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Novel aromatic oxy-Cope rearrangement. Participation of a benzene ring and intramolecular potassium-ion detachment by methoxy groups

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Abstract

The aromatic oxy-Cope rearrangement including a benzene ring took place when 1-methoxy-2-aryl-bicyclo[2.2.2]oct-5-en-2-*exo*-ols and 2-(2-methoxyphenyl)-bicyclo[2.2.2]oct-5-en-*exo*-2-ols were treated with KH in THF.

Keywords: *Rearrangements; Aromatisation; Ethers; Ketones*

There are a few examples of the oxy-Cope rearrangement that involve an aromatic substituent, such as 1- and 2-naphthyl, 2-furanyl, and 2-benzofuranyl groups.[1,2] To our knowledge, however, participation of a benzene ring as part of the pericyclic array has not been mentioned in the reaction courses.[3] We now report definite participation of phenyl and monosubstituted phenyl groups, especially an *o*-methoxyphenyl group, in the rearrangement.

In connection with our studies on construction of a carbocyclic skeleton through rearrangement of bridged polycyclic compounds,[4] exo-alcohols **1** were prepared as the major products from the corresponding ketones and Grignard reagents.[5] Treatment of **1a** with KH in boiling THF using a glassware connected with a balloon filled with argon gave the 1,2,4a,10a-tetrahydro-9(10H)-phenanthrenone **3a** in a moderate yield (Table 1, entry 2).[2] When 18-crown-6 was employed as an additive, **1a** was consumed at 20 °C and **3a** was obtained as the sole product in a practical yield (entry 3).
A similar transformation of the *o*-methoxyphenyl derivative **1b** went on in the absence of the crown ether giving **3b** in an excellent yield (entry 5). By treatment of **1b** with KH under a stream of argon, the oxy-Cope product **2b** was obtained as the major product along with **3b** (entry 6). The difference between entries 5 and 6 seemed to suggest that **3b** was an oxidation

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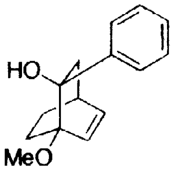
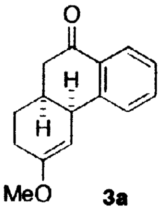
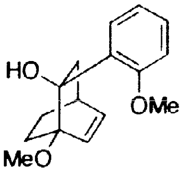
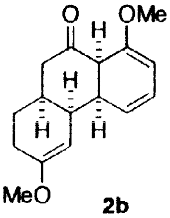
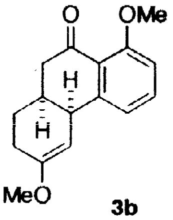
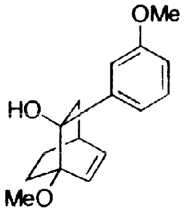
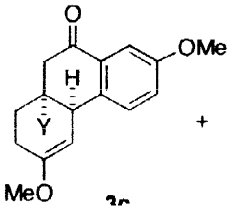
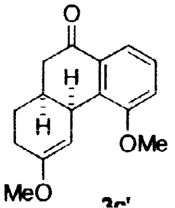
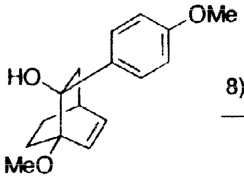
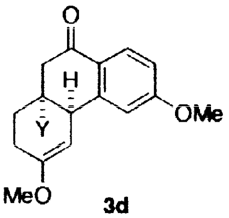
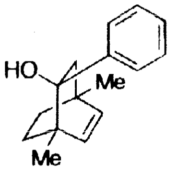
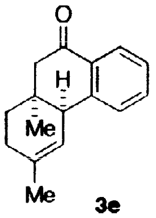
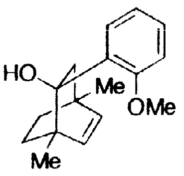
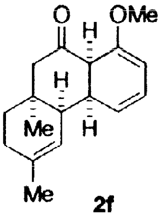
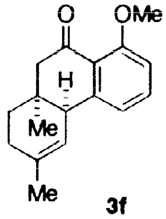
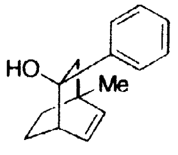
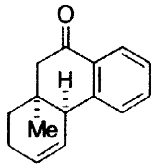
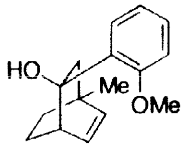
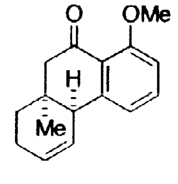
Table 1. Aromatic oxy-Cope rearrangement including a benzene ring.[a]

Entry	Oxy-Cope system	Conditions	Products (yield)
1	 **1a**	1) KH, 20°C, 4 h	**3a** (0%), **1a** (97%)[b]  **3a**
2		2) KH, 70°C,[c] 4 h	**3a** (59%), **1a** (28 %)[b]
3		3) KH, 18-crown-6, 20°C, 3 h	**3a** (82%)
4		4) KHMDS, 18-crown-6, 20°C, 2.5 h	**3a** (81%)
5	 **1b**	5) KH, 70°C,[c] 0.5 h	**3b** (91%)  **2b** +  **3b**
6		6) KH, 70°C,[c] 0.33 h[d]	**2b** (70%) **3b** (21%)
7	 **1c**	7) KH, 18-crown-6 20°C, 3 h	**3c** (64%) **3c'** (7%)  **3c** +  **3c'**
8	 **1d**	8) KH, 18-crown-6 ,20°C, 2.5 h	**3d** (70%)  **3d**
9	 **1e**	9) KH, 18-crown-6 ,70°C,[c] 2.5 h	 **3e**
10	 **1f**	10) KH, 70°C,[c] 0.5 h	**2f** (11%) **3f** (89%)  **2f** +  **3f**
11		11) KH, 70°C,[c] 0.33 h[d]	**2f** (59%) **3f** (32%)

12	 **1g**	12) KH, 18-crown-6 , 70°C,^{c} 2 h	**1g** (85%)^b $\not\longrightarrow$	 **3g**
13	 **1h**	13) KH, 70°C,^{c} 2 h	**1h** (99%)^b	 **3h**
14		14) KH, 18-crown-6 , 70°C,^{c} 4 h	**3h** (26%) **1h** (52%)^b	

a) Reactions were carried out with 3 equiv of KH and 2 equiv of 18-crown-6 in THF under argon atmosphere using a balloon unless otherwise noted. b) Recovered. c) Heated under reflux. d) Carried out under a stream of argon.

product of the enolate of **2b** by oxygen. Compound **3b** was derived in 66% yield, when **2b** was treated with KH using a glassware connected with an argon-filled balloon. A highly sensitive reaction to oxygen is known to occur under argon atmosphere using a balloon.[6] The *m*-methoxyphenyl derivative **1c** was converted regioselectively into **3c** and **3c'** under similar conditions to those used for the transformation of **1a** to **3a** (entry 7). A reaction of the *p*-methoxyphenyl derivative **1d** went on under similar conditions giving **3d** exclusively (entry 8). Those results indicate that the methoxy group *adjacent* to the hydroxy group accelerates the rearrangement. Accordingly, we employed the bridgehead-methyl derivatives (**1e** and **1f**) and the simpler substrates (**1g** and **1h**) to find out the roles of the bridgehead substituents in the rearrangement.

The alcohol **1e** was consumed by treatment with KH and 18-crown-6 in boiling THF, while no detectable amount of an oxy-Cope product such as **3e** was derived (entry 9). In contrast to **1e**, the *o*-methoxyphenyl derivative **1f** was transformed into a mixture of **2f** and **3f** under the same conditions as used for the rearrangement of **1b** (entries 10 and 11). Entry 12 suggests that the C_1-C_2 bond of **1g** did not cleave under very similar conditions to those employed for **1e** (entry 9). Treatment of **1h** with KH under the same conditions as used for the rearrangement of **1b** gave a mixture of **2h** and **3h** (entries 13 and 14). The differences between the results of entries 10 and 13 and those of entries 11 and 14 suggest that **1h** is less reactive than **1f**. Thus, the bridgehead-methoxy group is more efficient than the C-1 methyl group for the rearrangement. The *o*-methoxy group is preeminent over all substituents used for the transformation. Moreover, both methoxy groups are complementary to each other.

The bridgehead-methoxy group not only decreases the homolytic bond dissociation energy of the C_1-C_2 bond but also coordinates to the metal ion, forming a five-membered ring including the K-O-C bonds. The *o*-methoxy group forms a related six-membered ring. The latter seems to be more suitable than the former, since a six-membered ring is more flexible. The intramolecular coordination may weaken the ionic K-O bond and afford a more reactive alkoxide.

In conclusion, it is evident that the aromatic oxy-Cope rearrangement including a benzene ring takes place. An important point to promote the rearrangement is the selection of substituents on the carbon of the cleaving bond. Further investigation and synthetic application of the rearrangement are currently underway in this laboratory.

Acknowledgments

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[6] Nozaki K, Oshima K, Utimoto K. J. Am. Chem. Soc. 1987; 109: 2547-2549.

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[2] All new compounds reported here exhibit satisfactory spectral characteristics including HRMS. For instance, 3,8-dimethoxy-1,2,4,4a,4b,8a,10a-hexahydro-9(10H)-phenanthrenone (**2b**): mp 105.8—107.0 °C; IR (KBr) 1715, 1660, and 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta = 5.94$ (1H, ddd, dd, $J_{6,5} = 9.7$, $J_{6,5} = 6.0$, and $J_{6,4b} = 2.4$ Hz, H-6), 5.50 (1H, $J_{5,6} = 9.7$ and $J_{5,4b} = 3.6$ Hz, H-5), 5.08 (1H, d, $J_{7,6} = 6.0$ Hz, H-7), 4.65 (1H,broad d, $J_{4,4a} = 4.4$ Hz, H-4), 3.61 (3H, s, 8-OMe), 3.54 (3H, s, 3-OMe), 3.15 (1H, dd, $J_{8a,4b} = 8.9$ and 1.2 Hz, H-8a), 3.09 (1H, ddd, $J_{4b,8a} = 8.9$, $J_{4b,4a} = 5.8$, and $J_{4b,5} = 3.6$ Hz, H-4b), 2.82—2.79 (1H, m, H-4a), 2.50 (1H, ddd, $J_{10,10} = 13.5$, $J_{10,10a} = 6.3$, and $J_{10,8a} = 1.2$ Hz, H-10 (syn to H-10a)), 2.42 (1H. dd, $J_{10,10} = 13.5$ and $J_{10,10a} = 6.0$ Hz, H-10 (anti to H-10a)), 2.30 (1H, m, H-10a), 2.16—2.12 (2H, m, H-2), 1.75 (1H, m, H-1 (anti to H-10a)), and 1.62 (1H, m, H-1(syn to H-10a)); NOEDS: [H-4a ≈ H-4b, 6.4%], [H-4a ≈ H-10a, 4.8%], [H-4a ≈ H-8a, 3.2%], [H-4a ≈ H-4, 3.4%], [H-4a ≈ H-10 (syn to H-10a) 1.3%], [H-4b ≈ H-4a, 4.7%], [H-4b ≈ H-5, 3.0%], [H-8a ≈ H-4a, 2.8%], [H-8a ≈ H-10 (syn to H-10a), 1.8%], [H-10 (syn to H-10a) ≈ H-8a, 1.4%], [H-10 (syn to H-10a) ≈ H-10a, 4.9%], [H-10a ≈ H-4a, 4.4%], [H-10a ≈ H-10 (syn to H-10a), 3.0%], and [H-10a ≈ H-1 (syn to H-10a), 2.5%]. ^{13}C NMR ($CDCl_3$) $\delta = 209.9$ (C-9), 156.0 (C-3), 155.5 (C-8), 124.2 (C-6), 119.9 (C-5), 94.5 (C-7), 94.1 (C-4), 55.2 (8-OMe), 54.1 (3-OMe), 53.1 (C-8a), 44.4 (C-10), 43.2 (C-4a), 37.0 (C-10a), 35.6 (C-4b), 26.5 (C-2), and 26.0 (C-1). Found: *m/z* 260.1409. Calcd for $C_{16}H_{20}O_3$: M, 260.1412.