

A New Synthesis of *trans*-Iodohydrins using Iodine–Cerium(IV) Salts†

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The reaction of cycloalkene with iodine–cerium(IV) ammonium nitrate (CAN) in acetonitrile–water (10:1–1:1) affords the corresponding *trans*-iodohydrins and *trans*-iodonitrates; when iodine–cerium(IV) sulfate (CS) in acetonitrile–water (10:1) at 50 °C is used, *trans*-iodohydrins are obtained preferentially.

trans-Iodohydrins are highly reactive and are used as important intermediates in organic synthesis. There are many syntheses of *trans*-iodohydrins, namely, *trans*-addition to olefins using iodine–pyridinium dichromate,¹ bis(pyridine)iodine(1)–tetrafluoroborate² and *N*-iodosuccinimide–water,³ and epoxy-ring opening using LiI in acetonitrile using Amberlyst 15 resin.⁴ Mattos and Sanseverino have recently reported that the reaction of an alkene with iodine–iron(III) sulfate or copper(II) acetate in aqueous dioxane gives iodohydrins.⁵ A new synthesis of iodohydrin from an alkene using periodic acid with sodium bisulfate has also been recently reported.⁶

We have investigated novel iodination methods using iodine–copper(II) acetate.⁷ These methods, however, have some disadvantages in the fact that the produced iodide ions are consumed as copper(I) iodide. During the course of our studies of the reagents using iodine–cerium(IV) ammonium nitrate (CAN), we found some new reactions: a novel α -iodination of ketones in acetic acid or methanol⁸ and new alkoxyiodinations and nitroiodinations of olefins,⁹ α,β -unsaturated ketones and esters,¹⁰ a new oxidative aromatization of α,β -unsaturated cyclohexenones¹¹ and a new α,α' -diiodination of ketones¹² using iodine–CAN. Here we report that the reaction of cycloalkenes [cyclopentene (**1**), cyclohexene (**2**), cycloheptene (**3**), cyclooctene (**4**), 1-methylcyclohexene (**5**) and 1,4-dimethylcyclohexene (**6**)] and

Table 1 Reaction of cycloalkenes with I₂–CAN^a

Run	Substrate	MeCN:H ₂ O	T/°C	t/h	Products (%) ^b
1	1	10:1	50	5	8 (38) + 15 (35) ^c
2	1	10:1	50	10	8 (47) + 15 (31)
3	1	5:1	50	5	8 (56) + 15 (16)
4	1	1:1	50	5	8 (57) + 15 (7)
5	2	10:1	50	8	9 (47) + 16 (35) ^c
6	2	10:1	50	8	9 (45) + 16 (33)
7	2	10:1	reflux	5.5	9 (47)
8	2	1:1	50	8	9 (83) + 16 (5)
9	3	10:1	50	7	10 (63)
10	3	5:1	50	7	10 (78)
11	3	1:1	50	7	10 (90)
12	4	10:1	50	6	11 (16) + 18 (63)
13	7	10:1	50	3	14 (99)

^aThe ratio of I₂ of CAN is 1:2. ^bIsolated yields. ^cIsolated yield based on iodine.

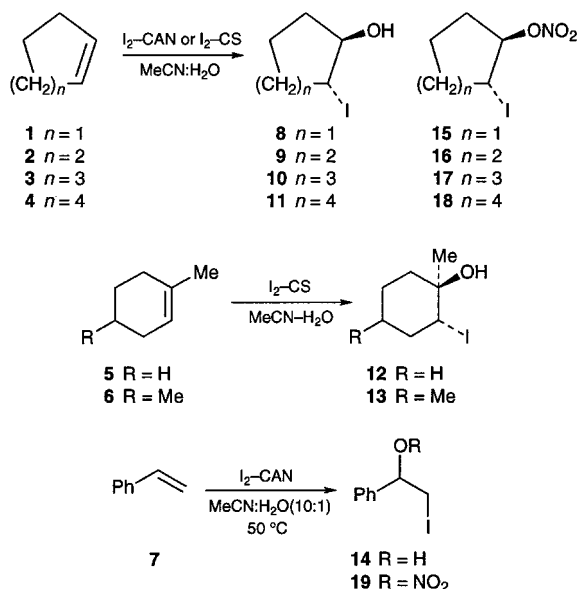
styrene (**7**) with iodine–cerium(IV) salts in acetonitrile–water readily yields the corresponding *trans*-iodohydrins. The reaction of cyclohexene (**2**) with iodine–CAN in acetonitrile–water (10:1) at 50 °C for 8 h gave *trans*-1-iodo-2-hydroxycyclohexane (**9**) (47%) and the *trans*-1-iodo-2-nitrato derivative **16** (35%). In acetonitrile–water (1:1), **9** and **10** were obtained preferentially. The results are summarized in Table 1.

As can be seen from Table 1, the reaction proved to be general in the synthesis of *trans*-iodohydrin cycloalkane derivatives. Moreover, it is particularly noteworthy that in contrast to the case of the cycloalkenes, the reaction of styrene (**7**) with iodine–CAN in acetonitrile–water (10:1) yielded iodohydrin compounds in high yield and with no iodonitrato compounds. In order to clarify the progress of the hydrolysis of iodonitrato compounds, the reaction of iodonitrato compounds with acetonitrile–water was followed. From these results, it was found that the *trans*-iodohydrin was formed by hydrolysis of the *trans*-nitrato compound. It was also found that in the case of styrene, the hydrolysis of the iodonitrato compound **19** is much faster than that of the other cyclic iodonitrato compounds. It was found that *trans*-2-iodo-cyclooctyl nitrate (**18**) is stable and the iodohydrin compound is unstable (run 11, Table 1; runs 12 and 12, Table 2).

We also developed the synthesis of *trans*-iodohydrins without *trans*-iodonitrato compounds being also produced. In the reaction of **2** with iodine–cerium(IV) sulfate tetrahydrate (CS) in acetonitrile–water (10:1), *trans*-1-iodo-2-hydroxycyclohexane (**9**) was obtained preferentially. The results are summarized in Table 2.

The ¹H NMR spectra of the iodination compounds showed a multiplet (*W*/2 19–22 Hz) at δ 4.04–4.47 for **8**–**11** and a multiplet (*W*/2 19–22 Hz) at δ 3.66–4.08 for **8**–**11**.

These results suggest that these iodohydrin compounds



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Table 2 Reaction of cycloalkenes with I₂-CS^a at 50 °C

Run	Substrate	MeCN:H ₂ O	CS:I ₂	t/h	Products (%) ^b
1	1	5:1	2	5	8 (79) ^c
2	1	1:1	2	6	8 (67)
3	1	5:1	3	3	8 (94) ^c
4	1	5:1	3	3	8 (93)
5	2	10:1	1	6	9 (53)
6	2	10:1	2	6	9 (77)
7	2	10:1	3	3	9 (99) ^c
8	2	10:1	3	3	9 (90)
9	2	Bu ^t OH-H ₂ O(10:1)	3	3	9 (81)
10	2	DMSO-H ₂ O(10:1)	3	1	9 (72)
11	3	10:1	2	7	10 (76)
12	3	10:1	3	3	10 (97)
13	4	10:1	2	9	11 (9)
14	4	DMSO-H ₂ O(10:1)	3	5	11 (14)
15	5	10:1	2	6	12 (35)
16	5	1:1	2	6	12 (36)
17	6	10:1	2	6	13 (24)
18	7	10:1	2	3	14 (86)

^aCS: Ce(SO₄)₂·4H₂O. ^bIsolated yields. ^cIsolated yields based on iodine.

have a *trans*-diequatorial conformation. The isolated compounds were shown to be one spot on TLC and of high purity by ¹H and ¹³C NMR spectroscopy.

As can be seen from Table 2, this synthesis of *trans*-iodohydrins is more efficient than the synthesis described above; the reaction provides a new simple preparation of *trans*-iodohydrins. The *trans*-iodohydrins of trisubstituted alkenes, *e.g.* **12** and **13**, are unstable and sensitive to light. These compounds cannot be allowed to stand for a long time above 30 °C since they decompose.

Experimental

IR spectra were measured using a Hitachi model 215 grating infrared spectrometer. NMR spectra were measured on a JOEL GSX 400 spectrometer in deuteriochloroform with TMS as internal standard. High-resolution MS spectra were measured on a JOEL JMS-SX 102 mass spectrometer equipped with a JMA-DA 7000 data system.

Typical Procedures.—Reaction of Cyclohexene (2) with Iodine-CAN in Acetonitrile-Water.—A mixture of cyclohexene (**2**) (1.00 g), iodine (190 mg, 0.75 mmol) and cerium(IV) ammonium nitrate (822 mg, 1.50 mmol) in acetonitrile-water (20 ml, 10:1) was stirred at 50 °C for 8 h. The reaction mixture was poured into water and extracted with diethyl ether. The ethereal solution was washed with aqueous sodium hydrogen carbonate and water, dried and then evaporated. The resulting oil was chromatographed on silica gel, eluting with hexane-diethyl ether (120 ml, 10:1) to give *trans*-2-iodocyclohexanol (**9**) (164 mg, 47%) and *trans*-2-iodocyclohexanol nitrate (**15**) (142 mg, 35%).

Reaction of Cyclohexene (2) with Iodine-CS in Acetonitrile-Water.—A mixture of cyclohexene (**2**) (1.00 g), iodine (190 mg, 0.75 mmol) and cerium(IV) sulfate tetrahydrate (930 mg, 2.3 mmol) in acetonitrile-water (20 ml, 10:1) was stirred at 50 °C for 3 h. The precipitated cerium salt was removed by filtration. The filtrate was poured into water and extracted with diethyl ether. The ethereal solution was washed with aqueous sodium hydrogen carbonate and water, dried with sodium sulfate and evaporated. The resulting oil gave pure product **9** (336 mg, 99%) after usual work-up.

Reaction of Cyclohexene (2) with Iodine-CS in Acetonitrile-Water.—A mixture of cyclohexene (**2**) (124 mg), iodine (190 mg, 0.75 mmol) and cerium(IV) sulfate tetrahydrate (930 mg, 2.3 mmol) in acetonitrile-water (20 ml, 10:1) was stirred at 50 °C for 3 h. After the usual work-up, the resulting oil gave pure product **9** (307 mg, 90%).

trans-2-Iodocyclopentanol (**8**). $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 3372; δ_{H} (CDCl₃) 1.65 (m, 1 H), 1.82 (m, 2 H), 2.05 (m, 1 H), 2.13 (m, 1 H), 2.36 (m, 1 H), 2.78 (brs, 1 H), 4.05 (m, 1 H) and 4.45 (m, 1 H); δ_{C} (CDCl₃) 22.0, 30.9, 34.2, 35.6 and 82.0 (Found: M⁺, 211.9706. C₅H₉IO requires M_r, 211.9699).

trans-2-Iodocyclohexanol (**9**). $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 3400; δ_{H} (CDCl₃) 1.21–1.57 (m, 4 H), 1.82–1.88 (m, 1 H), 1.99–2.16 (m, 2 H),

2.44–2.52 (m, 1 H), 2.57 (brs, 1 H), 3.66 (m, 1 H) and 4.04 (m, 1 H); δ_{C} (CDCl₃) 24.2, 27.9, 33.7, 38.6, 43.3 and 75.9 (Found: M⁺, 225.9819. C₆H₁₁IO requires M_r, 225.9855).

trans-2-Iodocycloheptanol (**10**). $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 3424; δ_{H} (CDCl₃) 1.41–1.79 (m, 7 H), 1.95–2.03 (m, 1 H), 2.11–2.21 (m, 1 H), 2.35–2.43 (m, 1 H), 2.43–2.51 (brs, 1 H), 3.93 (m, 1 H) and 4.24 (m, 1 H); δ_{C} (CDCl₃) 21.5, 26.5, 26.7, 32.5, 36.7, 47.0 and 79.9 (Found: M⁺, 240.0000. C₇H₁₃IO requires M_r, 240.0012).

trans-2-Iodocyclooctanol (**11**). $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 3456; δ_{H} (CDCl₃) 1.21–1.81 (m, 7 H), 1.96–2.29 (m, 6 H), 4.08 (m, 1 H) and 4.47 (m, 1 H); δ_{C} (CDCl₃) 25.4, 26.5, 25.8, 26.8, 32.4, 50.3 and 78.2 (Found: M⁺, 254.0151. C₈H₁₅IO requires M_r, 254.0169).

t-2-Iodo-*t*-1-methylcyclohexan-*r*-1-ol (**12**). $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 3420; δ_{H} (CDCl₃) 1.38 (s, 3 H), 1.53–1.61 (m, 1 H), 1.69 (brs, 1 H), 1.73–1.81 (m, 1 H), 2.00–2.11 (m, 3 H), 2.33–2.40 (m, 1 H) and 4.34 (dd, *J* 4.4, 12.1 Hz, 1 H); δ_{C} (CDCl₃) 23.2, 25.8, 28.0, 37.4, 50.0 and 72.3 (Found: M⁺, 239.9979. C₇H₁₃IO requires M_r, 240.0012).

t-2-Iodo-*t*-1,4-dimethylcyclohexan-*r*-1-ol (**13**). $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 3448; δ_{H} (CDCl₃) 0.98 (d, *J* 6.2 Hz, 3 H), 1.45 (s, 3 H), 1.56–1.68 (m, 3 H), 1.82 (brs, 1 H), 1.91–2.06 (m, 4 H) and 4.43 (m, 1 H); δ_{C} (CDCl₃) 20.1, 28.5, 29.5, 29.7, 33.0, 41.7, 43.6 and 71.8 (Found: M⁺, 254.0151. C₈H₁₅IO requires M_r, 254.0169).

2-Iodo-1-phenylethanol (**14**). $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 3828; δ_{H} (CDCl₃) 2.53 (brs, 1 H), 3.41 (dd, *J* 8.8, 10.0 Hz, 1 H), 3.48 (dd, *J* 3.6, 10.3 Hz, 1 H), 4.83 (dd, *J* 3.6, 8.8 Hz, 1 H), 7.30–7.38 (m, 5 H); δ_{C} (CDCl₃) 15.3, 74.0, 125.7, 128.4, 128.7 and 141.1 (Found: M⁺, 247.9736. C₈H₉IO requires M_r, 247.9699).

trans-2-Iodocyclopentyl nitrate (**15**). $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 1638 and 1278; δ_{H} (CDCl₃) 1.78–2.03 (m, 3 H), 2.07–2.29 (m, 2 H), 2.38–2.48 (m, 1 H), 4.35 (brt, 1 H) and 5.51–5.57 (m, 1 H); δ_{C} (CDCl₃) 22.6, 25.6, 28.0, 36.3 and 92.5 (Found: M⁺, 245.9552. C₅H₈INO₂ requires M_r, 256.9549).

trans-2-Iodocyclohexyl nitrate (**16**). $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 1646 and 1282; δ_{H} (CDCl₃) 1.35–2.43 (m, 8 H), 4.13 (m, 1 H) and 5.09 (m, 1 H); δ_{C} (CDCl₃) 23.0, 25.8, 26.4, 29.4, 36.9 and 84.9 (Found: M⁺, 270.9686. C₆H₁₀INO₂ requires M_r, 270.9706).

trans-2-Iodocycloheptyl nitrate (**17**). $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 1634 and 1280; δ_{H} (CDCl₃) 1.31–1.42 (m, 2 H), 1.54–1.65 (m, 2 H), 1.76–1.99 (m, 6 H), 2.04–2.18 (m, 2 H), 4.29 (m, 1 H) and 5.38 (m, 1 H); δ_{C} (CDCl₃) 25.0, 25.1, 26.6, 26.7, 31.6, 32.0, 36.36 and 90.3 (Found: M⁺, 284.9826. C₇H₁₂INO₂ requires M_r, 284.9863).

trans-2-Iodocyclooctyl nitrate (**18**). $\nu_{\max}/\text{cm}^{-1}$ (NaCl) 1638 and 1282; δ_{H} (CDCl₃) 1.31–1.42 (m, 2 H), 1.54–1.65 (m, 2 H), 1.76–1.99 (m, 6 H), 2.04–2.18 (m, 2 H), 4.29 (m, 1 H) and 5.38 (m, 1 H); δ_{C} (CDCl₃) 25.0, 25.1, 26.6, 26.7, 31.6, 32.0, 36.36 and 90.3 (Found: M⁺, 299.0031. C₈H₁₄INO₂ requires M_r, 299.0019).

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