

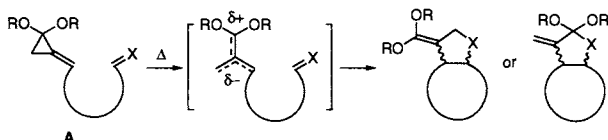
Intramolecular [3 + 2]Cycloaddition Reaction of Dipolar Trimethylenemethane

Masaharu Nakamura, Motoki Toganoh, Xio Qun Wang, Shigeru Yamago,[#] and Eiichi Nakamura*
 Department of Chemistry, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033

(Received March 16, 2000; CL-000261)

A variety of alkylidenecyclopropanone acetals possessing a terminal diylophile were allowed to undergo an intramolecular [3 + 2]cycloaddition via a dipolar trimethylenemethane to obtain bicyclo[4.3.0] and [3.3.0] carbo- and heterocycles in good yields. The product selectivities were rigorously controlled by the concerted or stepwise nature of the cycloaddition reaction.

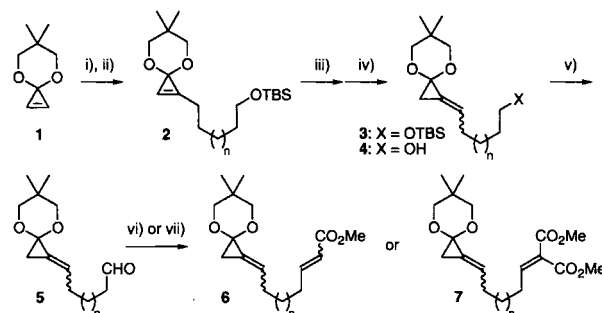
Diastereoselective intramolecular cycloaddition reaction has the potential for controlling several stereocenters in one operation and has found utility in syntheses of numerous complex natural products as exemplified by the Diels-Alder chemistry.¹ The endo addition rule and conformational constraint of intramolecular reaction often compete with each other and determine the course of the reaction. Through our previous studies,² we have shown that an alkylidenecyclopropanone acetal (**A**) serves as a versatile precursor to a dipolar trimethylenemethane (TMM). Mild thermolysis of the alkylidenecyclopropane reversibly generates the TMM that undergoes a [3 + 2]cycloaddition reaction if there is a suitable C=X or acetylenic acceptor in the reaction mixture (if none, it closes back to the cyclopropane).^{2a-h} We report herein the first example of intramolecular [3 + 2]cycloaddition of the dipolar TMM,³ where we identify factors that control the facility and the stereochemistry of the reaction.



Scheme 1. Intramolecular [3 + 2]cycloaddition of dipolar TMM generated from alkylidenecyclopropanone acetal.

We first needed to develop a route to the suitable substrates (**A**: **5**, **6** and **7** in Table 1) in which the TMM precursor and the diylophile are tethered with a three- to six-carbon tether. Cyclopropanone acetal **1** was lithiated with butyllithium, alkylated with an ω -siloxy alkyl iodide⁴ and isomerized to an alkylidenecyclopropanone acetal with a catalytic amount of *t*-BuOK with DMSO in ether.⁵ Desilylation with TBAF followed by Swern oxidation gave a terminal aldehyde **5**. The overall yield from **1** to **5** (4 steps) was 60–75%. Horner-Emmons reaction or Knoevenagel reaction on the aldehyde **5** afforded the monoester **6** or the geminal diester **7** (60–82% yield).

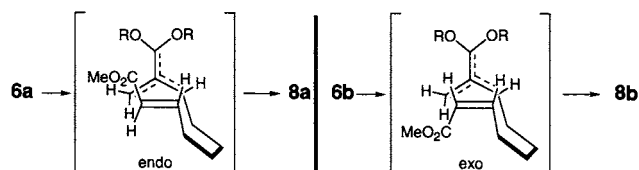
The chemistry of the monoester substrates **6a–6d** was examined first (Table 1). When **6a** bearing a four-methylene tether connected to *E*-unsaturated ester was heated in acetonitrile at 80 °C for 16 h, it cleanly afforded the bicyclo[4.3.0]nonane **8a** that bears a ketene acetal (Table 1, entry 1). ¹H and ¹³C NMR spectra of the crude reaction mixture showed a single diastereomeric product. The ring fusion is *cis* and the diylophile geometry was



Scheme 2. Reagents and conditions: i) *n*-BuLi, HMPA (2 eq); ii) I-(CH₂)_n-OTBS; iii) *t*-BuOK (0.3 eq) DMSO; iv) TBAF; v) (COCl)₂, DMSO then Et₃N; vi) (EtO)₂P=O(CH₂CO₂Me), NaH or (*o*-tolylO)₂P=O(CH₂CO₂Me), NaH; vii) CH₂(CO₂Me)₂ (2 eq), piperidine, AcOH, MS3A.

fully retained.⁶ The ketene acetal moiety is extremely moisture sensitive, and the product was isolated in 76% yield as a 6:4 mixture of the corresponding ester after hydrolysis.⁷ The reaction of the *Z*-unsaturated ester **6b** also cleanly gave a single diastereomer with retention of the diylophile geometry (entry 2). Together with the similar data previously obtained for intermolecular reactions, the retention of the diylophile geometry strongly suggests the concerted nature of the [3 + 2]cycloaddition to moderately electron-deficient olefins.^{2a,c}

In the above reactions, the endo rule of cycloaddition^{2c} and conformational constraint of bicyclic ring formation⁸ are apparently competing. The formation of single *cis*-fused products **8a** and **8b** from both the *E*- and *Z*-esters **6a** and **6b** indicates that conformational effects override the endo rule (Scheme 3).



Scheme 3. Endo and exo cycloaddition of *E*-TMM.

We have previously reported that an *E*-alkylidenecyclopropanone acetal generates TMM much faster than its *Z*-isomer, and that the *E*-TMM generated from the former reacts with retention of the stereochemistry while the *Z*-TMM from the latter undergoes rather quick isomerization to the *E*-TMM.^{2d} In consonance with these previous observations, only a single isomer of **8a** formed in 86% yield when an *E/Z* mixture (55:45) of the alkylidene isomer (**6c**) was heated at 80–100 °C. ¹H NMR monitoring of the reaction revealed that the *E*-alkylidene isomer quickly afforded **8a** while slow *Z*-to-*E* isomerization of **6c** was taking place concomitantly.

Attempts to synthesize a bicyclo[3.3.0]octane ring completely failed (entry 4). Under the assumption of a concerted

cycloaddition, molecular model studies indicated severe conformational effects that precluded the formation of the desired bicyclo[3.3.0]octane ring.

The mechanism of the cycloaddition changes from concerted to stepwise single electron transfer (SET), when the diylophile becomes much more highly electron-deficient than simple α,β -unsaturated ester. We considered that the SET cycloaddition would give us more flexibility in the ring construction. Indeed, not only cycloaddition leading to a bicyclo[4.3.0]nonane (entry 5) but also that leading to a bicyclo[3.3.0]octane⁹ (entry 6) took place smoothly in acetonitrile at 80 °C, when we used an alkylidene-malonate diylophile. The products were exomethylene acetals (**9a** and **9b**), namely, the products ascribed to the SET process.^{2e} Attempts to synthesize bicyclo[5.3.0]decane and bicyclo[6.3.0]undecane from the homologs of **7b** were not very successful. Intramolecular cycloaddition with the aldehyde acceptor (**5a,b**) took place smoothly to give an exomethylene adduct (**10a,b**). Although the SET intramolecular reactions partly circumvented the ring size issue, they were found to be poorly stereoselective.

Table 1. Intramolecular cycloaddition reactions of alkylidene cyclopropanone acetals^a

Entry	Substrate	Conditions	Product ^c	Yield ^d
1		80 °C 16 h		80% ^e , 76% (100:0) [100:0]
2		80 °C 32 h		82% ^e (100:0) [100:0]
3		80 °C 48 h 100 °C 36 h		86% ^e (100:0) [100:0]
4		80 °C 9 h		0%
5		80 °C 5 h		81% (36:64) [17:83]
6		80 °C 1.5 h		86% (33:67) [40:60]
7		100 °C 2 h		90% ^e (0:100) [46:54]
8		80 °C 1 h		55% (0:100) [45:55]

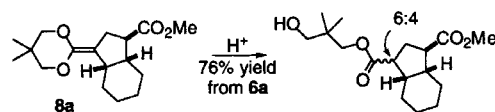
X, X = OCH₂C(CH₃)₂CH₂O

^aThe reactions were carried out in CH₃CN or CD₃CN (in a sealed tube) unless otherwise noted. ^bE:Z = 55:45. ^cMajor adduct is shown. The ketene acetals were hydrolytically unstable and were hydrolyzed for further characterization (cf. footnote 7). ^dThe data in parentheses show regioselectivity and those in square brackets diastereoselectivity of major adduct (determined by ¹H NMR, data accuracy: within 5%). ^eNMR yield using internal standard, and the others isolated yield.

In summary, we have prepared a variety of alkylidene-cyclopropanone acetals possessing a terminal diylophile, and performed their intramolecular [3 + 2]cycloaddition reactions. The regioselectivity and diastereoselectivity showed a high degree of dependence on the electron-demand of the diylophile: the concerted pathway was subject to conformational control to give a stereochemically well-defined product, while the SET pathway was more tolerant to the substrate structure but less stereoselective.

References and Notes

- # Department of Synthetic Chemistry and Biological Chemistry, Kyoto University, Sakyo-ku, Kyoto 606-8502.
- 1 D. F. Taber, "Intramolecular Diels-Alder and Alder Ene Reactions," Springer-Verlag, New York (1984).
- 2 a) S. Yamago and E. Nakamura, *J. Am. Chem. Soc.*, **111**, 7285 (1989). b) S. Yamago and E. Nakamura, *J. Org. Chem.*, **55**, 5553 (1990). c) E. Nakamura, S. Yamago, S. Ejiri, A. E. Dorigo, and K. Morokuma, *J. Am. Chem. Soc.*, **113**, 3183 (1991). d) S. Ejiri, S. Yamago, and E. Nakamura, *J. Am. Chem. Soc.*, **114**, 8707 (1992). e) S. Yamago, S. Ejiri, M. Nakamura, and E. Nakamura, *J. Am. Chem. Soc.*, **115**, 5344 (1993). f) S. Yamago, S. Ejiri, and E. Nakamura, *Angew. Chem., Int. Ed. Engl.*, **34**, 2154 (1995). g) S. Yamago, M. Nakamura, X. Q. Wang, M. Yanagawa, S. Tokumitsu, and E. Nakamura, *J. Org. Chem.*, **63**, 1694 (1998). h) S. Yamago, M. Yanagawa, and E. Nakamura, *Chem. Lett.*, **1999**, 879. i) M. Nakamura, M. Toganoh, H. Ohara, and E. Nakamura, *Org. Lett.*, **1**, 7 (1999).
- 3 R. D. Little, *Chem. Rev.*, **96**, 93 (1996).
- 4 M. Isaka, S. Ejiri, and E. Nakamura, *Tetrahedron*, **48**, 2045 (1992).
- 5 The product was a mixture of stereoisomers (E:Z = 79:21–81:11). This mixture could be partially separated by flash column chromatography.
- 6 Stereochemistry was determined by ¹H coupling constants estimated from decoupling experiment. ³J_{Ha-Hb} = 6.0 Hz, ³J_{Hb-Hc} = 11.2 Hz for **8a**; ³J_{Ha-Hb} = 5.0 Hz, ³J_{Hb-Hc} = 6.0 Hz for **8b**. cf. B. M. Trost, T. A. Grese, and D. M. T. Chan, *J. Am. Chem. Soc.*, **113**, 7350 (1991).
- 7 NMR data for **8a**: ¹H NMR (400 MHz, CD₃CN) δ 0.94 (s, 3H), 0.98 (s, 3H), 1.06–1.67 (m, 8H), 2.10–2.16 (m, 1H, Hb), 2.36 (dd, J = 8.8, 16.8 Hz, 1H), 2.53 (dd, J = 8.8, 16.8 Hz, 1H), 2.48–2.57 (m, 1H, Ha), 2.88 (ddd, J = 8.8, 8.8, 11.2 Hz, 1H, Hc), 3.53–3.65 (m, 4H), 3.61 (s, 3H); ¹³C NMR (100 MHz, CD₃CN) δ 22.2, 22.3, 22.4, 25.9, 26.4, 29.1, 30.9, 31.4, 40.8, 44.50, 44.56, 52.1, 77.5, 78.0, 102.4, 148.9, 176.7.



Physical data of the hydrolyzed product: IR (neat) 3505(br), 2925, 2855, 1718, 1649, 1539, 1459, 1269, 1169, 1052, 672; HRMS *m/z*; found: 313.2031, calcd for C₁₇H₂₉O₅ (M + H)⁺: 313.2015.

- 8 B. M. Trost and I. Fleming, "Comprehensive Organic Synthesis," Pergamon, Oxford (1991), Vol. 4, pp. 513-550.
- 9 The structure of the *cis*-fused isomer of **9b** was determined previously by X-ray crystallographic analysis: T. Yamada, H. Uekusa, Y. Ohashi, S. Yamago, X. Q. Wang, and E. Nakamura, *Acta Cryst.*, **C51**, 1137 (1995). Interestingly, upon exposure to silica gel, the *trans*-fused isomer of **9b** underwent hydrolysis of the C-C single bond between the acetal carbon and carbon connected to the two ester groups. This observation suggests us that the *cis*-fused [3.3.0] system is highly strained.