Preparation of Cyclohexene-d_{10} by H/D-Exchange Reaction

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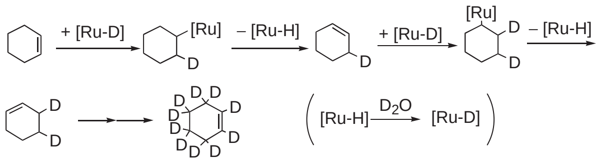
Preparation of fully deuterium-labeled cyclohexene by H/D-exchange reaction was performed efficiently in the presence of ruthenium catalyst under irradiation of microwaves. The reaction proceeds via a repetition of hydroruthenation and β-elimination.

While regio- and stereospecifically deuterium-labeled compounds have been used as fundamental research tools for biological, pharmaceutical, environmental, and mechanistic studies, fully deuterium-labeled compounds have also been important for analytical chemistry including NMR and neutron scattering studies.[1] In addition, recently, these compounds receive much attention as new materials.[2] The H/D-exchange reaction using deuterium oxide as an isotopic source is one of the most practical methods for the preparation of the fully deuterium-labeled compounds, considering its cost and low toxicity. The reaction has been performed in various ways. For example, a base catalyzed H/D-exchange reaction in supercritical or subcritical deuterium oxide was applied for the reaction of phenol and aniline derivatives,[3] and an acid-catalyzed H/D-exchange reaction was applied for alkenes.[4] The transition metal-catalyzed exchange reaction in hot deuterium oxide is also a useful method. The methods can be applied not only for unsaturated hydrocarbons but also for saturated ones.[5] Although these methods have been applied to many compounds, cyclohexene-d_{10}, which is one of the most useful perdeuterated hydrocarbon, cannot be obtained from cyclohexene efficiently by the existing methods. The only example of a direct H/D-exchange reaction of cyclohexene was Werstiuk's acid-catalyzed reaction in D_2O at 225 °C;[4a] but it gave 1-methylcyclopentene-d_{10} as a major product. As far as the reaction is acid-catalyzed, such skeletal rearrangement cannot be avoided. In the cases of transition metal-catalyzed H/D-exchange reactions, the formation of benzene is the major pathway of the reaction, as the dehydrogenation reaction from cyclohexene is also catalyzed by these metals to afford a stable aromatized product. One of the crucial intermediary compounds for dehydrogenation is supposed to be an allylic metal compound. Thus, some new reaction, which does not contain such an intermediate, should be designed for conversion from cyclohexene into cyclohexene-d_{10}.

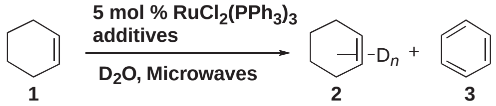
During the course of our study of ruthenium-catalyzed reactions in water under irradiation of microwaves, we have found a rapid repetition of hydrometallation and β-elimination, which makes the isomerization of ω-alkenol into saturated alkanone possible.[6] As the exchange reaction on ruthenium hydride in deuterium oxide was also known,[7] the reaction may be applied to the conversion of cyclohexene into cyclohexene-d_{10}. Moreover, the intermediate is considered to be a saturated cyclohexyl–metal compound, which does not have a step for formation of benzene (eq 1).



(1)

As shown in Table 1, the irradiations of microwaves to mixtures of cyclohexene, D_2O, and ruthenium catalyst were examined in the presence of various additives. An addition of

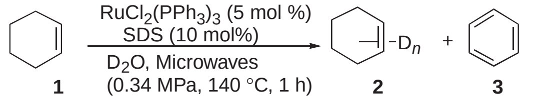
Table 1. The effect of additives on the ruthenium-catalyzed exchange reaction of cyclohexene



Run	Additive[a]	Condition[b]	Distribution of D in **2**[c]	**3**
1	none	140 °C, 0.34 MPa, 1 h	0	0
2	none	185 °C, 1.0 MPa, 1 h	30%D	5%
3	MeOH (20 mol %)	140 °C, 0.34 MPa, 1 h	0	0
4	MeOH (20 mol %)	185 °C, 1.0 MPa, 1 h	65%D	5
5	EtOH (20 mol %)	140 °C, 0.34 MPa, 1 h	13%D	0
6	EtOH (20 mol %)	185 °C, 1.0 MPa, 1 h	95%D	10
7	SDS (10 mol %)	140 °C, 0.34 MPa, 1 h	97%D	0
8	SDS (10 mol %)	140 °C, 0.34 MPa, 15 min	96%D	0
9	SDS (10 mol %)	120 °C, 0.14 MPa, 1 h	90%D	0
10	EtOH (20 mol %) SDS (10 mol %)	140 °C, 0.34 MPa, 1 h	96%D	0
11	EtOH (20 mol %) SDS (10 mol %)	185 °C, 1.0 MPa, 1 h	96%D	15

[a]SDS: Sodium dodecylsulfate. [b]Microwaves were irradiated using a Biotage Initiator™ in 10 mL vial. Power varied automatically between 0–100 W to maintain the temperature. The internal pressure was measured at the indicated temperature. Cyclohexene (1.0 mmol), Ru catalyst (0.05 mmol), D_2O (3 mL), and additives (as indicated in Table) are used. During the irradiation, the mixture was stirred by an electronic stirrer which is equipped in the Biotage machine. [c]Yields of the deuterated cyclohexene were 80–96%. The ratio of D-atom distribution was determined by ^1H and ^2H NMR using $CHBr_3$ and $CDCl_2$–$CDCl_2$ as internal standard individually.

Table 2. Efficiency of H/D-exchange under various ratios of cyclohexene to deuterium oxide



1 (2 mmol),	D_2O (150 mmol),	**2** (96%, 97%D),	**3** (0%)
1 (5 mmol),	D_2O (150 mmol),	**2** (90%, 86%D),	**3** (0%)
1 (10 mmol),	D_2O (150 mmol),	**2** (90%, 53%D),	**3** (0%)
1 (20 mmol),	D_2O (150 mmol),	**2** (90%, 8%D),	**3** (0%)

a catalytic amount of alcohol (Runs 4–6) improved the efficiency of exchange dramatically. These results can be explained by the ease of the formation of ruthenium hydride: A combination of a primary alcohol and $RuCl_2(PPh_3)_3$ affords ruthenium hydride and the corresponding aldehyde under equilibrium condition.[6,8] The ruthenium hydride can be converted into ruthenium deuteride in D_2O.[6–8] An addition of a catalytic amount of SDS (sodium dodecylsulfate) also accelerated the exchange reaction efficiently (Runs 7–10). Under the irradiation of microwaves at 120 °C/0.14 MPa for 1 h, SDS (1.0 mmol) in water (3 mL) afforded dodecanol in 4% yield. The treatment of SDS at 140 °C/0.34 MPa under the irradiation of microwaves for 1 h gave the alcohol in 85% yield. The use of ethanol and SDS together did not show a significant difference from the separate uses of each additive (Runs 10 and 11). The effect of SDS may be explained as follows: 1) partial hydrolysis of sulfate affords dodecanol, which is the source of ruthenium hydride, and 2) the ruthenium species are stabilized on the surface of the micelle that is formed by SDS.[9]

The easy isolation of the labeled product is also a beneficial point of the present method. After the reaction, the product and D_2O were separated into two phases in the reaction vial. The product can be purified by a bulb-to-bulb distillation of the organic phase.

The ratio of D_2O and cyclohexene in the reaction mixture was also studied. There are ten hydrogen atoms in cyclohexene, so five molar equivalents of deuterium oxide are indispensable at least. As shown in Table 2, the use of 15 times molar excess of D_2O over cyclohexene resulted in 53% D-atom distribution. Prolonged reaction time did not improve the ratio of deuterium atoms in the product. Irradiation of microwaves to the same reaction mixture for 2 h gave also cyclohexene having 53% D-atom distribution.

Irradiation of microwaves is not essential for the exchange reaction. It is, however, effective for shortening the reaction period.[10] The irradiation extensively heats the polar molecule, that is organoruthenium and alkoxyruthenium in this reaction (eq 1).[6] As shown in Run 8 of Table 1, irradiation of microwaves for 15 min gave the product having 96% D-atom distribution. On the contrary, heating at 150 °C in autoclave gave 90% D-atom distribution even after 12 h. This procedure for 2 h gave only 40% D-atom distribution in the product. No deuterium-labeled product was obtained under refluxing of D_2O with ruthenium catalyst at 100 °C for 2 h.[11]

Other cycloalkenes were examined for exchange reactions by the present method. As shown in Figure 1, cyclooctene, cyclodecene, cyclododecene, and cyclopentadecene were converted to perdeuterated cycloalkenes efficiently. Thus, ruthenium-catalyzed exchange reactions made the direct preparation of cyclohexene-d_{10} possible. The limitation of the present method is the low exchange efficiency of the reaction in an alkyl-substituted cycloalkene. For example, treatment of 1-methylcyclohexene under the same conditions as those of Run 7 of Table 1 for cyclohexene gave only 27% D-atom distribution. This method, however, is the first example of the efficient preparation of cyclohexene-d_{10} from unlabeled cyclohexene using D_2O as the deuterium source.[12] The procedure is quite simple and has opened the new way to the direct preparation of perdeuterated cycloalkenes.

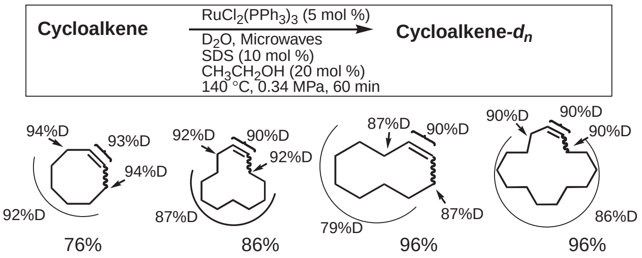


Figure 1. Exchange in various cycloalkenes.

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References and Notes

1 a) T. Junk, W. J. Catallo, *Chem. Soc. Rev.* **1997**, *26*, 401. b) N. Elander, J. R. Jones, S.-Y. Lu, S. Stone-Elander, *Chem. Soc. Rev.* **2000**, *29*, 239. c) J. L. Garnett, *Catal. Rev.* **1971**, *5*, 229. d) T. Kametani, K. Katoh, M. Tsubuki, T. Honda, *J. Am. Chem. Soc.* **1986**, *108*, 7055.

2 a) M. Yamamoto, Y. Yokota, K. Oshima, S. Matsubara, *Chem. Commun.* **2004**, 1714. b) T. Kurihara, N. Ooba, S. Toyoda, T. Maruno, *Oyobuturi* **2002**, *71*, 1508. c) T. Kaino, K. Jinguji, S. Nara, *Appl. Phys. Lett.* **1983**, *42*, 567. d) M. S. Miller, I. M. Klotz, *J. Am. Chem. Soc.* **1973**, *95*, 5694.

3 J. Yao, R. F. Evilia, *J. Am. Chem. Soc.* **1994**, *116*, 11229.

4 a) N. H. Werstiuk, G. Timmins, *Can. J. Chem.* **1985**, *63*, 530. b) N. H. Werstiuk, T. Kadai, *Can. J. Chem.* **1974**, *52*, 2169.

5 a) F. A. L. Anet, N. St. Jacques, *J. Am. Chem. Soc.* **1966**, *88*, 2585. b) J. L. Garnett, R. J. Hodges, *J. Am. Chem. Soc.* **1967**, *89*, 4546. c) J. G. Atkinson, M. O. Luke, R. S. Stuart, *Can. J. Chem.* **1967**, *45*, 1511. d) O. Desponds, M. Schlosser, *Tetrahedron Lett.* **1996**, *37*, 47. e) A. E. Shilov, A. A. Steinman, *Coord. Chem. Rev.* **1977**, *24*. 97. f) J. T. Golden, R. A. Andersen, R. G. Bergman, *J. Am. Chem. Soc.* **2001**, *123*, 5837. g) C. Hardacre, J. D. Holbrey, S. E. J. McMath, *Chem. Commun.* **2001**, 367. h) J. R. Jones, W. J. S. Lockley, S.-Y. Lu, S. P. Thompson, *Tetrahedron Lett.* **2001**, *42*, 331. i) S. Matsubara, Y. Yokota, K. Oshima, *Chem. Lett.* **2004**, *33*, 294. j) H. Sajiki, F. Aoki, H. Esaki, T. Maegawa, K. Horita, *Org. Lett.* **2004**, *6*, 1485. k) M. Yamamoto, K. Oshima, S. Matsubara, *Heterocycles* **2006**, *67*, 353. l) H. Esaki, N. Ito, S. Sakai, T. Maegawa, Y. Monguchi, H. Sajiki, *Tetrahedron* **2006**, *62*, 10954.

6 K. Ishibashi, M. Takahashi, Y. Yokota, K. Oshima, S. Matsubara, *Chem. Lett.* **2005**, *34*, 664.

7 R. F. R. Jazzar, P. H. Bhatia, M. F. Mahon, M. K. Whittlesey, *Organometallics* **2003**, *22*, 670.

8 M. Takahashi, K. Oshima, S. Matsubara, *Chem. Lett.* **2005**, *34*, 192.

9 D. Motoda, H. Kinoshita, H. Shinokubo, K. Oshima, *Angew. Chem., Int. Ed.* **2004**, *43*, 1860.

10 Microwaves in organic reaction, see: C. O. Kappe, *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. In our reaction, microwaves were irradiated using Biotage Initiator™ in a 10-mL vial. Power varied automatically between 0–100 W to maintain the temperature.

11 a) A. Kruse, E. Dinjus, *J. Suoercrit. Fluids* **2007**, *39*, 362. b) U. M. Lindström, *Chem. Rev.* **2002**, *102*, 2751.

12 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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