[3+3] Cycloaddition Reaction of Dipolar Trimethylenemethane with Active Methylene Compound

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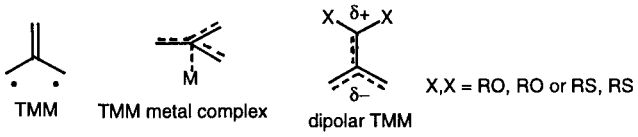
Dedicated to Professor Ryoji Noyori in recognition of his outstanding contribution to organic chemistry

Abstract: Under mild thermal conditions, a [3+3] cycloaddition reaction between an active methylene compound and a dipolar trimethylenemethane species, which is thermally generated from 2-methylenecyclopropanone acetal, provides a dihydropyran.

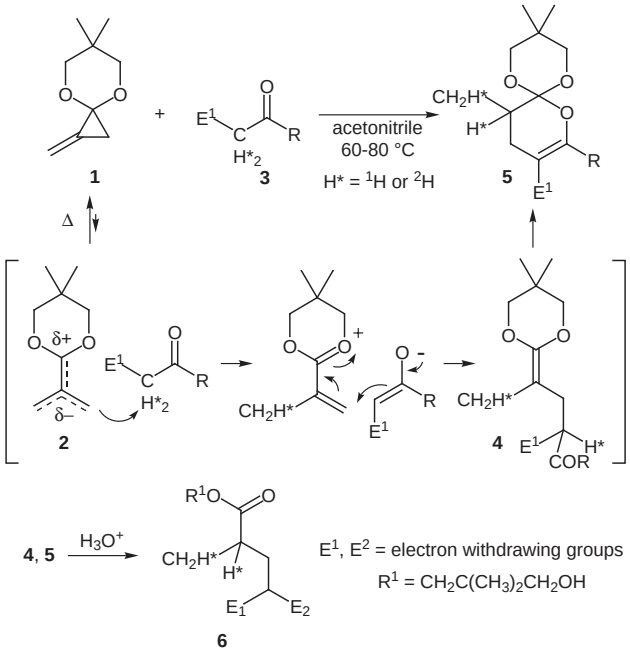
Key words: cycloaddition, trimethylenemethane, active methylene compound

Controlling the reactivity of trimethylenemethane (TMM) species by tuning its electronic state has provided a variety of synthetically useful chemical transformations.[1] Noyori's pioneering contribution to the use of transition metals in the TMM chemistry is noteworthy.[1c,1d] Introduction of hetero atom substituents, such as alkoxy and alkylthio groups, to TMM has been proven by our group to be effective to achieve fine-tuning of its reactivity.[2,3] Thus, it has been amply demonstrated that 2-methylenecyclopropanone acetal (MCPA) **1** serves as a stable precursor to a highly reactive dialkoxy trimethylenemethane **2**, which undergoes thermal [3+2] cycloaddition to an unsaturated compound to provide atom-economical synthetic entries to five-membered carbo- and heterocycles.



We now wish to report that the ambiphilic character of the dialkoxy TMM can be exploited in the reaction with a variety of active methylene compounds **3** that leads to the formation of dihydropyran **5**. This formal [3+3] cycloaddition reaction between MCPA **1** and the active methylene compound **3** involves C-C bond formation triggered by in situ deprotonation of **3** by TMM **2** and takes place without any extraneous additives[4] (Scheme 1).

The synthesis of the dihydropyran **5** by thermal reaction of **1** with an active methylene compound possessing an alkanoyl group was achieved through a very simple experimental procedure. For instance, a mixture of MCPA **1** (1.54 g, 10.0 mmol) and dimedone (1.41 g, 10.1 mmol) in 20 mL of acetonitrile was heated at 60 °C for 12 h. Concentration of the reaction mixture followed by silica gel chromatography afforded the dihydropyran **5** in 84% isolated yield (Table, entry 1).[5]

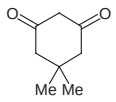
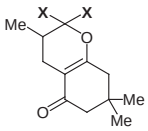
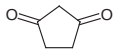
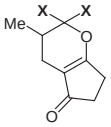
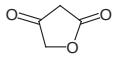
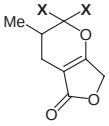
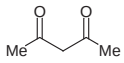
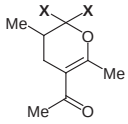
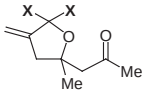
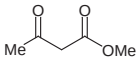
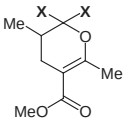
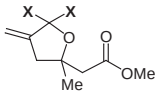
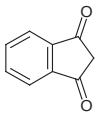
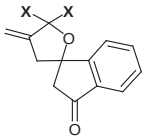
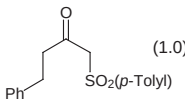
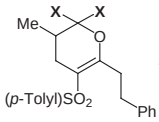
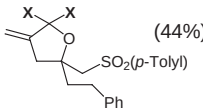
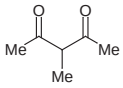
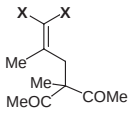
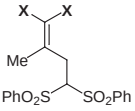
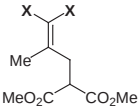


Scheme 1

The results of the [3+3] cycloaddition are summarized in entries 1-7 of Table. The reaction with a five-membered ring cyclic 1,3-diketone and keto ester proceeded smoothly to afford the expected bicyclic dihydropyran in high yield, which was identified in situ by NMR (entries 2 and 3). Treatment of the product with 1*N* HCl (30 μL) in THF (1.5 mL) for 30 min quantitatively afforded the hydrolysis product **6**. As in entries 4 and 5, an acyclic 1,3-dicarbonyl compound, such as acetylacetone or methyl acetylacetate, also took part in the [3+3] cycloaddition reaction to afford the expected dihydropyran product, accompanied by an α-methylene-γ-lactone acetal due to [3+2] cycloaddition of the TMM to the carbonyl group[2g] (ca. 10% yield). For 1,3-indandione shown in entry 6, the major product obtained was such a lactone acetal due to the [3+2] cycloaddition to one of the carbonyl groups.

As opposed to the ketones in entries 1-5, 1,3-indandione has no measurable content of enol (which is anti-aromatic) in $CDCl_3$ at room temperature, which provides a reason for predominant carbonyl participation rather than the enol participation necessary for the [3+3] pathway. Similarly, in entry 7, an α-sulfonyl ketone, which has no

Table Reaction of methylenecyclopropane **1** with active methylene compound

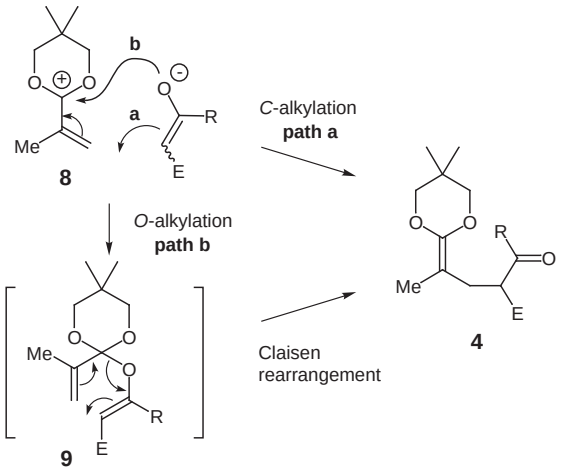
entry	active methylene compound (equiv)	conditions	product[a] (yield)	carbonyl [3 + 2] adduct (yield)
1	 (1.0-1.2)	60 °C, 6-8 h	 **5** (84-90%)	0%
2	 (1.0)	60 °C, 14 h	 **5** (90%)[b]	0%
3	 (1.2)	60 °C, 14 h	 **5** (91%)[b]	0%
4	 (2.0)	80 °C, 73 h	 **5** (65%)	 (10%)
5	 (1.0)	80 °C, 37 h	 **5** (52%)	 (17%)
6	 (1.2)	60 °C, 14 h	**5**, (<10%)[c]	 (52%)
7	 (1.0)	60 °C, 40 h	 **5** (10%)	 (44%)
8[d]	 (1.0)	80 °C, 26 h	 **4** (40%)[c]	ND[e]
9[d]	(1.0)	60 °C, 8 h	 **4** (75%)[b]	—
10[d]	(1.0)	110 °C, 20 h	 **4** (44%)[b]	—

[a]X,X = -$OCH_2C(CH_3)_2CH_2O$-. [b]Yield refers to the isolated yield of hydrolyzed product **6**.
[c]Determined by ^1H NMR. [d]Reaction was carried out in CD_3CN. [e]Not determined.

measurable enol content either, reacted with **1** to afford a [3+2] cycloadduct as the major product. These results suggest that the product selectivity, [3+3] vs. [3+2], largely depends on the ease of enol formation from the active methylene substrate.[6]

The reaction between **1** and 3-methylpentan-2,4-dione (entry 8), which has only one acidic proton, stopped at the stage of the ketene acetal **4**, which provides an experimental support to the mechanism of the [3+3] cycloaddition reaction shown in Scheme 1. With the active methylene compounds lacking an alkanoyl group (in entries 9 and 10), the reaction also stops at the stage of the ketene acetal formation, since the second enol formation necessary for the subsequent cyclization is either impossible or unfavorable. The ketene acetal product **4** is extremely labile toward moisture. Hence it was identified by NMR in a CD_3CN solution, and then, was isolated as the ester **6**.

The present reaction most likely proceeds through a sequence of deprotonation, coupling, proton transfer and cyclization of the resulting enol (Scheme 1). This sequence was not only supported by experimental observations mentioned above, but also by experiments using di-deuterated acetylacetone (H* = ^{2}H) that afforded the cycloadduct **5** bearing deuterium atoms only at the positions marked with H*. Ambiguity remains however in the details of the formation of **4** after protonation of the TMM **2**. One possibility involves direct C-C bond formation on the enol carbon atom in the ion pair (Scheme 2, **path a**), and another involves Claisen rearrangement of an intermediary vinyl ether **9**, that may result from the C-O bond formation at the most positively and the most negatively charged centers in the ion pair (Scheme 2, **path b**).



Scheme 2

According to the fact that the activation energy of the parent Claisen rearrangement (allyl vinyl ether) is more than 25 kcal/mol[7] and high temperature (>200 °C) is usually required for the reaction, one may conclude that **path b** is impossible. Density functional calculations, however, showed that the presence of both an acetal and a carbonyl groups as in **9** lowers the activation energy by nearly 9 kcal/mol from the values in literatures.[8] Therefore, both paths are equally plausible in the present [3+3] cycloaddition reaction.

In summary, a thermal [3+3] cycloaddition reaction of a dipolar trimethylenemethane species to an active methylene compound was described. This new cycloaddition reaction proceeds via ionic alkylation of the active methylene substrate under neutral and mild conditions, showing the viability of tuning the electronic state of TMM by installation of appropriate substituents.

Acknowledgement

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References and Notes

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(5) (a) **Preparation of the methylenecyclopropane 1**: A solution of sodium amide in ca. 400-mL liquid ammonia was prepared from pieces of sodium (total 21.44 g, 0.930 mol) and crystals of $Fe(NO_3)_3{\cdot}9H_2O$ (0.3 g). A solution of 2,2-bis-(chloromethyl)-5,5-dimethyl-1,3-dioxane (63.93 g, 0.300 mol) in 150 mL of dry Et_2O was added dropwise to the slurry of sodium amide in liq. NH_3 over 1 h at dry ice temperature. Cooling bath was removed, and the mixture was stirred for 3 h. The flask was cooled again with a dry ice/acetone bath. After 10 min, a solution of freshly distilled methyl iodide (44.71 g, 0.315 mol) in 80 mL of dry Et_2O was added during 1.0 h through a dropping funnel. After stirring for 15 min, the cooling bath was removed and the solution was stirred for 1 h. The mixture was cooled with a dry ice/acetone bath again and solid NH_4Cl (20.24 g, 0.378 mol) was added in several portions during 5 min. The dry ice condenser for refluxing of liq. NH_3 was removed and ammonia was allowed to evaporate through the open neck. The cooling bath was changed to a water bath (ca. 30 °C), and a 1:1 mixture of dry Et_2O and dry pentane (400 mL) was added through the dropping funnel during 10 min with vigorous stirring. The water bath temperature was maintained between 25-30 °C. After most of ammonia was allowed to evaporate in a period of 1.5 to 2 h, the ethereal solution was filtered by suction through a pad of Hyflo super cell. The filter cake was washed three times with 80 mL of Et_2O. The combined filtrate was distilled to yield the title compound as a colorless oil (34.77 g, 75%; bp 58-61 °C, 6-7 mmHg) (To obtain good yield, it was most important to carry out the distillation quickly (<25 min), and with the bath temperature below 100 °C.)
(b) **Reaction of 1 with dimedone**: A solution of **1** (1.54 g, 10 mmol) and dimedone (1.41 g, 10 mmol) in 20 mL of CH_3CN was heated at 60 °C for 12 h under nitrogen atmosphere. The

reaction mixture was concentrated in vacuo to afford crude yellow oil. Crude product was purified by flash chromatography (eluent: 90:10 hexane/EtOAc) to obtain cycloadduct (**5**) as white solid (2.46 g, 84%yield). Physical data of the product (entry 1, Table) *Rf* 0.30 (80:20 EtOAc/hexane); IR (neat) 2960(m), 2919(m), 2877(m), 1656(w), 1634(s), 1387(m), 1372(m), 1142(m), 1098(s), 1067(m), 984(m), 893(s), 884(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.80 (s, 3 H, CH_3 from **1**), 1.07 (s, 3 H, CH_3 from dimedone), 1.08 (s, 3 H, CH_3 from dimedone), 1.08 (d, *J* = 6.4 Hz, 3 H, C*H*$_3$CH), 1.20 (s, 3 H, CH_3 from **1**), 1.95-2.04 (m, 2 H, CH_3C*H* and C*H*HCH), 2.24 (d, *J* = 3.2 Hz, 2 H, C*H*$_2$C=O), 2.29 (distorted t, *J* = 1.8 Hz, 2 H, C*H*$_2$C(OR) = C), 2.45 (ddt, *J* = 16.0, 9.6, 1.8 Hz, 1 H, C*H*HCH), 3.36 (dd, *J* = 10.4, 2.6 Hz, 1 H, OC*H*H), 3.41 (dd, *J* = 10.4, 1.6 Hz, 1 H, OC*H*H), 3.83 (d, *J* = 10.8 Hz, 1 H, OC*H*H), 4.00 (d, *J* = 10.4 Hz, 1 H, OC*H*H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4 (*C*H_3CH), 22.0 (CH_3 from **1**), 22.6 (CH_3 from **1**), 24.3 (*C*H_2C(OR)), 28.0 ((CH$_3$)$_2$*C* from **1**), 28.9 (CH_3 from dimedone), 29.3 (CH_3 from dimedone), 32.4 (*C*H_2CH), 34.2 (CH$_3$*C*H), 41.8 ((CH$_3$)$_2$*C* from dimedone), 50.6 (*C*H_2C=O), 70.1 (OCH_2), 70.3 (OCH_2), 110.8 (C(OR)$_2$(OR')), 111.8 (*C*=C(OR)CH$_2$), 165.6 (C=*C*(OR)CH$_2$), 197.5 (C=O). Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.21; H, 8.84.

(6) The enol/keto ratios of the active methylene compounds in $CDCl_3$ are as follows: 6.14 for acetylacetone (entry 4), 1.50 for 1,3-cyclopentanedione (entry 2), 0.11 for dimedone (entry 1), 0.09 for methyl acetylacetate (entry 5), 0 for 1,3-indanedione (entry 6) and 1-(*p*-toluenesulfonyl)-4-pheny-2-butanone (entry 7). There is not a simple liner relationship between the [3+3]/[3+2] ratio and the enol/keto ratio. The predominant formation of [3+2] cycloadduct observed for 1,3-indanedione (entry 6) and 1-(*p*-toluenesulfonyl)-4-pheny-2-butanone (entry 7), however, strongly indicates the participation of the enol tautomer in the [3+3] coupling reaction.

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(8) Details of the calculations will be reported in a full paper.

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