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Iodohydroxylation of Alkylidenecyclopropanes. An Efficient Synthesis of Iodocyclopropylmethanol and 3-Iodobut-3-en-1-ol Derivatives

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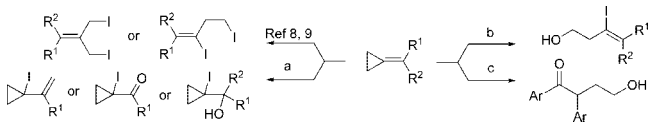

A variety of iodocyclopropylmethanol and 3-iodobut-3-en-1-ol derivatives were readily prepared in good to excellent yields via the simple iodohydroxylation reaction of alkylidenecyclopropanes with I_2 and H_2O. An unexpected rearrangement to give 4-hydroxy-1,2-diphenyl-butan-1-one derivatives was observed compared to the halohydroxylation products.

Alkylidenecyclopropanes (ACPs) are highly strained but readily available molecules that have served as useful building blocks in organic synthesis.[1] So far, increasing attention has been paid to the transition metal-catalyzed reactions of unsubstituted methylenecyclopropanes, which have been employed for the construction of complex organic molecules.[2,3] Examples of Lewis acid or Brønsted acid mediated reactions of ACPs have also been disclosed.[4] An attractive but often troublesome feature of methylenecyclopropanes is their multiform reactivities that may lead to formation of a variety of products through addition to a C=C double bond and cleavage of proximal or distal bonds of the three-membered ring. Moreover, for the reactions with unsymmetrical ACPs, the regiochemistry generally affords different possible products. Thus, the regio- and stereoselectivity of the insertion and ring-opening methods have been the highlight of methylenecyclopropane chemistry.[5]

We have found that ACPs **1** can be opened by using electrophiles and nucleophiles to give the corresponding dihalogenation or Ritter-type derivatives in good yields under mild conditions.[6] These interesting results encouraged us to investigate further unique addition reactions with different electrophile/nucleophile systems to give novel products. Although halohydroxylations of C=C of olefins[7] are conventional methods, reports on the halohydroxylation of ACPs are limited,[8,9] probably because the regiochemistry makes the reaction complicated. In this paper, we wish to disclose our recent results of addition reactions of ACPs **1** with iodine and water to give ring-opening or ring-keeping products and that, in most of the cases studied, the reactions are clean and efficient.

First, we carried out the iodohydroxylation of various ACPs **1** with 2.0 equiv of iodine in aqueous acetone at room temperature. We found that (1-iodocyclopropyl)methanol **2** was obtained as the major product efficiently. The results are summarized in Table 1. Starting from **1a**−**h**, the corresponding **2a**−**h** were obtained in moderate to excellent yields (Table 1, entries 1−8). On the other hand, reaction of **1a** and **1j** with bromine under similar conditions also successfully provided the corresponding bromohydroxylation adducts **3a** and **3j** in 88% and 92% yields within 0.5 h (Table 1, entries 9 and 10, respectively).

However, for ACPs **1e**−**g** and **1k** having a hydrogen atom, we observed that the reaction proceeded smoothly to afford useful product **4** using 5.0 equiv of I_2. The results are summarized in Table 2.

Furthermore, for unsymmetric aliphatic ACP **1h**, we observed that iodine cation can easily add to the C=C bond without cleavage of the cyclopropane ring to give the vinylcyclopropane derivative **5a** as a single product in good yield (eq 1).

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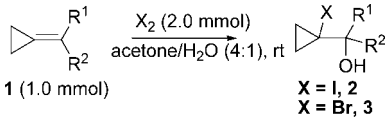
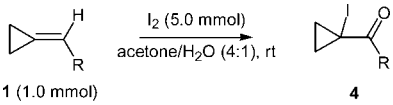
TABLE 1. Iodohydroxylation and Bromohydroxylation of ACPs 1[a]



entry	ACP 1 (R^1/R^2)	X_2	time/h	yield of **2** or **3** (%)[b]
1	C_6H_5/C_6H_5(**1a**)	I_2	1	**2a**, 95
2	*p*-ClC_6H_4/*p*-ClC_6H_4(**1b**)	I_2	5	**2b**, 84
3	*p*-FC_6H_4/*p*-FC_6H_4(**1c**)	I_2	12	**2c**, 96
4	*p*-MeC_6H_4/*p*-MeC_6H_4(**1d**)	I_2	18	**2d**, 65
5	C_6H_5/H(**1e**)	I_2	20	**2e**, 75
6	*p*-MeC_6H_4/H (**1f**)	I_2	5	**2f,** 85
7	*o*-$MeOC_6H_4$/H (**1g**)	I_2	6	**2g,** 87
8	*p*-$MeOC_6H_4$/CH_3 (**1h**)	I_2	5	**2 h,** 36[c]
9	**1a**	Br_2	0.5	**3a,** 88
10	*p*-$MeOC_6H_4$/ *p*- ClC_6H_4 (**1j**)	Br_2	0.5	**3j,** 92

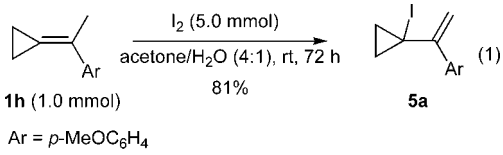
[a] Unless otherwise specified, the reaction was carried out with **1** (1.0 mmol) and X_2 (2.0 mmol) in acetone aqueous. [b] Isolated yields and the reaction time are determined by TLC on the basis of consuming the starting materials **1.** [c] 8% of **5a** was isolated as byproduct.

TABLE 2. Iodohydroxylation of Monosubstituted ACPs



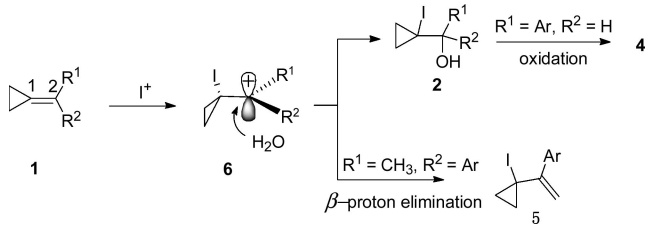
entry	ACP 1 (R)	time/h	yield of **4** (%)[a]
1	**1e**	72	**4e**, 78
2	**1f**	72	**4f**, 60
3	**1g**	72	**4g**, 75
4	*p*-BrC_6H_4 (**1k**)	48	**4k**, 81

[a] Isolated yields.

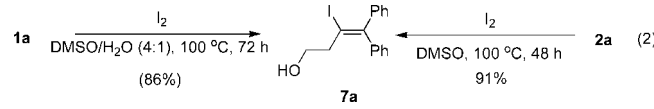


A possible mechanistic pathway for the formation of **2**−**5** is shown in Scheme 1. First, electrophilic addition of I^+ to the C-1 position of the electron-rich double bond provides cyclopropylcarbinyl cation **6**. Subsequent water attacks the C-2 positon of **6** affording the product **2.** Previously, the iodination of **1** in aprotic solvents (CH_2Cl_2, DCE) has been reported to yield the regular diiodide addition adduct in the presence of an excess of the reagent.[8d,e] The fact indicates that in acetone/water the cation **6** may be stabilized by solvation and therefore has no tendency to stabilize itself by rearrangement.[10] Product **4** must arise via oxidation of **2** (R^1 = Ar, R^2 = H) by excessive I_2.[11] If the R^1 group is methyl, the carbonium ion intermediate gives product **5** via β-proton elimination.[12]

SCHEME 1. Proposed Mechanistic Pathway for the Reaction in Tables 1 and 2 and Eq 1

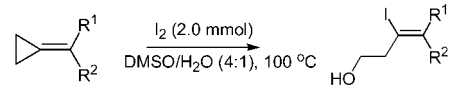


Controlled experiments with varying solvents revealed an interesting reactivity pattern, leading to entirely different products. In the presence of 2.0 equiv of I_2 in DMSO/H_2O, **1a** was consumed after 72 h at higher reaction temperature to afford **7a** as a major product in 86% yield (eq 2). To confirm the formation route, we carried out the reaction of 1 equiv of iodine with a solution of **2a** in DMSO at 100 °C, which resulted in the smooth conversion of **2a** into the same compound **7a** (91%). And we also examined the reaction in anhydrous DMSO, which gave **7a** in 61% yield,[13] suggesting that the OH group has to come from starting material **2a**.



This reaction also appears to be general and the results are summarized in Table 3. When a solution of **1** in DMSO/H_2O was treated with 2 equiv of iodine, the substrate was converted cleanly into the 3-iodobut-3-en-1-ol **7**. Using unsymmetric ACP **1e**, we obtained only the *Z* isomer.

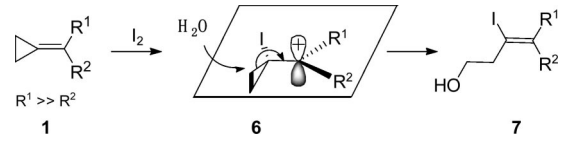
TABLE 3. Iodohydroxylation of ACPs in Aqueous DMSO[a]



entry	ACP **1** (R^1/R^2)	time/h	yield of **7** (%)[b]
1	**1a**	72	**7a**, 86
2	**1b**	72	**7b**, 80
3	**1c**	72	**7c**, 90
4	**1d**	24	**7d,** 95
5	**1e**	24	(*Z*)-**7e,** 46
6	**1i**	72	**7i**, 71
7	*p*-*i*-$BuOC_6H_4$/ *p*-*i*-$BuOC_6H_4$ (**1m**)	24	**7m**, 75

[a] Unless otherwise specified, the reaction was carried out with **1** (1.0 mmol) and I_2 (2.0 mmol) in DMSO/H_2O and then quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$. [b] Isolated yields.

SCHEME 2. Proposed Mechanistic Pathway for the Reaction in Table 3



Apparently, products **7** are derived from the cation **6** (Scheme 2). [14] In this case, strain release is more favorably accomplished by ring opening of the intermediate and bond migration. The observed selectivity was assigned based on the mechanism. Nucleophilic attack of the H_2O competitive with its iodine trapping produces the stereospecific ring-opened *Z* isomer.

Iodohydroxylation of the ACP **1i** with an electron-donating substituent on the benzene ring in aqueous DMSO gave the single product **2i** (Scheme 3). Furthermore, a big different product **8i** was obtained when the reaction was carry out in aqueous acetone, instead of DMSO, albeit in low yield. Besides the products **8i** and **8n**, a number of side products were

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(12) Liu, L.-P.; Shi, M. *J. Org. Chem.* **2004**, *69*, 2805.
(13) See the Supporting Information for experimental details.
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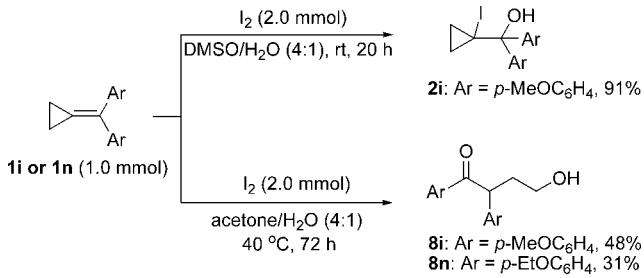
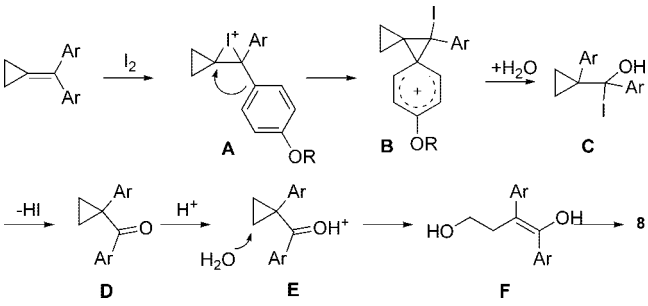
SCHEME 3. Iodohydroxylation of ACPs with an Electron-Donating Substituent on the Benzene Ring



SCHEME 4. Proposed Mechanism for the Reaction in Scheme 3



produced. It is noteworthy that substitutent and solvation did significantly affect the reaction.

Although the mechanistic underpinnings of the reaction are not clearly known, the following rationalization may be advanced to explain the product formation (Scheme 4). Presumably, I^+ first add to ACPs bearing an electron-donationg substituent (methoxyl or ethoxyl group) on the aromatic ring to give the intermediate **A**. Consequently, rapid interconversion occurred between **A** and ions **B**, which attacked by the H_2O to give **C**. [15] The addition of H^+ to **D** produces the intermediate **E**, which undergoes the cyclopropane ring-opening reaction to form the intermediate **F**. Finally isomerization of **F** furnishes the derivative **8**.

In conclusion, we have developed the novel reactions of ACPs with the I_2/H_2O system leading to two different products with or without ring opening under mild conditions. In one case, the bifunctional cyclopropane derivatives **2**−**5** can be obtained in good to excellent yields. In the other case, the ACPs are converted to 3-iodobut-3-en-1-ol derivatives efficiently with ring opening. These clean/convenient available products bearing two functional groups −X and −OH may be converted to other interesting and useful structural units in organic synthesis.[16] In addition, different solvents can lead to selective synthesis of diverse products. For example, in contrast to **2** and **7**, rearrangement product **8** can also be obtained from the same starting material. Further studies to expand the scope and synthetic utility of this method are currently underway.

Experimental Section

Preparation of (1-Iodocyclopropyl)diphenylmethanol (2a): Typical Procedure 1. To a solution of ACP **1a** (206 mg, 1.0 mmol) in 8 mL of acetone was added H_2O (2 mL). Then I_2 (508 mg, 2.0 mmol) was subsequently added. The progress of the reaction was monitored by TLC, and the mixture was stirred until the starting material disappeared (1 h). Then a saturated aqueous solution of $Na_2S_2O_3$ was added. The mixture was extracted with ether (2 × 25 mL) and dried over $MgSO_4$. Evaporation and column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) afforded **2a** (332 mg, 95%) as a solid. **2a:** white solid; mp 80−81 °C; IR (ATR) ν_{max} 3539, 3054, 1779, 1658, 1489, 1444, 1323, 1227, 1141, 1079, 917, 754, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 7.6 Hz, 4H), 7.29−7.21 (m, 6H), 2.95 (s, 1H), 1.22 (t, J = 6.6 Hz, 2H), 0.92 (t, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.8, 127.6, 127.5, 82.0, 20.7, 15.4; MS (EI) m/z (%) 350 (M^+, 2.5), 223 (16.0), 183 (100), 105 (83.1), 77 (50.2); HRMS m/z (ESI) calcd for $C_{16}H_{15}OI$ (M^+) 350.0168, found 350.0179.

Preparation of 3-Iodo-4,4-diphenylbut-3-en-1-ol (7a): Typical Procedure 2. To a solution of ACP **1a** (206 mg, 1.0 mmol) in 8 mL of DMSO was added H_2O (2 mL). Then I_2 (508 mg, 2.0 mmol) was subsequently added. The reaction was then heated to 100 °C for 3 days. The course of the reaction was monitored by TLC. Then a saturated aqueous solution of $Na_2S_2O_3$ was added. The mixture was extracted with ether (2 × 25 mL) and dried over $MgSO_4$. Evaporation and column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) afforded **7a** (301 mg, 86%) as a solid. **7a:** white solid; mp 112−114 °C; IR (ATR) ν_{max} 3407, 3053, 2882, 1592, 1491, 1438, 1263, 1185, 1073, 1030, 1006, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.26 (m, 10 H), 3.89 (t, J = 6.2 Hz, 2H), 2.87 (t, J = 6.4 Hz, 2H), 1.66 (b, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 146.6, 140.1, 128.6, 128.4, 128.2, 127.3, 127.2, 104.0, 62.4, 44.4; MS (EI) m/z (%) 350 (M^+, 26.1), 319 (4.5), 191 (56.4), 165 (36.2), 115 (45.5), 61 (100); HRMS m/z (ESI) calcd for $C_{16}H_{15}OI$ (M^+) 350.0168, found 350.0157.

Preparation of 4-Hydroxy-1,2-bis(4-methoxyphenyl)-butan-1-one (8i): Typical Procedure 3. To a solution of ACP **1i** (266 mg, 1.0 mmol) in 8 mL of acetone was added H_2O (2 mL). Then I_2 (508 mg, 2.0 mmol) was subsequently added. The reaction was then heated to 40 °C for 3 days. Then a saturated aqueous solution of $Na_2S_2O_3$ was added. The mixture was extracted with ether (2 × 25 mL) and dried over $MgSO_4$. The mixture was concentrated under reduced pressure, and residue was subjected to chromatography eluting with petroleum ether/ethyl acetate = 3:1 to give **8i** (144 mg, 48%) as an oil. **8i:** colorless oil; IR (ATR) ν_{max} 3436, 2933, 2837, 1666, 1598, 1508, 1245, 1168, 1028, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.85−6.80 (m, 4H), 4.76 (t, J = 7.2 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 3H), 3.67−3.61 (m, 1H), 3.59−3.54 (m, 1H), 2.41−2.34 (m, 1H), 2.01−1.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.8, 163.2, 158.5, 131.4, 131.0, 129.5, 129.2, 114.3, 113.6, 60.4, 55.3, 55.1, 48.7, 36.3; MS (EI) m/z (%) 300 (M^+, 2.5), 282 (15.6), 165 (14.1), 148 (24.2), 135 (100); HRMS m/z (ESI) calcd for $C_{18}H_{20}O_4$ (M^+) 300.1362, found 300.1370.

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Note Added after ASAP Publication. Due to a production error, the equation in Table 2 was incorrect and the equation in Table 3 was missing some bonds. The corrected version was published ASAP on May 31, 2008.

Supporting Information Available: General experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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