

Exclusive Formation of α -Methyleneoxetanes in Ketene–Alkene Cycloadditions. Evidence for Intervention of Both an α -Methyleneoxetane and the Subsequent 1,4-Zwitterion

Takahisa Machiguchi,^{*,†} Junko Okamoto,[†] Junpei Takachi,[†] Toshio Hasegawa,[†] Shinichi Yamabe,^{*,‡} and Tsutomu Minato[§]

Contribution from the Department of Chemistry, Faculty of Science, Saitama University, Shimo-Ohkubo, Sakura-ku, Saitama 338-8570, Japan; Department of Chemistry, Nara University of Education, Takabatake-cho, Nara 630-8528, Japan; and Institute for Natural Science, Nara University, Misasagi-cho, Nara 631-8502, Japan

Received March 25, 2003; E-mail: machiguc@chem.saitama-u.ac.jp

Abstract: This paper describes a new mechanistic feature for the Staudinger ketene–alkene cycloaddition reactions to give cyclobutanones. Low-temperature NMR (¹³C, ¹⁹F, and ¹H) monitoring of a reaction between bis(trifluoromethyl)ketene (**1**) and ethyl vinyl ether (**2**) has shown that the Staudinger reaction proceeds to form initially and exclusively an α -methyleneoxetane (**3**) by [2 + 2]_{C=O} cycloaddition across the ketene C=O bond. The initial intermediate **3** undergoes ring cleavage to produce a 1,4-zwitterion (**4**), which is converted to the final [2 + 2]_{C=C}-type product, cyclobutanone (**5**). The key intermediate **3** has been isolated in its pure form and was found to be converted to the final products **5** on warming, via the 1,4-zwitterion **4**. The α -methyleneoxetane **3** is so reactive that it reacts with methanol rapidly even at –80 °C via solvolysis to afford an adduct **7**. The ion **4** derived from the pure isolated oxetane **3** was intercepted with acetone by a 1,4-dipolar cycloaddition to give a 1,3-dioxane **8**. An open-chain α,β -enone (**6**) has been also obtained from **3**. We conclude that the (1 + 2) reaction proceeds in a new three-step mechanism; formation of an α -methyleneoxetane **3**, a [2 + 2]-type cycloadduct across the C=O bond of ketene, followed by ring cleavage to give the zwitterion **4** and by recombination to form the final product, cyclobutanone **5**. The zwitterion **4** is *not* equilibrating with reactants **1** and **2** but comes from the α -methyleneoxetane **3**. Exclusive formation of another oxetane **12** has been observed in a reaction between diphenylketene (**9**) and methyl isopropenyl ether (**11**). The selectivity of initial formation of cyclobutanone or oxetane has been generalized with aid of frontier-orbital theory and ab initio calculations.

We report herein a new mechanistic feature of ketene–alkene (2π system) cycloadditions including an exclusive formation of an α -methyleneoxetane. Some ketenes react with activated alkenes (e.g., alkyl enol ether here) across the ketene C=O bond to form initially a [2 + 2]_{C=O} cycloadduct. The α -methyleneoxetane is isomerized via a *zwitterion* to the [2 + 2]_{C=C} product, cyclobutanone.

The pioneering studies on ketene¹ and its cycloaddition by Staudinger in the early years of the 20th century have been followed by a large number of experiments.² They showed the preference for ketenes to react with alkenes across the C=C rather than the C=O bond. There have been many arguments on the mechanism of whether ketene–alkene reactions proceed in two steps^{2a} via zwitterions in analogy to that of ketene–imine cycloadditions.³

We have recently shown that diphenylketene C=O bond reacts with *s-cis* 1,3-dienes (4π system) to yield cyclobutanones eventually.^{4,5} Dimerization of ketenes is usually faster than cycloaddition to simple unactivated alkenes.⁶ However, activated alkenes (very nucleophilic alkenes such as enol ethers) react stereospecifically with ketenes much more readily than simple alkenes.⁷ It is of great interest to examine whether a ketene undergoes such a [2 + 2] cycloaddition across its C=O group with activated alkenes.

Precedent for addition to the C=O bond of ketene exists.^{8,9} However, those reactions are quite rare and have been regarded as exceptions or side reactions in ketene–alkene reactions.² They

[†] Saitama University.

[‡] Nara University of Education.

[§] Nara University.

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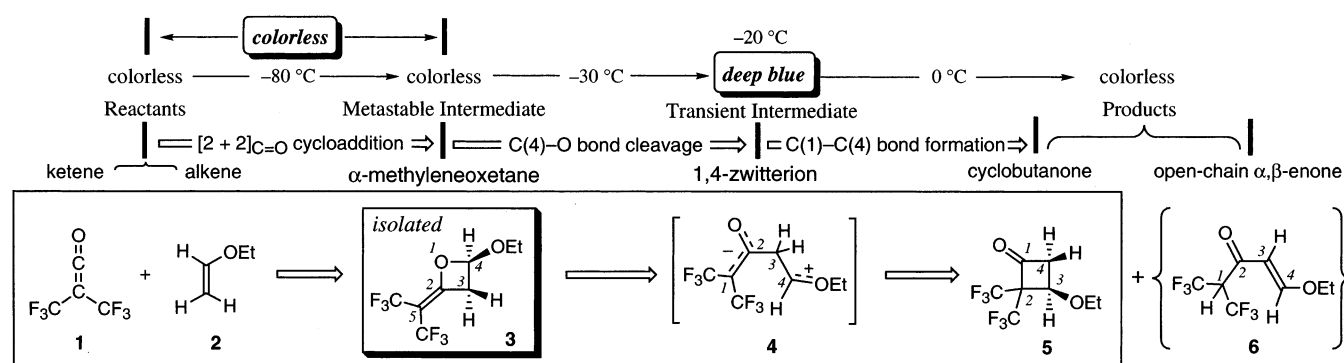
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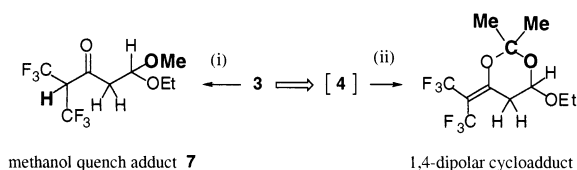
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Scheme 1. New Mechanistic Scheme Obtained in a Ketene–Alkene Reaction^a

^a Experiments were carried out in CH_2Cl_2 (1.0 mol/L).

Scheme 2. MeOH and Acetone Quench Reactions^a

^a Conditions: (i) pure isolated **3** + MeOH, $-80\text{ }^\circ\text{C}$, 4 h, 98%; (ii) pure isolated **3** + acetone, $-30\text{ }^\circ\text{C}$, overnight, 92%.

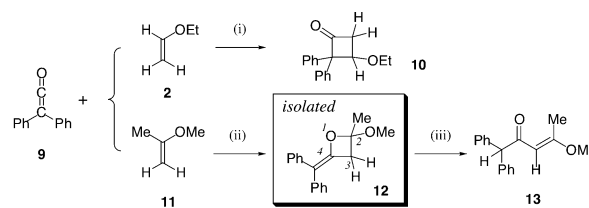
appear not to be concerned with the continuing conversion to cyclobutanones.⁸ We have become aware that a ketene [bis-(trifluoromethyl)ketene]^{8a} (**1**) reacts initially with an activated alkene [ethyl vinyl ether (**2**)] across its $\text{C}=\text{O}$ bond to form *exclusively* a $[2+2]_{\text{C}=\text{O}}$ cycloadduct, α -methyleneoxetane (**3**) at $-80\text{ }^\circ\text{C}$. The α -methyleneoxetane intermediate **3** undergoes ring cleavage to generate a zwitterion (**4**) at $-20\text{ }^\circ\text{C}$. The oxetane **3** is isomerized via the ion **4** to a $[2+2]_{\text{C}=\text{C}}$ product, cyclobutanone (**5**) in 92% along with an open-chain product α,β -enone¹⁰ (**6**) in 8% yield. To provide experimental evidence to the reaction mechanism, we elected to examine the reaction of **1** (an isolable and weight-measurable ketene) with alkene **2** spectroscopically (^{19}F and ^1H NMR). Careful low-temperature experiments were conducted to monitor the time course of the reaction.

Schemes 1 and 2 summarize the present experimental results. Choosing experimental conditions precisely, we have observed by NMR spectroscopy an exclusive formation of meta-stable oxetane intermediate **3** at $-80\text{ }^\circ\text{C}$. We have succeeded in the low-temperature isolation of **3** (colorless prisms, mp $-43\text{ }^\circ\text{C}$).¹¹ The oxetane **3** is so reactive toward the protic solvent methanol that an adduct **7** is formed rapidly even at $-80\text{ }^\circ\text{C}$ (solvolysis). The color of the solution changed dramatically [colorless ($-80\text{ }^\circ\text{C}$) \rightarrow slight blue ($-30\text{ }^\circ\text{C}$) \rightarrow deep blue ($-20\text{ }^\circ\text{C}$) \rightarrow colorless] depending on temperatures.¹²

(10) The facile isomerizations, **3** \rightarrow **6** and **12** \rightarrow **13**, are related both to the high acidity of methylene protons [$\delta_{\text{H}} = 3.4\text{--}3.7$ similar to $\delta_{\text{H}} = 3.36$ of $\text{CH}_2\text{-(COOMe)}_2$] and to the basicity of the exocyclic vinyl carbons in **3** and **12**. Study of the isomerization pathways is now in progress.

(11) Selected spectroscopic data for the reported compounds, **3** and **12**: IR ν_{max} (CH_2Cl_2) cm^{-1} ; NMR (CD_2Cl_2 , Me₄Si or C₆F₆) [^1H (δ_{H}), ^{13}C (δ_{C}), and ^{19}F (δ_{F})]. **3** ($-70\text{ }^\circ\text{C}$): $\nu_{\text{max}}(\text{C}=\text{C})$ 1703; δ_{H} 3.42 (ddqg), 3.70 (ddqg), 5.94 (dd); δ_{C} 38.85 (t, $J_{\text{CH}} = 145.0$ Hz, C-3), 92.04 (sept, $^2J_{\text{CF}} = 35.6$ Hz, C-5), 107.95 (d, $J_{\text{CH}} = 183.1$ Hz, C-2); δ_{F} -57.91 (qt), -57.18 (qt). **12** ($-30\text{ }^\circ\text{C}$): $\nu_{\text{max}}(\text{C}=\text{C})$ 1680; δ_{H} 3.15 (d, $J = 16.5$ Hz), 3.60 (d, $J = 16.5$ Hz); δ_{C} 37.91 (t, $J_{\text{CH}} = 143.0$ Hz, C-3), 107.12 (s/qqt, C-2), 111.18 (s, C-5).

(12) Deep blue color of the entropy-favored **4** appeared as in Scheme 1. We cooled the solution to $-80\text{ }^\circ\text{C}$. If a (**4** \rightleftharpoons **3**) equilibrium is assumed, the enthalpy-favored **3** should be recovered according to the thermal Le Chatelier law. But, the color did not decay at $-80\text{ }^\circ\text{C}$ at all (at least 1 month). The equilibrium does not hold for the present reaction.

Scheme 3. Two Concerted $[2+2]$ Cycloadditions (i and ii) and a Subsequent Isomerization (iii)^a

^a Conditions: (i) CH_2Cl_2 , $25\text{ }^\circ\text{C}$, 4 h, 98%. (ii) CH_2Cl_2 , $-25\text{ }^\circ\text{C}$, 2 days, 90% (isolated yield). **12**, mp $56\text{ }^\circ\text{C}$. (iii) CH_2Cl_2 , $25\text{ }^\circ\text{C}$, 6 h, 97%.

^a Conditions: (i) CH_2Cl_2 , $25\text{ }^\circ\text{C}$, 4 h, 98%; (ii) CH_2Cl_2 , $-25\text{ }^\circ\text{C}$, 2 days, 90% (isolated yield). **12**, mp $56\text{ }^\circ\text{C}$; (iii) CH_2Cl_2 , $25\text{ }^\circ\text{C}$, 6 h, 97%.

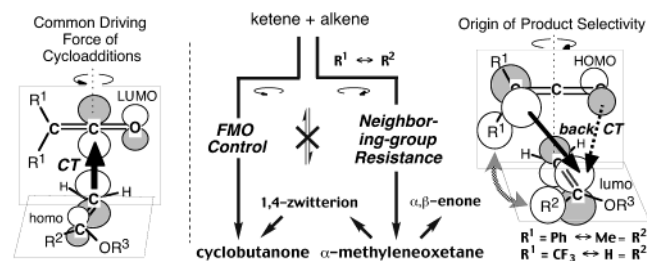
These prominent color changes strongly suggest that the 1,4-zwitterion **4** is formed *after* the initial formation of oxetane **3**. We have also succeeded in trapping the intermediate **4** which was generated from pure isolated **3** with acetone to give a 1,4-dipolar cycloadduct **8** [bp $50\text{ }^\circ\text{C}$ (0.7 mmHg)]. The addition path obtained by B3LYP/6-31G* SCRF calculations¹³ is shown in Figure 1 (Supporting Information). The ion **4** is polar enough to react with acetone solvent. The result indicates the intervention of the zwitterion **4** *after* formation of the oxetane **3** in the reaction scheme. As crucial evidence, the (**1** + **2**) reaction in acetone solvent gives also **3** (not **8**) *exclusively* at $-80\text{ }^\circ\text{C}$ and the generation of acetone-quench adduct **8** was observed only above $-30\text{ }^\circ\text{C}$ (see Supporting Information). Intervention of the zwitterion **4** prior to the formation of **3** is ruled out entirely at $-80\text{ }^\circ\text{C}$.

As usual, diphenylketene **9** (another isolable and weight-measurable ketene) reacts with **2** to give a cyclobutanone **10** (Scheme 3, step i).¹⁴ However, **9** reacts with methyl isopropenyl ether (**11**), resulting in an α -methyleneoxetane **12** (colorless prisms, mp $56\text{ }^\circ\text{C}$) *exclusively* and *concertedly* (Scheme 3, step ii). As the next step, a zwitterion derived from **12** is unstable, because the acetone quench adduct has not been obtained. The cyclobutanone ring closure is prohibited by the two geminal substituents in **12**. The oxetane was isomerized to α,β -ene (**13**) *exclusively* at room temperature (Scheme 3, step iii).

For **1** + **2**, the transition-state (TS) geometry of the concerted addition path to the cyclobutanone **5** was not found out, and

(13) GAUSSIAN 94 (revision C.4) was used for DFT calculations.

(14) The kinetic data of diphenylketene–vinyl ethers cycloadditions indicate large negative entropy change ($\Delta\Delta^\ddagger = -40$ eu) similar to those of a Diels–Alder reaction. (a) Huisgen, R.; Feiler, L. A.; Otto, P. *Tetrahedron Lett.* **1968**, 4485–4490. (b) Huisgen, R.; Feiler, L. A.; Otto, P. *Chem. Ber.* **1969**, 102, 3444–3459.

Scheme 4. Selectivity in Ketene-Activated Alkene Cycloadditions^a

^a $R^1 \leftrightarrow R^2$ means a steric repulsion.

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that to the oxetane **3** was obtained (Figure 2 in Supporting Information). The zwitterionic intermediate **4** does not form from association of reactants **1** and **2** but does from the oxetane **3** (Figure 3 in Supporting Information). Thus, calculations agree with the new mechanism in Scheme 1. For **9** + **2**, two cycloaddition paths coexist, and the cyclobutanone-formation channel has a lower activation energy than that leading to the oxetane. For **9** + **11**, only the TS of the oxetane-formation path was found. Those results of concerted cycloadditions of (**9** + **2**) and (**9** + **11**) are entirely consistent with the experimental evidence of Scheme 3, steps i and ii.

Ketene–alkene reactions are illustrated concisely in Scheme 4. Basically, there are two concerted cycloadditions. The first channel leading to cyclobutanones is more favorable through the (HOMO → lumo) back charge-transfer (CT) interaction (“FMO control” in Scheme 4).¹⁵ However, when the substituent

R^1 of the ketene contains heteroatoms or is bulky, a steric neighboring interaction interferes with the cyclobutanone ring closure (“neighboring-group resistance” in Scheme 4). The second channel gives the oxetane. Thus, the selective formation of either cyclobutanone or oxetane is a general aspect of ketene–alkene cycloadditions, which is consistent with the present results. Zwitterions are not in equilibrium with the reactants, ketene and alkene. They remain after oxetane formation to become more stable species such as cyclobutanones and quenched products. Carbon and oxygen are host atoms in ketene–alkene reactions and are *hard*.¹⁶ Zwitterions with incomplete covalent bonds are not formed initially, and cycloadditions precede.

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Supporting Information Available: Selected NMR spectra for the reported compounds and three figures of computed reaction paths of (**4** + acetone), four [2 + 2] cycloadditions, and the **3** formation along with their Cartesian coordinates and a concluding schematic figure (Scheme 4A). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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