68.00, 69.90, 126.34 (2C), 127.00 (2C), 127.44, 128.41(2C), 129.16, 129.21 (2C), 136.14, 137.41, 140.44, 142.93, 167.51; Anal. Calcd for $C_{23}H_{29}NO_5S$: C, 64.01; H, 6.77; N, 3.25. Found: C, 63.98; H, 6.59; N, 3.17.