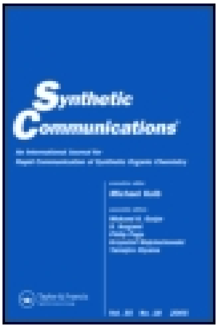

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Iodohydrins: An Easy Route to Epoxides from Alkenes

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IODOHYDRINS: AN EASY ROUTE TO EPOXIDES FROM ALKENES

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ABSTRACT: The preparation of epoxides is efficiently achieved by reaction of alkenes with I_2 in aqueous dioxane in the presence of $Cu(OAc)_2.H_2O$ followed by treatment with KOH in a biphasic system (H_2O/ether/pentane).

Epoxides are versatile reagents in organic synthesis and there are several methodologies for the preparation of these valuable compounds,[1] among them, the oxidation of alkenes with peracids and the cyclization of halohydrins (β-haloalcohols) with bases are the most employed. Peracids and their analogs[2] have been regularly used to prepare epoxides, even though these reagents must be manipulated with care, due to their tendency to explosion[3]. Chloro- and bromohydrins have also found wide use in

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*to whom correspondence should be addressed; *e-mail*: mmattos@iq.ufrj.br epoxide synthesis[1c,1d], and the halogenation of alkenes in dilute aqueous solutions is an effective way to prepare these intermediates[4]. It should be noted that epoxides are rarely obtained from iodohydrins because of their difficult preparation from alkenes due to the reversibility of the addition of iodine[1c,4] to the double bonds. Frequently an iodide ion scavenger is needed to obtain satisfactory yields[1c]. In fact, iodohydrins are frequently prepared from epoxides[5], α-iodo-ketones[6], or others halohydrins[7]. Others methods include reaction of alkenes with oxidizing agents[4, 8], with H_5IO_6 / $NaHSO_3$[9] and with N-iodo-succinimide in aqueous media[10], this latter reagent being comparatively more expensive than iodine and as well as moisture sensitive.

In previous work[11], we reported an easy and efficient synthesis of iodohydrins from alkenes by reaction with iodine in aqueous dioxane promoted by diverse metal salts, the most effective being the ready available and inexpensive $Fe_2(SO_4)_3$ and $Cu(OAc)_2.H_2O$. This method is cheaper than similar procedures that use silver(I) oxide / iodine for *in situ* formation of some epoxides[12].

Iodohydrins yield epoxides on treatment with $Ca(OH)_2$[4], KOH in dry ether[1c, 4, 8b], Ag_2O[12d] , and DBU[10a]. About ten years ago, Brown and Pai[6] reported the conversion of styrene bromohydrin to its oxide in excellent yield with KOH / H_2O in a biphasic system of ether-pentane. They have also converted styrene iodohydrin to the oxide, but no yield was reported.

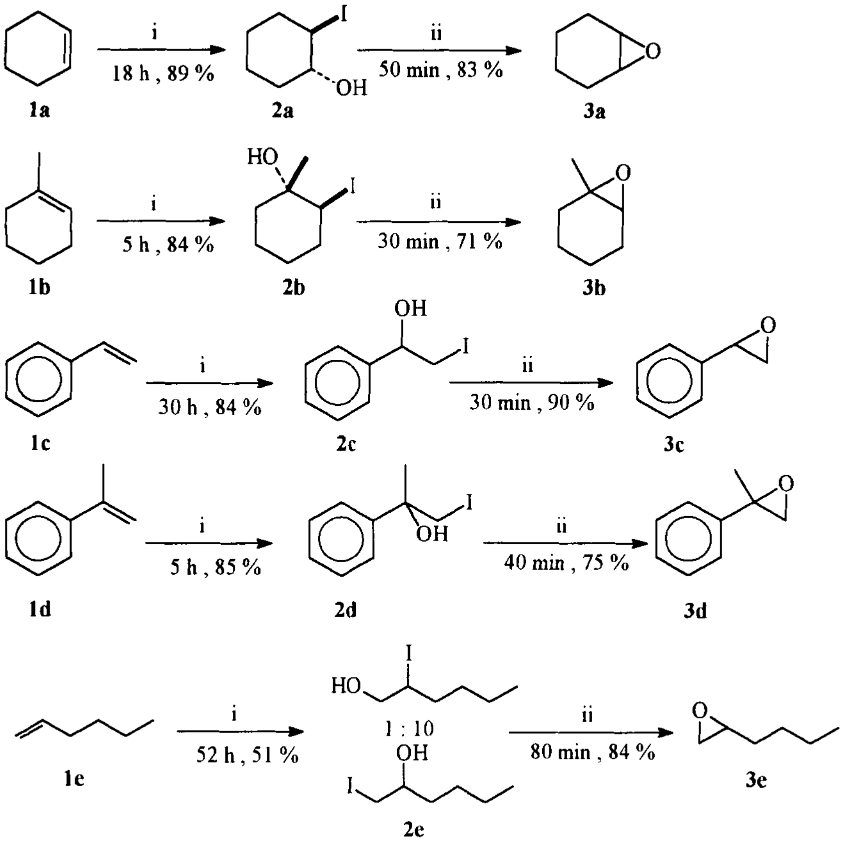
Since there is no generally used protocol for epoxide preparation using this approach we decided to communicate our results.

RESULTS

The iodohydrins (**2a-e**) shown in Scheme are easily prepared on a multigram scale in mild conditions by reaction of alkenes (**1a-e**) with iodine in dioxane/water in the presence of copper(II) acetate and the yields are satisfactory to good. The purity of products **2a-d** was greater than 95 % by High-Resolution-Gas-Chromatography (HRGC) and spectrometric methods. The same reaction conditions applied to 1-hexene gave predominantly 1-iodo-2-hexanol (**2e**) along with its regioisomer (10:1, determined by HRGC). In addition, we found that $NaBH_4$ was a suitable reagent for the reduction of unreacted iodine to iodide during the reaction work-up, proving to be an excellent option to other commonly employed reagents such as $Na_2S_2O_3$ and Na_2SO_3 which are nucleophilic. No formation of alcohols from the iodohydrins (**2**) was detected by HRGC and this multigram scale preparation is an alternate to two others that have already been described in the 70's, which use oxidizing agents[4, 8b].

The conversions of the iodohydrins (**2a-e**) to the epoxides (**3a-e**) by reaction in a biphasic media (KOH / H_2O / Et_2O / pentane) were very clean and good yields were obtained for all compounds as shown in the Scheme.

Scheme



Reagents and conditions: i: $Cu(OAc)_2.H_2O$ / I_2 / 1,4-dioxane / rt
ii: KOH / H_2O / Et_2O / pentane / rt

The epoxides proved to have greater than 95 % purity (by HRGC[13] and spectrometric methods) and their identities were confirmed by analytical data as well as by co-injection with authentic samples in HRGC with two chromatographic columns of different polarities (CARBOWAX and RTX-

5). Only traces of aldehydes were found in the ^1H NMR and we could recover only small amounts of diols from the aqueous layers (less than 3 %). Similar yields were obtained by reaction of the iodohydrins with KOH in ether, but this is less practical due to the low solubility of KOH and longer reaction times (3-6 h) with the necessity of addition of more KOH after some time to complete the reaction. The reaction of iodohydrins with other bases such as K_2CO_3, pyridine and triethylamine proved very slow.

In summary, the preparation of epoxides by reaction of alkenes with iodine in aqueous dioxane promoted by $Cu(OAc)_2.H_2O$, followed by cyclization with KOH in a biphasic system is efficiently achieved. This simple methodology is an alternate route for the epoxidation of acid-sensitive alkenes or the epoxidation of alkenes yielding acid-sensitive epoxides. All reagents are cheap and ready available and total good yields are obtained.

EXPERIMENTAL

General. The alkenes (**1a-e**) were purified by standard methods[14]. Solvents and inorganic reagents were used without further purification. Room temperature refers to 23-33 °C. Analyses by HRGC were performed on a HP-5890-II gas chromatograph with FID by using a 30 m (length), 0.25 mm (ID) and 25 μm (phase thickness) RTX-5 silica capillary column and H_2

(flow rate 50 cm s^{-1}) as carrier gas (split 1:20). Oven temp.: 70 °C then 8 °C / min to 280 °C (5 min), injector temp.: 260 °C, detector temp.: 280 °C. The HRGC analysis were also performed on a Varian 3400 CX gas chromatograph using a CARBOWAX 20 M capillary column, 30 m (length), 0.25 mm (ID), 0.25 μm (phase thickness). Oven temp.: 70 °C then 8 °C / min to 230 °C (8 min), injector temp.: 260 °C, detector temp.: 280 °C, being the other conditions the same as previous. Mass spectra were obtained on Hewlett-Packard HP5896-A HRGC-MS using electron impact (70 eV). ^{1}H NMR and ^{13}C NMR were acquired on a Bruker DRX-300 (300 MHz and 75 MHz, respectively) or on a Bruker AC-200 (200 MHz and 50 MHz, respectively) spectrometers for $CDCl_3$ solutions with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin Elmer 1600 FT-IR or on a Nicolet 740 FT-IR spectrometers (NaCl film). High-Resolution-Mass-Spectrometry (HRMS) were performed on a VG Autospec at 70 eV. In all the reactions, the purity of the isolated product was confirmed by ^{1}H NMR, ^{13}C NMR, IR and HRGC.

Typical Procedure for Iodohydrin* (2a-e) *formation: to a stirred solution of the appropriate alkene (50 mmol) and $Cu(OAc)_2.H_2O$ (25 mmol) in dioxane / water (110 / 15 mL for **1a**, 40 / 10 mL for **1b** and **1c**, 40 / 10 mL for **1d** and 40 / 5 mL for **1e**) was added iodine (37.5 mmol) in small portions at room temperature. After the specified time (see Scheme), Cu_2I_2 was filtered off and CH_2Cl_2 (equal volume of dioxane / water) was added (if necessary this solution was filtered again). The resulting solution was treated with a suspension of $NaBH_4$ (1 g) in ethanol (100 mL) - caution: gas liberation! - until complete discharge of the iodine color. After that, the solution was washed with water (four times), the organic extract was dried over anhydrous Na_2SO_4 and filtered trough a small column of SiO_2. The solvent was evaporated on a rotatory evaporator, then concentrated under reduced pressure[15] (2 Torr) and 50 °C (bath) to give the pure iodohydrin (**2a-e**) as colorless or light orange oil[16]. The analytical data for the iodohydrins **2a-e** are in accordance with those previously reported.[11]

trans*-2-Iodocyclohexanol (2a):** ***^{1}H NMR: δ 4.03-3.99 (m, 1H, $J_{\mathrm{CHI-CHOH}}$ 9.7 Hz); 3.64 (m, 1H); 2.65 (broad s, 1H); 2.07-1.99 (m, 2H); 1.81-1,79 (m, 2H); 1.55-1.25 (m, 4H) ppm. ***^{13}C NMR:*** δ 75.6; 42.9; 38.3; 33.5; 27.7; 24.2 ppm. ***IR:*** ν 3380; 2920; 2840; 1440; 1350; 1150; 1060; 940 cm^{-1}. ***MS:*** m/z (%) 81 (100); 99; 127; 141; 155; 170; 180; 226 (M^+, 5). ***HRMS:*** $C_6H_{11}IO$ requires M_r 225.985467, found M^+ 225.984899. ***HRGC:*** t_R 5.7 min (RTX-5).

trans*-2-Iodo-1-methylcyclohexanol (2b):** ***^{1}H NMR: δ 4.29-4.24 (dd, 1H); 2.32-2.27 (m, 2H); 2.03-1.97 (m, 2H); 1.71-1.53 (m, 1H); 1.42-1.37 (m, 4H); 1.34 (s, 3H) ppm. ***^{13}C NMR:*** δ 71.8; 49.3; 37.3; 37.1; 27.6; 25.5; 22.9

ppm. ***MS:*** m/z (%) 95 (100); 113; 127; 141; 154; 197; 225 (M^+-Me, 20). ***HRGC:*** t_R 6.4 min (RTX-5).

2-Iodo-1-phenylethanol (2c): ***^{1}H NMR:*** δ 7.36 (m, 5H); 4.84-4.81 (m, 1H); 3.51-3.36 (m, 2H); 2.80 (d, 1H) ppm. ***^{13}C NMR:*** δ 141.1; 128.5; 128.2; 125.6; 73.8; 15.3 ppm. ***IR:*** ν 3410 (broad); 3029; 2956; 2892; 1175; 1055; 845; 764; 700 cm^{-1}. ***HRMS:*** C_8H_9IO requires M_r 247.969817, found M^+ 247.968167. ***HRGC:*** t_R 10.4 min (RTX-5).

1-Iodo-2-phenyl-2-propanol (2d): ***^{1}H NMR:*** δ 7.36 (m, 5H); 3.65 (d, 2H); 2.45 (broad s, 1H); 1.74 (s, 3H) ppm. ***^{13}C NMR:*** δ 141.1; 128.3; 127.3; 124.5; 66.9; 28.8; 24.0 ppm. ***IR:*** ν 3530 (broad); 3057; 3024; 2957; 2929; 2891; 1275; 1168; 1030; 849; 780; 700 cm^{-1}. ***MS:*** m/z (%) 121 (100); 135; 169; 204; 244; 262 (M^+, 5). ***HRMS:*** $C_9H_{11}IO$ requires M_r 261.985467, found M^+ 261.985432. ***HRGC:*** t_R 10.9 min (RTX-5).

1-Iodo-2-hexanol (2e):[17] ***^{1}H NMR:*** δ 3.77-3.18 (m, 3H); 2.09-1.20 (m, 7H); 0.91 (t, 3H) ppm. ***^{13}C NMR:*** δ 71.0; 36.3; 27.8; 22.5; 16.8; 14.0 ppm. ***MS:*** m/z (%) 55 (100); 69; 83; 101; 127; 142; 171; 228 (M^+, 12). ***HRMS:*** $C_6H_{13}IO$ requires M_r 228.001117, found M^+ 228.003282. ***HRGC:*** t_R 5.3 min (RTX-5).

Typical procedure for epoxide* (3a-e) *formation: in a 50 mL flask was placed the appropriated iodohydrin (**2a-e**, 10 mmol) and an ether-pentane solution (20 mL, 1:1 v/v). At room temperature and with stirring was added a solution of KOH (0.63 g) in water (6 mL). After the time shown in the Scheme, the layers were separated and the organic phase was washed with water (3 x 7 mL). The organic extract was dried over anhydrous Na_2SO_4, filtered and the solvent was removed in a rotatory evaporator to give the epoxide (**3a-e**) as colorless or pale yellow liquid which was confirmed by co-injection with authentic samples in HRGC. Analytical data of the known compounds **3a-e** are in agreement with literature values.[18]

Cyclohexene oxide (3a): bp: 129 °C (lit.[19] 131.5 °C). ***^1H NMR:*** δ 3.05 (s, 2H); 1.87-1.74 (m, 4H); 1.37-1.16 (m, 4H) ppm. ***^{13}C NMR:*** δ 51.1; 23.4; 18.4 ppm. ***IR:*** ν 2900; 2820; 1440; 945; 810; 760 cm^{-1}. ***MS***: m/z (%) 41; 55; 83 (100); 97; 98 (M^+, 4). ***HRGC:*** t_R 1.8 min (RTX-5); 2.0 min (CARBOWAX).

1-Methylcyclohexene oxide (3b): bp: 143 °C (lit.[20] 60-61 °C / 40 Torr, corrected[19] for 760 Torr: *ca.* 144 °C). ***^1H NMR:*** δ 2.87 (broad s, 1H); 1.82-1.78 (m, 2H); 1.59 (m, 2H); 1.36-1.31 (m, 2H); 1.22-0.94 (m, 5H); ppm. ***^{13}C NMR:*** δ 59.6; 57.8; 29.9; 25.0; 22.7; 20.1; 19.7 ppm. ***MS:*** m/z (%) 43; 55; 97 (100); 111; 112 (M^+, 4). ***HRGC:*** t_R 2.0 min (RTX-5); 2.3 min (CARBOWAX).

Styrene oxide (3c): bp: 192 °C (lit.[19] 194 °C). ***^1H NMR:*** δ 7.36-7.28 (m, 5H); 3.69 (dd, 1H); 3.10 (dd, 1H); 2.79 (dd, 1H) ppm. ***^{13}C NMR:*** δ 137.7;

128.7; 128.2; 125.1; 52.3; 51.1 ppm. ***IR:*** ν: 3040; 2972; 2904; 1605; 1498; 981; 873; 758; 697 cm^{-1}. ***MS:*** m/z (%) 54; 89; 90; 91 (100); 119; 120 (M$^+$, 30). ***HRGC:*** t$_R$ 2.9 min (RTX-5); 7.9 min (CARBOWAX).

α-Methylstyrene oxide (3d): bp: 205 °C (lit.[21] 84-85 °C / 14 Torr, corrected[19] for 760 Torr: *ca.* 203 °C). ***^1H NMR:*** δ 7.30 (m, 5H); 2.99 (d, 1H); 2.82 (d, 1H); 1.69 (s, 3H); ppm. ***^{13}C NMR:*** δ 141.3; 128.5; 127.6; 124.9; 57.1; 56.9; 21.9 ppm. ***IR:*** ν 3057; 3021; 2985; 1605; 1497; 1443; 1250; 1050; 856; 754; 694 cm^{-1}. ***MS:*** m/z (%) 78; 103; 105; 106; 133 (100); 134 (M$^+$, 20). ***HRGC:*** t$_R$ 3.4 min (RTX-5); 8.2 min (CARBOWAX).

1-Hexene oxide (3e): bp: 116 °C (lit.[22] 117-119 °C). ***^1H NMR:*** δ 2.83 (m, 1H); 2.65 (dd, 1H); 2.38 (dd, 2H); 1.47-1.32 (m, 6H); 0.87-0.82 (t, 3H); ppm. ***^{13}C NMR:*** δ 52.5; 47.2; 31.7; 26.8; 22.1; 14.1 ppm. ***IR:*** ν 3020; 2920; 2900; 2825; 1450; 1250; 1100; 890; 810 cm^{-1}. ***HRGC:*** t$_R$ 1.7 min (CARBOWAX).

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15.We noted that the yield is somewhat reduced if the iodohydrin was left for a long time under reduced pressure. *trans*-2-Iodocyclohexanol (**2a**) was reported to sublime under vacuum: Heilbron, M.I. and Bunbury, H.M. ed. "Dictionary of Organic Compounds", vol II, Oxford University

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16. Our experience showed that all iodohydrins are sufficiently stable to be handled at room temperature for hours, except for **2b** which decomposed to iodine and a mixture of unidentified products after being left at room temperature overnight. All iodohydrins could be stored without decomposition in a freezer for at least one month. In this large scale preparation crystallization may occur for some iodohydrins after some time in the freezer, or just after their preparation.

17. **2e** was obtained with 2-iodo-1-hexanol [*ca.* 10% by HRGC, ***MS:*** m/z (%) 55 (100); 83; 101; 126; 171; 228 (M^+, 1), ***HRGC:*** t_R 5.4 min (RTX-5)].

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