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LETTERS

Effect of substitution and temperature on the reactivity of bicyclo[3.1.0]hex-1-ene system

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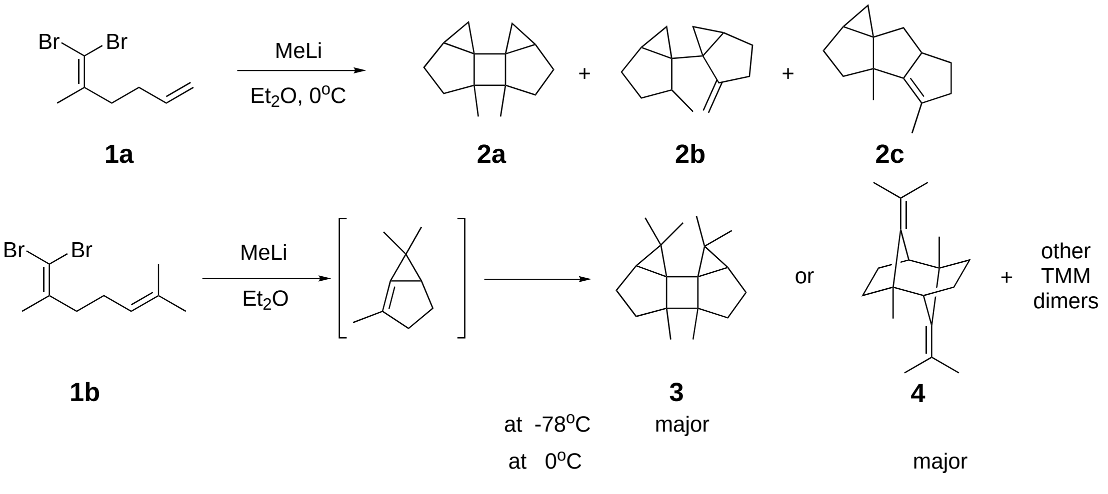
Abstract—Anions of allylmeldrum's acids reacted with phenyl(propynyl)iodonium salt to produce bicyclo[3.1.0]hex-1-enes as the reactive intermediates through cyclopropanation reaction to yield various dimerization products. Depending on the substitution pattern on the intermediates, various dimeric products were obtained. © 2001 Elsevier Science Ltd. All rights reserved.

Alkylidene carbenes have been utilized for the preparation of alkynes[1] and C–C bond formation through C–H insertion[2] or cyclopropanation.[3] Alkylidene carbenes are so reactive that they can even form strained and reactive bicyclo[3.1.0]hex-1-ene systems through intramolecular cyclopropanation. This reactive intermediate can undergo further transformation through dimerization or dimerization after rearrangement. This reaction was first explored by Koebrich[4] and thoroughly investigated by Berson.[5] Bicyclo[3.1.0]hex-1-enes underwent direct dimerization or rearrangement to trimethylenemethane (TMM)s depending on the reaction temperature and substitution patterns (Scheme 1).

We became interested in utilizing bicyclo[3.1.0]hex-1-ene systems to prepare TMMs for [2+3] cycloaddition reaction with olefins,[6] since the reactivity of bicyclo[3.1.0]hex-1-ene appeared tunable through temperature adjustment for an intended reaction pathway. If successful, this would provide a new synthetic strategy for constructing polycyclic structures through sequential reactions starting from alkylidene carbenes. However, Feldman reported yet another reaction pathway of a heterocyclic bicyclo[3.1.0]hex-1-ene, where strained double bond rearranged into exocyclic olefin (Scheme 2)[7] instead of dimerization or rearrangement. This new reaction pathway prompted us to start investigating the reactivity of the bicyclo[3.1.0]hex-1-ene system with



Scheme 1.

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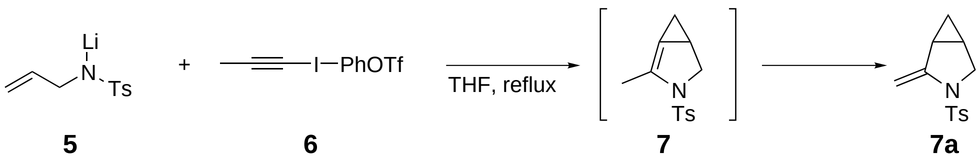


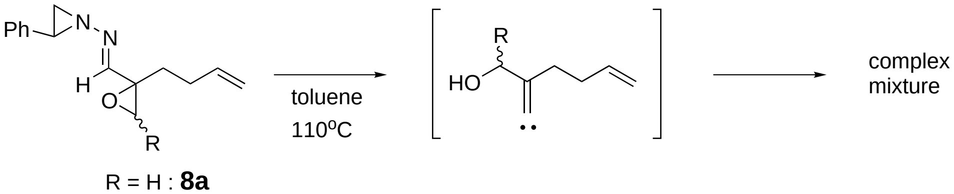
Scheme 2.

various substitution patterns prepared from alkylidene carbenes generated from epoxyaziridinylimines or alkynyl iodonium salts, since they could provide a wide range of substrates for the reaction and a variety of reaction conditions.

Epoxyaziridinylimines generate alkylidene carbenes effectively at 110°C and undergo C–H insertion reactions.[8] Since alkylidene carbenes are generated through thermolysis of expoxyaziridinyl imines under neutral condition and at a much higher temperature than other methods, epoxyaziridinylimines could exhibit quite different reactivities from other methods of generating alkylidene carbenes and could ensure the rearrangement of the bicyclic system into the TMM diyl system. This will in turn be expected to eliminate various modes of dimerization reactions except the dimerization of TMMs. However, when **8a** or **8b** were heated in refluxing toluene, a complex mixture of products was obtained without formation of any major products (Scheme 3). Though high temperature ensures the formation of TMM intermediates before the dimerization reaction, the high temperature seems to eliminate the preferential mode of dimerization that occurred at the much lower temperature. This result hinted that the reaction temperature might affect the reactivity of the bicyclo[3.1.0]hex-1-ene system. Thus, we were prompted to examine the reaction of **5** with **6** under varying temperature. Since the reported reaction condition of **5** could have influenced the course of the rearrangement of bicyclic intermediate **7**, **5** was allowed to react with **6** at ambient temperature or at 0°C to afford **7a** in 45% yield. This confirmed that the temperature did not affect the formation of **7a**. That left the nitrogen atom in **7** to be responsible for the formation of **7a**.

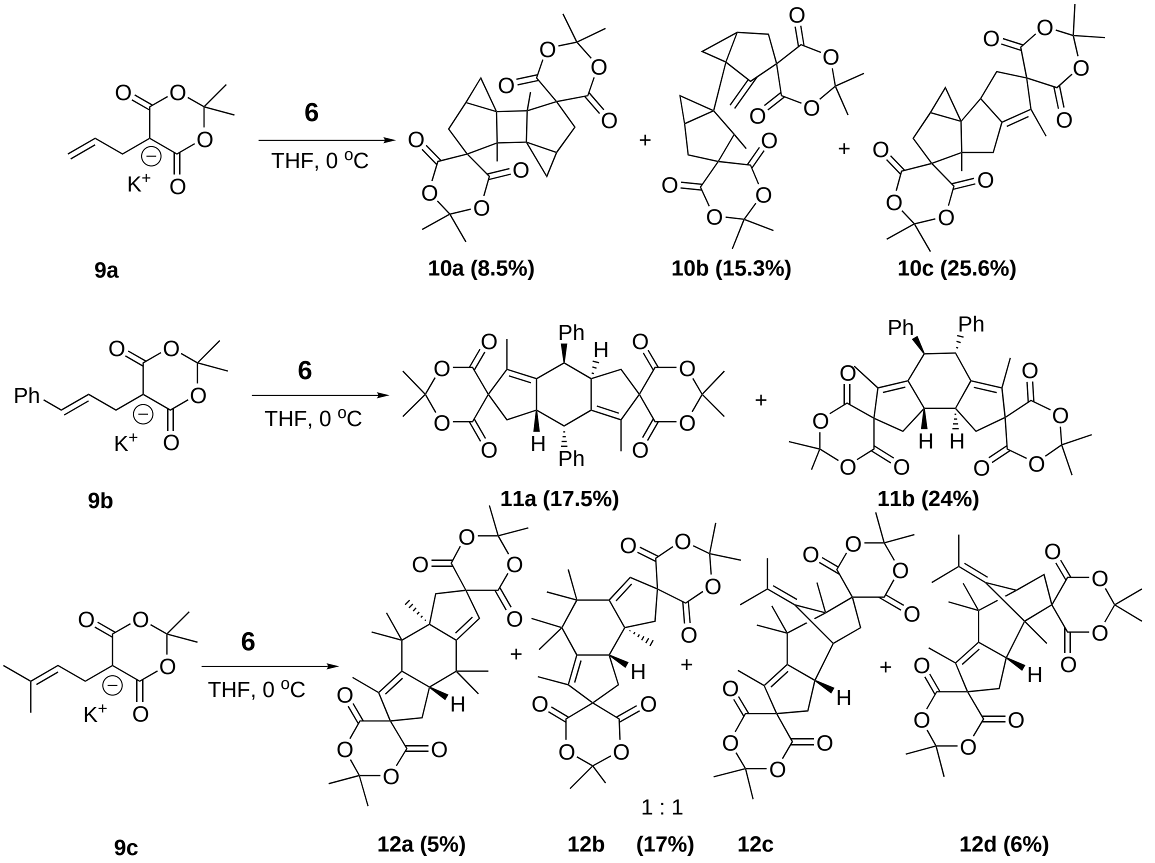
To clarify the importance of the nitrogen atom in the rearrangement, carbon analogs of **5** were tested for the reaction with alkynyliodonium salt **6** (Scheme 4). Since derivatives of meldrum's acid have reacted reliably with alkynyliodonium salts[9] to form alkylidene carbenes, **9a** was tested first as the carbon analog of **5** for the same reaction. When **9a** was reacted with **6** either at −78 or 0°C, the reaction yielded a similar composition of dimerization products (**10a**,[11] **10b**, and **10c**)[10] to that of the reaction of **1a** in Scheme 1. All the products were dimerization products of the bicyclo[3.1.0]hex-1-ene system without rearranging into the TMM. The source of a alkylidene carbene or substitution pattern remote from the cyclopropane ring did not appear to alter the reactivity of the bicyclo[3.1.0]hex-1-ene system. This result implies that either the size or the electronic nature of nitrogen is responsible for the rearrangement of **7** to **7a**. However, when the terminal olefin has other substituents, the reactivity of the bicyclo[3.1.0]hex-1-ene system changed dramatically. When a phenyl group was substituted at the terminal olefin (**9b**), rearrangement of the methylenecyclopropane ring of the bicyclic intermediate to the TMM diyl occurred at 0°C and the reaction produced dimerization products of the TMM diyl. Interestingly, the same TMM dimerization was observed when the reaction temperature was −78°C. This result was quite surprising since the rearrangement of the bicyclo[3.1.0]hex-1-ene structure to the TMM structure was known to occur only at relatively high temperature. Another difference between this reaction and the reaction of **1** was that the major products were **11a** and **11b**[12] instead of products corresponding to **4**. The relative stereochemistry of **11a** and **11b** was assigned based on the NOE experiment, as the benzylic proton of **11a** showed strong effect with the allylic proton (9.4%) and the allylic proton, in turn, showed the interaction with the phenyl ring (11.3%). In **11b**, the benzylic proton showed no NOE with allylic proton. The stereochemistry of **11a** and **11b** along with the fact that no bridged symmetric dimer formed in the reaction can be explained by steric interaction of TMM intermediates. Meldrum's acid portion of TMM prevented the formation of bridged dimers and **11a** and **11b** were obtained through *exo*-mode of cyclization to minimize steric interaction.

On the other hand, **9c** showed a reactivity pattern quite different from **1** or **9b**. There were no major products as in the case of **1**. Instead, unsymmetrical dimers **12a**, **12b**, **12c**, and **12d** were obtained.[13] These products



R = H : **8a**
R = Me : **8b**

Scheme 3.



Scheme 4.

appeared to be the compounds corresponding to the minor products in Berson's report[5] and unidentified dimeric products from the reaction of **1** in the Koebrich's report.[4] Owing to the unsymmetric nature of products from **9c**, the relative stereochemistry of these products was assigned completely. The structures of **12a** and **12d** were assigned from their NOSEY spectral data. Since **12b** and **12c** were obtained as an inseparable mixture, the structures of **12b** and **12c** were assigned from the NOSEY spectrum of the mixture based on the assignment of the spectral data of **12a** and **12d**.[14]

These results indicate that the reactivity of the bicyclo[3.1.0] hex-1-ene system or TMM diyl system is greatly affected by the substitution patterns of the TMM diyls and the reactivity does not appear to rely on the way it is generated.

In summary, the reactivity of the bicyclo[3.1.0]hex-1-ene system varies mostly on the substitution pattern of the cyclopropane ring of the bicyclic ring system. Though varying reaction temperature does not affect the chemistry of bicyclo[3.1.0]hex-1-enes, high temperature that ensures the formation of TMM diyls completely eliminates the selectivity of the dimerization reaction of the TMM diyl system. Based on the current observation, we are currently developing a new synthetic methodology using TMM diyls generated from alkynyliodonium salts.

Acknowledgements

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10. Structures of **10a**, **10b**, and **10c** were assigned based on the comparison of characteristic signals of ^{1}H NMR with

the reported data for **2a**, **2b** and **2c** by Berson.[5] Therefore, the structures could be isomeric products derived from alternative regioisomeric dimerization, as stated in Ref. 5.

11. Compound **10a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.10 (2H, dd, $J=14.8$, 6.5 Hz), 2.45 (2H, d, $J=14.8$ Hz), 1.68 (6H, s), 1.54 (2H, m), 1.46 (6H, s), 1.43 (6H, s), 0.89 (2H, dd, $J=6.2$, 4.6 Hz), 0.33 (2H, dd, $J=6.2$, 8.8 Hz).
12. Compound **11a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.19 (10H, m), 4.13 (2H, d, $J=7.2$ Hz), 3.85–3.83 (2H, m), 2.27 (2H, dd, $J=12.9$, 8.3 Hz), 2.11 (2H, dd, $J=12.9$, 8.6 Hz), 1.65 (6H, d, $J=2.7$ Hz), 1.64 (6H, s), 1.57 (6H, s). Compound **11b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.19 (10H, m), 4.32 (2H, s), 3.20 (2H, bs), 2.62 (2H, dd, $J=13.1$, 8.1 Hz), 2.11 (2H, dd, $J=13.0$, 4.6 Hz), 1.74 (6H, s), 1.71 (6H, s), 1.63 (6H, d, $J=1.0$ Hz).
13. Compound **12a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (1H, t, $J=2.4$ Hz), 3.10–3.09 (1H, m), 3.09 (1H, dd, $J=16.3$, 2.1 Hz), 2.66 (1H, dd, $J=16.3$, 2.8 Hz), 2.24 (1H, dd, $J=13.3$, 9.1 Hz), 2.17 (1H, dd, $J=13.3$, 7.0 Hz), 1.78 (3H, s), 1.74 (6H, s), 1.70 (3H, d, $J=2.2$ Hz), 1.61 (3H, s), 1.51 (3H, s), 1.37 (3H, s), 1.33 (3H, s), 1.15 (3H, s), 1.03 (3H, s). Compound **12b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (1H, dd, $J=3.0$, 2.0 Hz), 3.54–3.50 (1H, m), 3.12 (1H, dd, $J=16.3$, 2.0 Hz), 2.79 (1H, dd, $J=16.3$, 3.1 Hz). Compound **12c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43–3.39 (1H, m), 2.99 (1H, dd, $J=7.6$, 2.6 Hz), 2.71 (1H, d, $J=13.2$ Hz), 2.37 (1H, dd, $J=12.8$, 7.9 Hz), 2.18 (1H, dd, $J=12.7$, 8.1 Hz), 2.04 (1H, dd, $J=13.2$, 7.7 Hz). Compound **12d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38–3.31 (1H, m), 2.63 (1H, d, $J=8.0$ Hz), 2.58 (1H, d, $J=13.9$ Hz), 2.23–2.16 (3H, m), 1.76 (3H, s), 1.75 (3H, s), 1.72 (6H, s), 1.71 (3H, s), 1.68 (3H, d, $J=2.6$ Hz), 1.56 (3H, s), 1.47 (3H, s), 1.46 (3H, s), 1.14 (3H, s).
14. From the NOSEY spectrum of the mixture of **12b** and **12c**, all the proton signals except the methyl signals were assigned unequivocally.