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Lewis acid-catalyzed successive skeletal rearrangement of cyclobutene-fused diphenylhomoquinone

Ken Kokubo, Takuya Koizumi, Hiroshi Yamaguchi and Takumi Oshima*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Toyonaka, Osaka 560-0043, Japan

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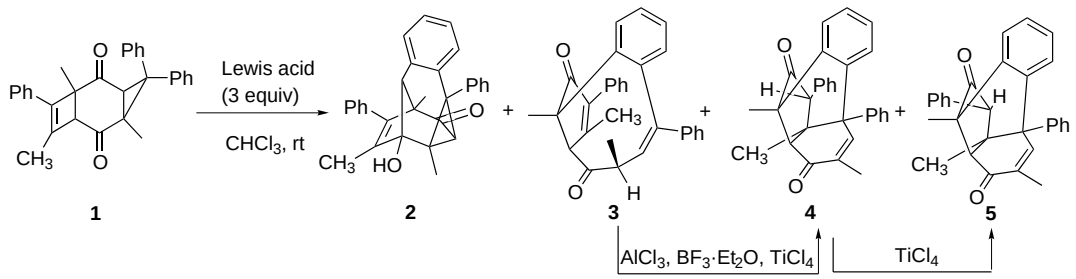
Abstract—The tricyclic enedione, which was synthesized in the [2+2] photocycloaddition of homoquinone with alkyne, underwent a novel Lewis acid-mediated skeletal rearrangement to provide bi-, tri- and tetracyclic cage compounds, depending on the identity of the Lewis acid used. The prolonged reaction and the independent treatment of the intermediary products by other Lewis acids revealed that the reaction proceeds through successive, multi-step transformations involving a cyclobutene ring-cleavage, an intramolecular Friedel–Crafts addition, and a cyclopropane ring-opening as well as an intramolecular cyclization. The product distributions were governed by the identity of the Lewis acid and the coordinated carbonyl site.

Polycyclic ketones bearing high strain energy have great potential to induce a skeletal rearrangement in the presence of an acid or a Lewis acid catalyst.[1] The product polycyclic compounds usually have a unique carbon skeleton and are rather difficult to synthesize by the usual multi-step method. The application to natural product synthesis has also been of interest in synthetic organic chemistry.[2] By appropriate design of the starting substrates, the reactions can occur in succession, the so-called tandem reaction.[3] We have recently reported the acid-catalyzed rearrangement of cyclobutane-fused homoquinones via a successive ring cleavage of cyclobutane and cyclopropane to produce dihydro-*o*-benzoquinone monomethide or dihydrobenzofuran derivatives.[4]

In this paper we report that *cyclobutene*-fused homoquinone **1** undergoes a novel tandem skeletal rearrangement on treatment with various Lewis acid catalysts and that the reaction sequence can be significantly controlled by the identity of the Lewis acid used.

Substrate **1** was synthesized by the [2+2] photoaddition of methylphenylacetylene to the corresponding homoquinone.[5] The reaction of **1** (30 mM) was carried out with 3 equiv. of $AlCl_3$ in $CHCl_3$ at room temperature for 14 and 60 h to give **2**, **3** and **4** (Eq. (1), Table 1, entries 1 and 2).[6]

The phenylene-bridged structures of these compounds were determined by X-ray structure analyses.[7] The time-dependent product distributions show that prolonged reaction (60 h) resulted in an increment of **4** by 15% but a decrement of **3** by 16% as compared with the short-time reaction (14 h). However, the relative amount of **2** (27–28%) is essentially the same irrespective of the reaction time. The observed material balance obviously indicates the transformation of primary product **3** into **4** on standing with $AlCl_3$. In contrast to the $AlCl_3$ reaction, the $TiCl_4$-catalyzed reaction was completed within 2 h to yield a predominant amount of **4** (88%) along with the equivalent quantities (6%) of **2** and a new compound **5**,[6] but **4** was significantly con-



1 2 3 4 5 (1)

* Corresponding author. E-mail: oshima@ch.wani.osaka-u.ac.jp

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Table 1. Lewis acid catalyzed rearrangement of **1** in chloroform

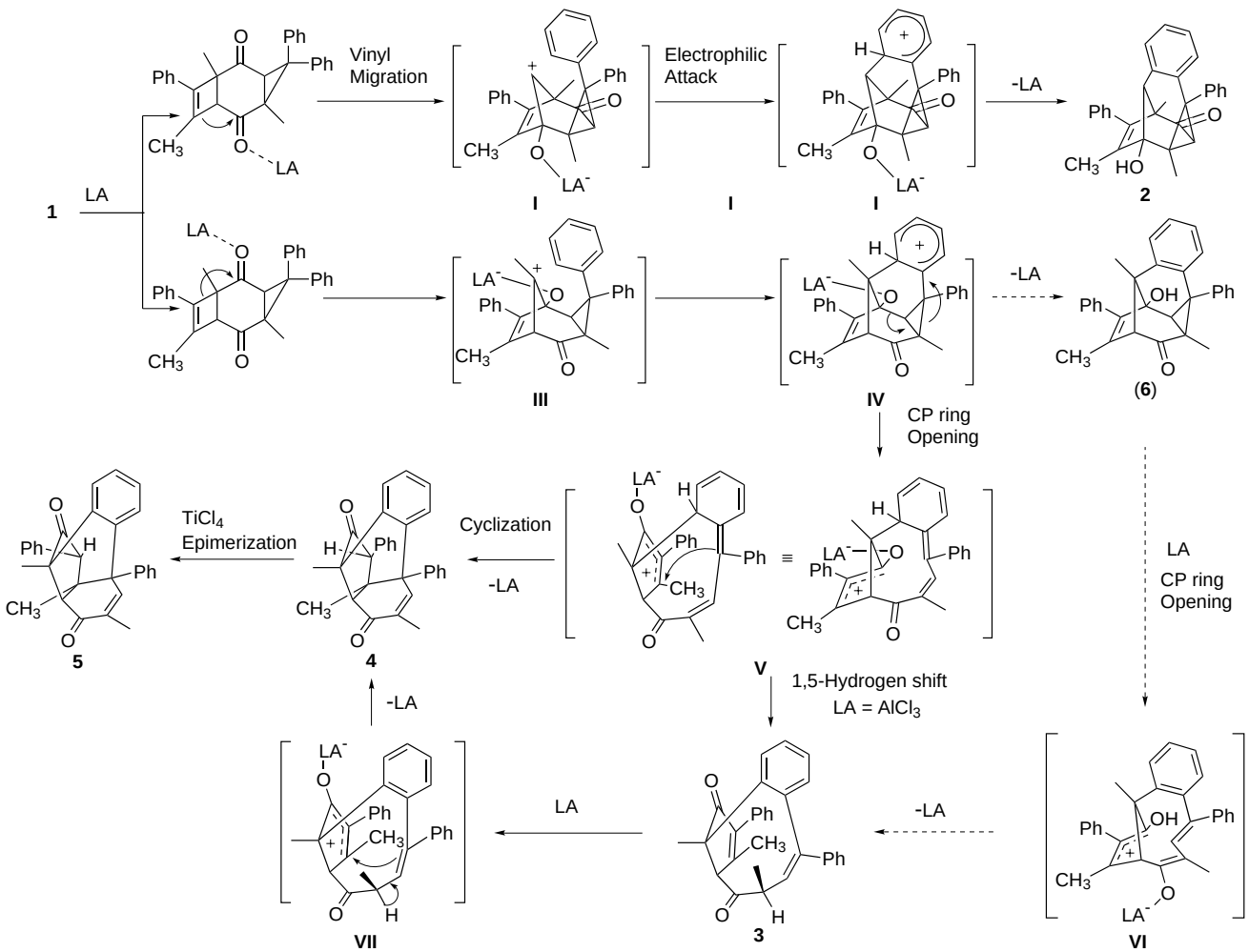
Entry	Lewis acid[a]	Time (h)	Conv. (%)	Yield (%)[b]			
				2	**3**	**4**	**5**
1	$AlCl_3$	14	84	27	31	42	–
2	$AlCl_3$	60	94	28	15	57	–
3	$TiCl_4$	2	100	6	–	88	6
4	$TiCl_4$	66	100	7	–	33	60
5	$BF_3{\cdot}Et_2O$	2	100	40[c]	–	60[c]	–

[a] 3 equiv. of Lewis acid was used with respect to **1**.
[b] Based on consumed **1**.
[c] Unchanged even on standing for 40 h.

verted into **5** on about 3 days' standing (entries 3 and 4). It is also noted that **2** (6–7%) remains intact likewise in the $AlCl_3$ reaction. The quantitative conversion of **4** into **5** was independently confirmed by treatment of the isolated **4** with $TiCl_4$ under similar reaction conditions. The structure of **5** was determined by X-ray analysis and found to be an epimer of **4**.[7]

Next, we attempted the skeletal rearrangement with $BF_3{\cdot}Et_2O$. The reaction of **1** (30 mM) with $BF_3{\cdot}Et_2O$ (3 equiv.) in chloroform at room temperature proceeded rapidly to give **2** and **4** in yields of 40 and 60%, respectively (entry 5).[8] No other transient product was observed during the reaction. Unlike the $AlCl_3$ and $TiCl_4$ reactions, the prolonged reaction up to 40 h, even under the addition of 3 more equiv. of $BF_3{\cdot}Et_2O$, caused no appreciable change in the product distribution.

As described above, a successive skeletal rearrangement of **1** with the aid of Lewis acid proceeds according to the product sequence **1→3→4→5**. In contrast, the



Scheme 1.

product **2** can be envisaged as arising from a different course of reaction in view of the fact that, regardless of the prolonged reaction time, the original cyclopropane ring was retained. These findings imply that the Lewis-acid mediated cyclobutene ring-cleavage of **1** is a trigger of the tandem skeletal rearrangements and hence the two cleavage modes are feasible due to the presence of the two carbonyl functions. Therefore, as shown in Scheme 1, the acid-coordinated **1** would produce the bridged carbocation intermediate **I** and **III** via the spontaneous vinyl migration to the adjacent carbonyl carbon atom, respectively depending on which C=O group is bound by the Lewis acid. A similar mechanism to this process is proposed by Cargill for the acid-catalyzed skeletal rearrangement of β,γ-unsaturated ketones.[9] The resulting **I** and **III** can perform the intramolecular Friedel–Crafts reaction with the nearly faced *endo*-phenyl group to give the cyclized intermediates **II** and **IV**, respectively. The **II** will provide **2** via the liable rearomatization. Strangely, the **IV** showed no indication of the formation of the corresponding tetracyclic **6** via a possible rearomatization. Instead, **IV** suffered the cyclopropane-ring opening to lead to the common allyl cation intermediate **V** for **3** (via 1,5-hydrogen shift) and for **4** (via cyclization). Although we have no sophisticated explanation for the difference in reactivity between **II** and **IV** at the present time, it is conceivable that the former would generate the nascent secondary carbocation associated with the incipient cyclopropane ring-cleavage, while the latter generates the more stable tertiary one by the relevant cyclopropane ring-cleavage. However, it can not be completely ruled out that the possible **6** rapidly rearranges to **3** via the intermediate **VI** arising from the acid-catalyzed cyclopropane ring cleavage. The **3** seems to undergo the acid-catalyzed cyclization to **4** by way of the intermediate **VII**. Finally, only in the case of $TiCl_4$, **4** epimerizes at the cyclopentanone α-carbon atom to become the more stable **5**.

In conformity with the above-described sequential product transformations, the calculated enthalpies (ΔH_f) of formation of these products by the MOPAC PM3 method declined in the order of **1** (58.5 kcal/mol)>**6** (36.3)>**3** (33.3)>**4** (30.2)>**5** (22.2).[10]

The relative yields of **2** tend to decrease with the increasing bulkiness of the Lewis acids used (Table 1), and a detailed study on the marked affection of the identity of the Lewis acid is now in progress.

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5. The detail will be described elsewhere.
6. Spectral data of **2**: ^{1}H NMR ($CDCl_3$): δ 0.98 (s, 3H), 1.13 (s, 3H), 1.80 (s, 1H, br), 2.10 (s, 3H), 2.60 (s, 1H), 3.56 (s, 1H), 6.58 (d, 2H, J=7.3 Hz), 7.05–7.18 (m, 7H), 7.24–7.64 (m, 5H). IR (KBr): 3434 (br, OH), 1672 (C=O) cm^{-1}. **3**: ^{1}H NMR ($CDCl_3$): δ 0.91 (d, 3H, J=6.6 Hz), 1.71 (s, 3H), 2.20 (s, 3H), 2.83–2.94 (dq, 1H, J=8.9, 6.6 Hz), 3.64 (s, 1H), 6.55 (d, 1H, J=8.9 Hz), 6.89–6.97 (m, 3H), 7.22–7.27 (m, 9H), 7.38–7.44 (td, 1H, J=7.9, 1.3 Hz), 7.61 (d, 1H, J=7.9 Hz). IR (KBr): 1705 (C=O) cm^{-1}. **4**: ^{1}H NMR ($CDCl_3$): δ 1.52 (s, 3H), 1.74 (s, 3H), 1.75 (d, 3H, J=1.3 Hz), 2.79 (s, 1H), 3.68 (s, 1H), 6.07 (d, 1H, J=7.9 Hz), 6.38–6.45 (m, 3H), 6.88 (q, 1H, J=1.3 Hz, vinyl), 6.89–7.24 (m, 8H), 7.31–7.38 (td, 1H, J=7.9, 1.3 Hz), 7.42–7.46 (dd, 1H, J=7.9, 1.3 Hz). IR (KBr): 1742, 1653 (C=O) cm^{-1}. **5**: ^{1}H NMR ($CDCl_3$): δ 0.58 (s, 3H), 1.75 (s, 3H), 1.77 (d, 3H, J=1.5 Hz), 2.99 (s, 1H), 4.44 (s, 1H), 6.52 (br, 2H, Ar), 7.04 (d, 1H, J=7.6 Hz), 7.12–7.13 (m, 3H), 7.18 (t, 1H, J=7.6 Hz), 7.24–7.27 (m, 2H, Ar+vinyl), 7.35 (d, 1H, J=7.6 Hz), 7.39–7.51 (m, 5H). IR (KBr): 1749, 1659 (C=O) cm^{-1}.
7. Crystal structure of **2**: $C_{30}H_{26}O_2$, M=418.53, monoclinic, space group $P2_1/a$ with a=12.644(1), b=12.974(1), c=14.0462(9) Å, β=99.205(1)°, V=2274.4(3) Å^3, Z=4, Dc=1.222 g/cm^3, R=0.093 and Rw=0.138 for 5195 reflections with I>0.0$\sigma(I)$. A crystal of 0.20×0.30×0.10 mm was used. Data were collected on a Rigaku RAXIS-Imaging Plate diffractometer with graphite monochromated Mo-Kα radiation at room temperature. No. of variables were 394. The structure was solved by direct method (SIR-88) and refined on F^2 by full-matrix least-squares method. Crystal structure of **3**: $C_{30}H_{26}O_2$, M=418.53, monoclinic, space group $P2_1/a$ with a=15.2418(8), b=8.2652(4), c=17.7642(9) Å, β=94.232(1)°, V=2231.8(2) Å^3, Z=4, Dc=1.246 g/cm^3, R=0.056 and Rw=0.108 for 5116 reflections with I>−10.0$\sigma(I)$. A crystal of 0.38×0.25×0.10 mm was used. Data were collected on a Rigaku RAXIS-Imaging Plate diffractometer with graphite monochromated Mo-Kα radiation at room temperature. Number of variables were

394. The structure was solved by direct method (SIR-92) and refined on F^2 by full-matrix least-squares method. Crystal structure of **4**: $C_{30}H_{26}O_2$, $M=418.53$, triclinic, space group $P\bar{1}$ with $a=10.810(2)$, $b=12.26(1)$, $c=8.886(4)$ Å, $\alpha=102.52(5)$, $\beta=102.51(3)$, $\gamma=88.01(4)°$, $V=1122(1)$ Å^3, $Z=2$, $Dc=1.238$ g/cm^3, $R=0.048$ and $Rw=0.052$ for 4020 reflections with $I>2.0\sigma(I)$. A crystal of 1.50×0.70×0.40 mm was used. Data were collected on a Mac Science MXC3 diffractometer using graphite monochromated Mo-Kα radiation at room temperature. Number of variables were 393. The structure was solved by direct method (SIR-92) and refined on F^2 by full-matrix least-squares method. Crystal structure of **5**: $C_{30}H_{26}O_2$, $M=418.50$, triclinic, space group $P\bar{1}$ with $a=10.2179(2)$, $b=11.0567(7)$, $c=10.151(1)$ Å, $\alpha=90.212(8)$, $\beta=99.919(4)$, $\gamma=83.632(2)°$, $V=1122.5(1)$ Å^3, $Z=2$, $Dc=1.238$ g/cm^3, $R=0.149$ and $Rw=0.199$ for 3446 reflections with $I>1.0\sigma(I)$. A crystal of 0.25×0.10×0.10 mm was used. Data were collected on a Rigaku RAXIS-imaging plate diffractometer with graphite monochromated Mo-Kα radiation at room temperature. Number of variables were 394. The structure was solved by direct method (SIR–92) and refined on F^2 by full-matrix least-squares method. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 162122–162125.

8. The observed first-order rate constant (2.39×10^{-4} s^{-1}) with the half-life period of 0.80 h at 25°C was obtained by monitoring the degradation of **1** in $CDCl_3$ by ^{1}H NMR.
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10. The ΔH_f of compound **2** was calculated to be 32.8 kcal/mol.