ORGANIC
LETTERS

1999
Vol. 1, No. 1
7−9

Cycloaddition Reactions of Trimethylenemethane Radical Cation Generated from Methylenecyclopropanone Thioacetal

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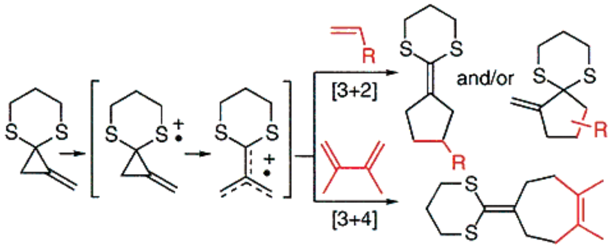
Received March 9, 1999

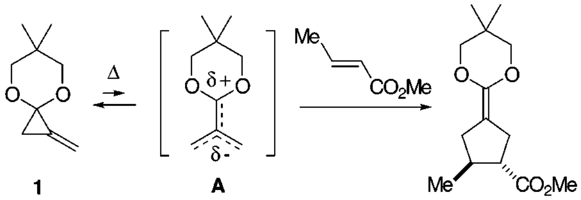
ABSTRACT



A new trimethylenemethane precursor, methylenecyclopropanone thioacetal 2, was synthesized. Trimethylenemethane species generated from 2 showed broad reactivities toward electron-deficient and electron-rich olefins under thermal or photochemical conditions.

Dialkoxy trimethylenemethane (TMM) **A**, which is thermally generated from methylenecyclopropanone acetal (MCPA, **1**), reacts with various unsaturated compounds to afford five-membered ring carbo- and heterocycles with high efficiency (cf. Scheme 1).[1] Whereas the dialkoxy TMM **A** generated from **1** represents a synthetically versatile free TMM species, one drawback of **A** may be its nucleophilic reactivity which allows only electrophilic unsaturated compounds to take part in the cycloaddition reaction. In this Letter, we report the synthesis of a new TMM precursor, methylenecyclopropanone thioacetal (MCPT **2**) and its [3 + 2] and [3 + 4] cycloaddition reactions with both electron-deficient and electron-rich acceptors (Scheme 2). The unique reactivity profile of **2** originates from the mechanism that involves the formation of TMM radical cation **E** as a reactive intermediate.

Scheme 1



MCPT (**2**) was synthesized as shown in Scheme 3. The reaction of epichlorohydrin with lithiated 1,3-dithiane[2] proceeded at −30 °C to afford the relatively unstable oxirane **3** through an intramolecular S_N2 reaction in the presence of sodium fluoride. The oxirane **3** was not isolated and was directly subjected to cyclization conditions to obtain cyclo-

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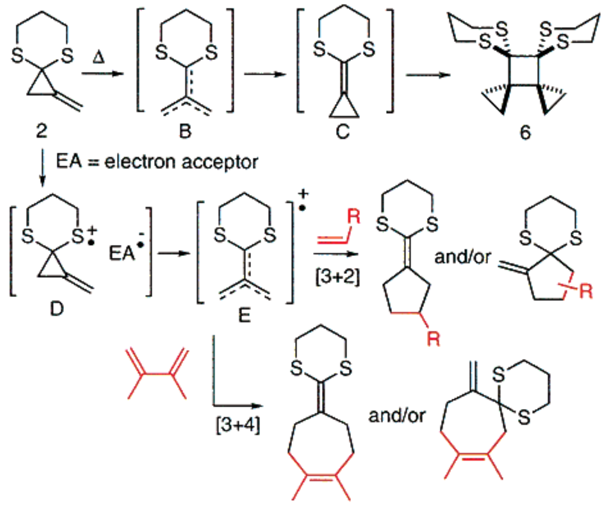
[1] (a) Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.* **1989**, *111*, 7285. (b) Yamago S.; Nakamura, E. *J. Org. Chem.* **1990**, *55*, 5553. (c) Ejiri, S.; Yamago S.; Nakamura, E. *J. Am. Chem. Soc.* **1992**, *114*, 8707. (d) Yamago, S.; Ejiri S.; Nakamura, E. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2154. (e) Yamago, S.; Nakamura, M.; Wang, X.-Q.; Yanagawa, M.; Tokumitsu S.; Nakamura, E. *J. Org. Chem.* **1998**, *63*, 1694. (f) Yamago, S.; Tokuyama, H.; Nakamura, E.; Kikuchi, K.; Kananishi, S.; Sueki, K.; Nakahara, H.; Enomoto, S.; Ambe, F. *Chem. Biol.* **1995**, *2*, 385.

[2] Braun, M.; Seebach, D. *Chem. Ber.* **1976**, *109*, 669.

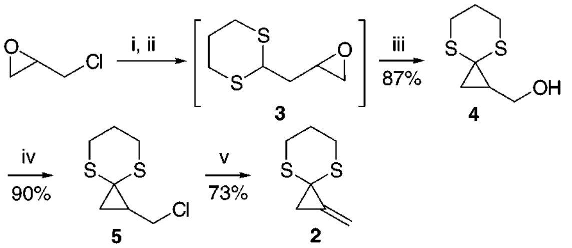
10.1021/ol9900055 CCC: $18.00

Scheme 2



propyl methanol **4** in 87% yield based on epichlorohydrin. After conversion of the alcohol **4** to the corresponding chloride **5** (90% yield), base-induced dehydrohalogenation afforded the desired MCPT (**2**) in 73% yield.[3]

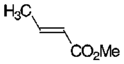
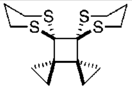
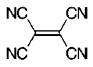
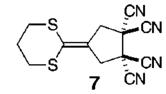
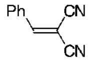
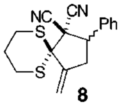
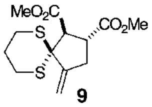
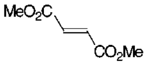
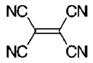
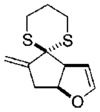
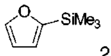
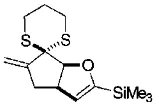
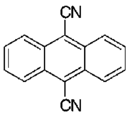
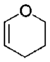
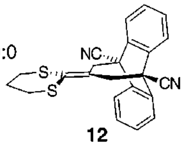
Scheme 3



(i) 2-lithio-1,3-dithiane, -30 °C; (ii) NaF, 25 °C, 8h; (iii) *n*-BuLi, -30 °C, 0.5 h; (iv) $(COCl)_2$, DMF, pyridine (0.95 eq), 25 °C, 3 h; (v) *t*-BuOK, THF/DMSO (9:1), 15 °C, 4 d

The different reactivities of **1** and **2** became immediately apparent upon attempted cycloaddition with methyl crotonate. Whereas MCPA (**1**) reacted smoothly at 60 °C to afford the [3 + 2] cycloadduct (Scheme 1), MCPT (**2**) started to react only at 120 °C to give exclusively the head-to-head dimer **6** in 70% yield, leaving the crotonate unchanged (Table 1, entry 1). The dimer **6** is a [2 + 2] cycloadduct of dimethyleneketene thioacetal **C** formed via dithio TMM intermediate **B**

Table 1. Cycloaddition Reactions of MCPT (2) under Thermal and Photosensitized Conditions[a]

entry	olefin[b]	conditions	yield[c]	KA:EM	major product
1		72 h	0% (70%)	–	 **6**
2		15 min	98% (0%)	100:0	 **7**
3		60 °C, 8 h	82% (0%)	100:0	
4		23 h	80% (0%)	45:55	 **8**
5		72 h	46% (32%)	48:52	 **9**
6		36 h	59% (17%)	37:63	**9**
7[d]		hν, 0 °C, 12 h	85% (0%)	100:0	**7**
8[e,f]		hν, 25 °C, 4 h	27%	0:100	 **10**
9[e,f]		hν, 25 °C, 48 h	19%	0:100	 **11**
10[g]		hν, 25 °C, 5 h  (3 eq)	70%	100:0	 **12**

[a] The reactions were carried out at 120 °C in CH_3CN or CD_3CN unless otherwise noted. [b] Equimolar amounts of olefinic substrate and **2** were used. [c] Yield of adduct. In the parentheses is shown the yield of dimer **6**. [d] No reaction took place at 0 °C without irradiation. [e] The reactions were carried out in the presence of 9,10-dicyanoanthracene (DCA) (30 mol %). [f] A mixture of a furan substrate and CH_3CN (1:15) was used as solvent. [g] Ten equivalents of **2** were used. The yield was based on DCA.

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(3) Synthetic procedures and spectral data of **2**, **3**, **4**, and **5**. To a solution of 1,3-dithiane (8.29 g) in 100 mL of THF (degassed by argon flow for 15 min) was added 45.8 mL of *n*-BuLi (1.59 M in hexane) at −30 °C. The reaction mixture was stirred for 3 h and cooled to −78 °C. Epichlorohydrin (8.16 mL) was added over 5 min, and the reaction mixture was stirred at −78 °C for 2.5 h and at 25 °C for 12 h. Aqueous workup gave an oily product (14.78 g). The crude product was purified on silica gel to obtain the epoxide **3** (10.13 g, 79% yield). To a solution of **3** (8.1 g) was added 32 mL of *n*-BuLi (1.6 M in hexane) at −30 °C, and then the reaction mixture was stirred for 17 h. Water (20 mL) and saturated NH_4Cl (10 mL) were added. Aqueous workup gave an oily product (9.7 g), which was purified on silica gel to afford cyclopropylmethanol **4** as a white solid (6.2 g, 76% yield). To a solution of oxalyl chloride (6.46 mL) in 370 mL of THF was added dropwise DMF (5.73 mL) at 0 °C over 10 min. The white suspension was vigorously stirred for 1 h. A mixture of **4** (6.50 g) and pyridine (2.83 mL) in THF (30 mL) was added at 25 °C, and the reaction mixture was stirred for 3 h. Aqueous workup afforded a dark brown oil (7.27 g). The crude product was purified on silica gel to give chloride **5** (6.47 g, 90% yield). To a solution of *t*-BuOK (5.02 g), in 12 mL of DMSO and 58 mL of THF was added a solution of the chloride **5** (5.79 g) in THF (40 mL) at 0 °C. After stirring for 4 days at 15 °C, ether and pentane (50 mL each) were added, and the reaction mixture was filtered through a pad of Florisil. Evaporation of solvent afforded an oily product (16.4 g). Purification on silica gel followed by bulb-to-bulb distillation (2 mmHg, bath temperature 100 °C) gave an analytically pure sample of the MCPT (**2**) (3.42 g, 73% yield). MCPT (**2**) can be stored without any decomposition for several months in a freezer (ca −20 °C): IR (neat) 2993 (w), 2948 (m), 2932 (m), 2899 (s), 1744 (w), 1420 (m), 1272 (m), 1038 (w), 900 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (dd, J = 1.8, 2.6 Hz, 2H), 2.05−2.23 (m, 2H), 2.93 (ddd, J = 2.8, 6.7, 13.9 Hz, 2H), 3.03 (ddd, J = 3.2, 9.4, 14.0 Hz, 2H), 5.50 (t, J = 1.8 Hz, 1H), 5.79 (t, J = 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 26.1, 30.9, 31.0 (2C), 105.3, 137.7. Anal. Calcd for $C_7H_{10}S_2$: C, 53.12; H, 6.37; S, 40.51. Found: C, 52.89; H, 6.25; S, 40.59.

(Scheme 1).[4,5] Clearly, the neutral TMM **B** is unreactive toward methyl crotonate.

On the other hand, the reaction with tetracyanoethylene (TCNE) proceeded smoothly to afford the ketene acetal (KA) cycloadduct **7** in 87% yield at 60 °C and 98% yield at 120 °C (entries 2 and 3).[6] The occurrence of the cycloaddition below the temperature of the thermal generation of the neutral TMM **B** suggests that the reaction did not take place via **B**. MCPT (**2**) reacted also with benzylidenemalononitrile to give a [3 + 2] cycloadduct in high yield as shown in entry 4. The product was a 55:45 mixture of exomethylene (EM) cycloadduct **8** and the KA cycloadduct (not shown), suggesting the involvement of radical cation intermediate **E**.[7] Formation of none of the dimer **6** in these reaction suggests that the cycloaddition reaction via **D** and then **E** occurs much more rapidly than the formation of **C**. The stepwise nature of the cycloaddition was confirmed by the reactions with dimethyl maleate and dimethyl fumarate, which gave the same trans-substituted EM and KA cycloadducts (i.e., complete scrambling of olefin geometry).

The charge transfer (CT) ability of MCPT (**2**) to an electron acceptor was verified by the appearance of a CT band upon mixing with a strongly electron accepting olefin. Upon mixing **2** with TCNE in CH_3CN, we observed characteristic red coloration of the solution, which showed a CT absorption at 469 nm. The electron transfer may be facilitated by UV light irradiation. When an equimolar mixture of **2** and TCNE was irradiated with a high-pressure mercury lamp, the cycloaddition reaction took place even at 0 °C in excellent yield (entry 7). Thus, unlike the parent MCPT (**2**) which generates the neutral TMM **B** only at high temperature, the MCPT radical cation **D** formed by the loss of an electron rapidly ring-opened to generate the TMM radical cation **E**.

We found that photoinduced [3 + 2] cycloaddition with electron-rich olefins, such as furans, also took place upon irradiation with UV light in the presence of 30 mol % of 9,10-dicyanoanthracene (DCA) as sensitizer. As shown in entry 7, the reaction with furan afforded EM cycloadduct **10** as a single regioisomer in 27% yield. In contrast, regioisomeric cycloadduct **11** was obtained in the cycloaddition with 2-trimethylsilylfuran, where the regioselectivity of the cycloaddition is opposite to that with furan (entry 8). Most interestingly, MCPT (**2**) underwent a [3 + 4] cycloaddition to DCA under photochemical conditions. Thus, DCA reacted with **2** to give the [3 + 4] cycloadduct **12** in 70% yield in the presence of an excess of 2,3-dihydropyran. It is notable that the presence of a vinyl ether or furan was necessary for this [3 + 4] cycloaddition reaction.

In summary, we have synthesized a new trimethylenemethane precursor (MCPT, **2**). The synthetic route to **2** will be applicable also to the synthesis of methylenecyclopropanes possessing various electron-withdrawing groups. The TMM radical cation **E** generated from **2** shows broader reactivities than the dialkoxy TMM **A** and undergoes [3 + 2] and [3 + 4] cycloaddition reactions with not only electron-deficient but also electron-rich olefins and dienes. The present results will lead to further progress of TMM radical cation chemistry[8] in organic synthesis.

Acknowledgment. This work was supported by Monbusho, Grant-in-Aid for Scientific Research on Priority Area (No. 283, Innovative Synthetic Reactions).

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[4] Yamago, S.; Takeichi, A.; Nakamura, E. *J. Am. Chem. Soc.* **1994**, *116*, 1123. Yamago, S.; Takeichi, A.; Nakamura, E. *Synthesis* **1996**, 1380.

[5] Molecular orbital calculations indicated the difference of electronic state of TMM intermediates **A** and **B**. The results will be published elsewhere.

[6] A solution of MCPT (**2**) (0.42 mL, 3 mmol) and TCNE (426.4 mg, 3.3 mmol) in 6 mL of CH_3CN was heated at 60 °C for 12 h. The reaction mixture was concentrated in vacuo to give a crude product. Recrystallization from ethanol gave an analytically pure sample of the adduct **7** (700 mg, 82% yield): IR (CH_2Cl_2) 2922 (m), 2850 (w), 2254 (w), 1606 (s), 1429 (m), 1200 (w), 1113 (w), 1093 (w), 928 (m), 845 (w); ^1H NMR (400 MHz, $CDCl_3$) δ 2.21 (distorted quintet, $J = 6.4$ Hz, 2H), 3.00 (t, $J = 6.4$ Hz, 4H), 3.45 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4, 29.0 (2C), 41.2 (2C), 43.4 (2C), 110.2 (4C), 119.0, 133.1. Anal. Calcd for $C_{13}H_{10}N_4S_2$: C, 54.52; H, 3.52; N, 19.56; S, 22.39. Found: C, 54.45; H, 3.70; N, 19.70; S, 22.31.

[7] Yamago, S.; Ejiri, S.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **1993**, *115*, 5344.

[8] Ikeda, H.; Nakamura, T.; Miyashi, T.; Goodman, J. L.; Akiyama, K.; Tero-Kubota, S.; Houman, A.; Wayner, D. D. M. *J. Am. Chem. Soc.* **1998**, *120*, 5832 and references therein.