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Cycloaddition reactions of trimethylenemethane diyls generated from alkynyl iodonium salts

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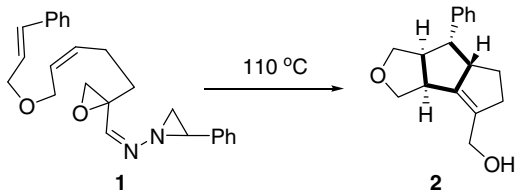
ABSTRACT

Intramolecular [2+3] cycloaddition reaction of trimethylenemethane diyls that were generated successfully from the reaction of malonate anions containing diene units with propynyl iodonium salts via alkylidene carbene intermediates produced linearly fused triquinanes.

Cycloaddition reactions are powerful tools for the synthesis of complex target molelcules as they provide quick entries into complex structures with good control of regiochemistry and stereochemistry.[1] [2+3] Cycloaddition reactions of trimethylenemethanes (TMMs), either as TMM diyls or as TMM zwiterionic precursors, have been used for efficient construction of cyclopentane ring system.[2] TMM diyls could be generated from diazenes or alkylidene carbenes,[3] and TMM diyls generated from diazenes have been applied to organic synthesis.[4] Recently, we reported an application of alkylidene carbene routes to TMM diyls as a new synthetic methodology for the construction of linearly fused triquinanes through cycloaddition reaction of TMM diyls generated from acyclic linear starting materials (Scheme 1).[5]

We were also interested in the formation of TMM diyls from alkylidene carbenes generated from alkynyl iodonium salts[6] since convergent route or multi-component route to polycyclic compounds from linear precursors was deemed plausible. However, our initial attempt failed to provide TMM diyl derived cycloaddition reaction products as reaction of propynyl iodonium salt with various nitrogen nucleophiles produced azabicyclo[3.1.0]hexane **5** instead of generating the TMM diyl (Scheme 2).[7]



1 2

Scheme 1. TMM diyl from epoxyaziridinyl imine and cycloaddition reaction.

The reason for failure to form TMM diyls was believed that the nitrogen atom in the intermediate **5′** altered the stability and reactivity of methylenecyclopropane intermediates.[8] This explanation was supported by the formation of TMM diyls from the reaction of propynyl iodonium salt with the anion of allyl Meldrum's acid as evidenced by the formation of diyl dimers.[9] The dimer formation indicated that the formation of TMM diyls from alkynyl iodonium salts was feasible, and guided us to explore the development of a convergent synthetic route to triquinane compounds from alkynyl iodonium salts and proper carbon nucleophiles.

Herein, we report the synthesis of linearly fused triquinanes from alkynyl iodonium salts with proper carbon nucleophiles. Propynyl iodonium salt was selected for the alkylidene carbene precursor to avoid competing reactions like C–H insertion reaction or rearrangement reaction after the formation of alkylidene carbenes.[10] Mono-substituted malonate ester derivatives, **6**, were selected as the counter part of propynyl iodonium salt for the formation of alkylidene carbene intermediates. When the anion of malonate derivative **6a**, that was prepared from allylated diethyl malonate, 1,4-dibromo-2-butene, and diethyl malonate through sequential alkylation reactions, was reacted with propynyl iodonium salt at room temperature, one major product and a minor product were obtained in good yield. The reaction proceeded through anticipated addition of malonate anion to propynyl iodonium salt to generate alkylidene carbene. The subsequent intramolecular

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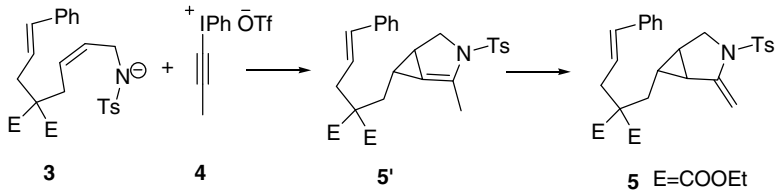
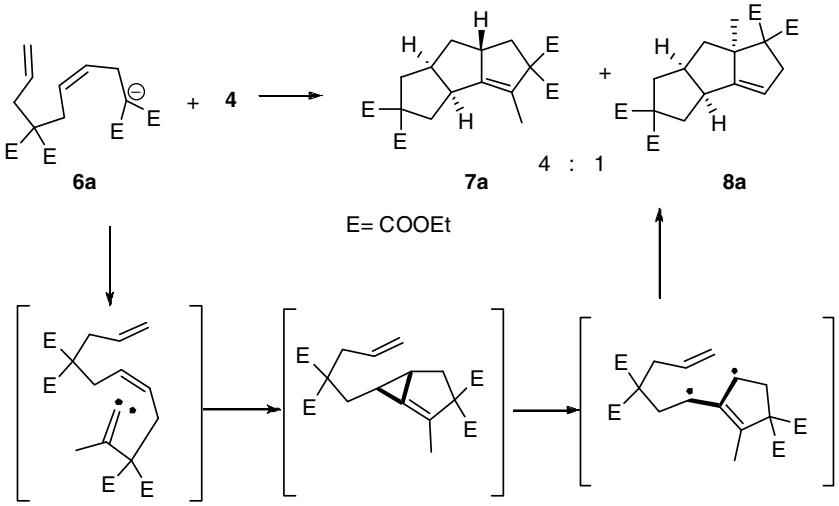


Scheme 2. Rearrangement of methylenecyclopropane.

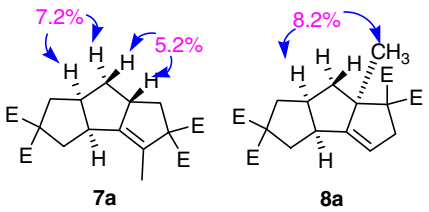


Scheme 3. Triquinanes from alkynyl iodonium salt.

cyclopropanation, contrary to the previously observed results from nitrogen nucleophile **3**, produced TMM diyl intermediate that underwent [2+3] cycloaddition reaction to produce **7a** in 42% yield as the major product along with a minor product **8a** in 11% yield (Scheme 3).[11]

The structures of the major and minor products were deduced from the NMR spectroscopic data, and relative stereochemistry was assigned unambiguously through the NOE experiment (Scheme 4). The major product had cis-*anti* triquinane structure, and the minor product had cis–*syn* triquinane structure. The current result of formation of the minor product with *cis–syn* stereochemistry, and the ratio of the major product and the minor product are similar to the result of symmetrical TMM cycloaddition reaction.[12]

This result was somewhat unexpected since our previous reports of [2+3] cycloaddition reaction of unsymmetric TMM diyls produced only the *cis-anti* isomers as the isolated products and no other isomers were identified in a significant amount. The different selectivity might be attributed to the conformational difference in the transition state due to different substitution patterns of TMM diyls that could provide subtle difference in steric and electronic environment.



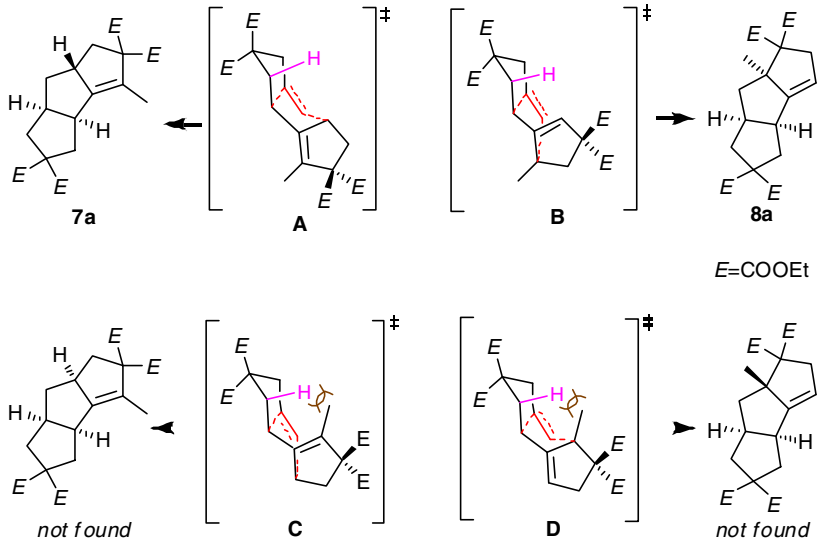
Scheme 4. N.O.E. experiments of **7a** and **8a**.

The relative stereochemistry of **7a** and **8a** indicated that both isomeric products were formed from the same conformation, and only difference was the connecting points. Comparison of four possible transition states for the cyclization could explain, at least in part, the stereoselectivity of the cyclization reaction. Transition states **C** and **D** are clearly disfavored due to the interaction between axially oriented hydrogen of the tether and the methyl group. This is why we did not observe products derived from transition state **C** or **D** in this Letter or in the previous reports. In the previous reports where there were no malonate unit attached to TMM diyls, the transition state **B** appeared disfavored due to interaction of vinylic hydrogen with cyclopentene ring, and only the products derived from the transition state **A** were observed.

In the current reaction, the transition state **A** shows the steric interaction between vinylic hydrogens and one ester unit of the malonate part. This interaction might have diminished the clear preference of the transition state **A** during the cycloaddition reaction, and the reaction produced a mixture of **7a** and **8a** though the transition state **A** is favored. This explanation was supported by the selectivity obtained from the substrates with Meldrum's acid instead of malonate unit.

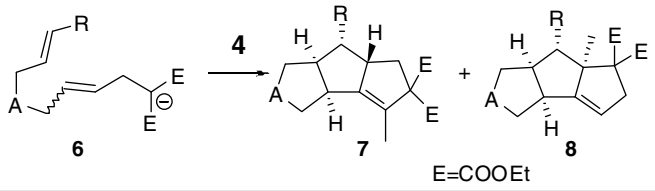
When the reaction was applied to various substrates, the selectivity of the reaction was similar in all cases (Table 1).

Among the results in the Table 1, entries 3–5 are noteworthy since the acidic nature of the allylic protons of the substrates prevented the formation of alkylidene carbenes under strong basic conditions in the previous report.[13] The results of entries 3, 4, and 5 showed that high acidity of the malonate protons of the substrates allowed the formation of the desired products though in low yield. The current protocol would be applicable to wide variety of substrates as it offers milder reaction conditions than previous reports. Since Meldrum's acid anion was known to be more stable and the better nucleophile for alkynyl iodonium salts than malonate



Scheme 5. Transition states of the cycloaddition reaction.

Table 1
Cycloaddition reaction of TMM diyls[16]



Entry	Substrate	A	R	Product (yield) (%)	
1	**6a**	$C(COOEt)_2$	H	**7a** (42)	**8a** (11)
2	**6b**	$C(COOEt)_2$	Ph	**7b** (43)	**8b** (12)[a]
3	**6c**	O	H	**7c** (16)	**8c** (4)
4	**6d**	O	Ph	**7d** (17)	**8d** (4)
5	**6e**	NTs	H	**7e** (23)	**8e** (8)

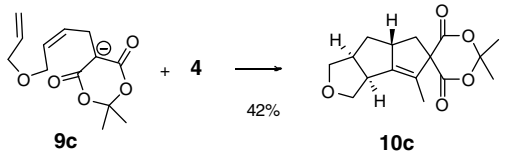
[a] These products were isolated as an inseparable mixture.

anion,[14] we tested the substrates with anions of Meldrum's acid derivatives corresponding to the substrate **6c** for the better result.

As anticipated, the Meldrum's acid anion produced the desired compound in better yield as 42% of **10c**. This result clearly showed that Meldrum's acid containing substrate **9c** generated the desired anion better than the malonate analog **6c**. Contrary to the malonate analog **6c**, the minor stereo-isomer was not detected in isolable amount (Scheme 6).

The better selectivity from the reaction of **9c** than **6c** could well be due to cyclic structure of Meldrum's acid that reduces steric hindrance of the transition state **A** as shown in Scheme 5.

The structure of **10c** was confirmed through X-ray crystallography as it showed the *cis-anti* triquinane structure (Figure 1).[15] These data supported the assignment of structures **7** and **8** from the cycloaddition reaction.



Scheme 6. Meldrum's acid route to TMM diyl.

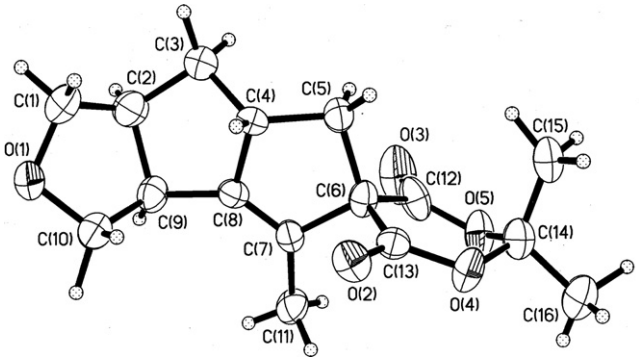


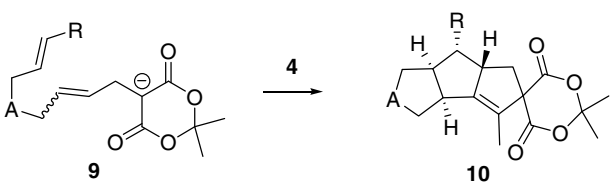
Figure 1. X-ray crystal structure of compound **10c**.

The reaction was extended to other substrates and showed the better or similar efficiency for the production of the major products, and no other minor isomers were identified in significant amounts (Table 2).

For the substrates with acidic functional groups (entries 3 and 4), the reaction proceeded much better than the corresponding substrates with malonate unit, and for other substrates the reaction yielded similar result.

In summary, we have demonstrated that a mild synthetic route to linearly fused triquinane compounds from malonate anions and

Table 2
Cycloaddition reaction of TMM diyls[16]



Entry	Substrate	A	R	Product (yield) (%)
1	**9a**	$C(COOEt)_2$	H	**10a** (31)
2	**9b**	$C(COOEt)_2$	Ph	**10b** (29)
3	**9c**	O	H	**10c** (42)
4	**9d**	O	Ph	**10d** (43)
5	**9e**	Me_2C	H	**10e** (46)

propynyl iodonium salts and the stereoselectivity of [2+3] cycloaddition reaction of TMM diyls with olefins are sensitive to the structure of the substrates. The compatibility of the current synthetic methodology with relatively acidic functional groups widened the scope of substrates, and could be applicable to the preparation of various complex structures.

Acknowledgments

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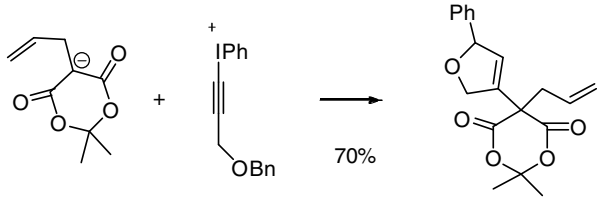
10. The competing reaction between C–H insertion and intramolecular cyclopropanation reaction produced insertion reaction as the major product and did not show any cyclopropanation derived product



11. *Reaction condition and spectral data of* **7a** *and* **8a**, *reaction condition:* To a stirred solution of **6a** (78 mg, 0.189 mmol) in THF (18 mL) was added KHMDS (454 μL of 0.5 M solution in toluene, 0.227 mmol) at 0 °C. After being stirred for 30 min, the reaction mixture was allowed to warm to room temperature and a solution of 1-propynyl(phenyl)iodonium triflate[17] (97 mg, 0.246 mmol) in THF (18 mL) was added for 40 min *via* cannula. The reaction mixture was stirred for 4 h. The resulting product was quenched with saturated NH_4Cl solution (10 mL) and extracted with EtOAc (5 mL × 3). The organic layers were combined and dried over $MgSO_4$. The filtrate was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (EtOAc/Benzene = 1:30) to yield 36 mg (0.08 mmol, 42%) of **7a** and 9 mg (0.02 mmol, 11%) of **8a**, spectral data, Compound **7a:** ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20–4.11 (8H, m), 3.19 (1H, m), 3.03–2.96 (1H, m), 2.94–2.85 (1H, m), 2.82–2.77 (1H, dd, J = 12.6, 7.0 Hz), 2.66–2.60 (1H, ddd, J = 13.0, 8.8, 2.2 Hz), 2.50–2.44 (1H, ddd, J = 12.9, 8.1, 2.1 Hz), 1.84–1.75 (2H, m), 1.74–1.73 (3H, d, J = 2.4 Hz), 1.70–1.67 (1H, m), 1.62–1.57 (1H, m), 1.25–1.18 (13H, m).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 171.4, 171.2, 170.7, 155.1, 125.0, 73.4, 62.5, 61.3, 61.3, 61.1, 61.0, 47.0, 45.2, 40.6, 40.3, 39.5, 38.8, 36.7, 14.1, 14.1, 14.0, 14.0, 12.2.; **8a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.07 (1H, d, J = 1.5 Hz), 4.20–4.10 (8H, m), 3.39–3.35 (1H, ddd, J = 16.4, 4.0, 1.5 Hz), 3.10–2.97 (2H, m), 2.86–2.81 (1H, ddd, J = 16.4, 3.1, 1.5 Hz), 2.61–2.56 (1H, ddd, J = 12.8, 8.0, 1.5 Hz), 2.53–2.48 (1H, ddd, J = 13.2, 8.0, 1.5 Hz), 2.00–1.95 (1H, dd, J = 12.9, 9.0 Hz), 1.95–1.90 (1H, dd, J = 13.1, 8.5 Hz), 1.72–1.71 (2H, d, J = 7.8 Hz), 1.26–1.17 (12H, m), 1.08 (3H, s).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 171.2, 170.9, 170.7, 158.5, 113.4, 67.2, 64.4, 64.0, 61.3, 61.2, 61.0, 60.9, 46.4, 43.2, 40.7, 39.7, 39.3, 38.0, 22.4, 14.1, 14.1, 14.1, 14.1.
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15. *Crystal data for* **10c**: $C_{16}H_{20}O_5$, F_W = 292.32, monoclinic, a = 6.1734(3) Å, b = 19.5389(9) Å, c = 12.2444(6) Å, α = 90°, β = 90.484(2)°, γ = 90°, V = 1476.88(12) A^3, Z = 4, R = 0.1221, spectral data of **10c:** ^{1}H NMR (400 MHz, $CDCl_3$): δ *3.94–3.87* (2H, m), 3.57–3.47 (3H, m), 3.15–3.08 (2H, m), 2.61–2.56 (1H, dd, J = 12.6, 7.6 Hz), 2.16–2.11 (1H, dd, J = 12.6, 7.4 Hz), 1.80–1.75 (1H, dd, J = 12.4, 7.6 Hz), 1.73 (3H, s), 1.71 (3H, s), 1.57–1.56 (3H, d, J = 2.4 Hz), 1.51–1.43 (1H, m).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.2, 156.4, 125.4, 104.8, 75.2, 73.1, 69.1, 48.7, 48.6, 42.3, 41.1, 36.4, 29.7, 28.2, 11.4.
16. Reaction conditions for the cyclization are the same as the reaction condition of **6a** in Ref. 11 and all the isolated products showed satisfactory spectroscopic data and purity.
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