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Selenium-catalyzed iodohydrin formation from alkenes

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Abstract—A new simple method for catalyzed iodohydroxylation of alkenes using stoichiometric amounts of water is described. The iodohydrins were prepared in good yields from the corresponding alkenes using *N*-iodosuccinimide, 2 equiv of H_2O, and catalytic amounts of diphenyl diselenide in MeCN.

Halohydrin formation is a versatile reaction in organic synthesis, allowing the stereoselective functionalization of carbon–carbon double bonds.[1] In particular, bromo- and iodohydrins have been repeatedly used in total synthesis. However, although the direct preparation of bromohydrins from the reaction of dilute aqueous solutions of halogens with alkenes is a well-established methodology,[2] the preparation of iodohydrins using the same procedure is hampered by the ready reversibility of the addition of hypoiodous acid. In this case an iodide ion scavenger is generally used to obtain satisfactory yields.[3]

Other methodologies of the formation of iodohydrins from alkenes include the use of $H_5IO_6/NaHSO_3$,[4] *N*-iodoimides,[5] *N*-iodosaccharin,[6] bis(pyridine)iodine(I) salts,[7] dimethyldioxirane/MeI,[8] triodide ion,[9] and the reaction with iodine mediated by clays in aqueous media.[10] Alternatively, iodohydrins are derived from the epoxides using different reagents, such as hydroiodic acid,[11] iodine, and crown ethers as catalyst,[12] the $Ti(O\text{-}i\text{-}Pr)_4/I_2$ complex,[13] metal iodides,[14] or a ionic liquid.[15] Iodohydrins could also be prepared from other halohydrins by halogen exchange,[16] or from carbonyl compounds by iodomethylation with CH_2I_2 in the presence of SmI_2.[17]

The iodohydrin formation from alkenes is usually carried out in polar media, which help to stabilize the formation of charged intermediates and thus increase the rate, allowing the reaction to proceed in reasonably short times. Considering its high polarity, water is almost always used in a large excess for halohydrin formation, acting both as a reagent and as a solvent. Exceptions to this procedure are given by Dalton method, which uses DMSO as the sole solvent,[18] and some special cases of halohydrin formation involving an anchimeric assistance from an oxygenated functional group already present in the molecule, such as a sulfoxide, followed by a subsequent attack by water.[19]

In connection with our ongoing effort to prepare marine natural products from cyclohexadienediols of microbial origin, several oxygen-labeled halohydrins were needed.[20] We thus began by investigating procedures to prepare them using water in stoichiometric amounts. Dalton's method is not adequate in this instance, since the oxygen atom in the resulting iodohydrin is supplied by the DMSO used as solvent. Other reported methods utilize water in very large excesses,[21] and even a procedure to produce labeled epoxides via iodohydrins uses 10 equiv of water-^{18}O.[3d]

Preliminary studies using standard methods[5] showed that the reaction rate is highly dependent on the amount of water present (vide infra). The use of a few equivalents of water resulted in excessively long reaction times, which makes the reaction unsuitable for preparative purposes. For instance, more than 160 h were needed for the complete conversion of 2 mmol of diene **2** using 20 equiv of water, and no reaction was observed after 72 h using 2 equiv of water. In this context a catalyst seems to be necessary in order to accelerate the reaction. There are reports of catalyzed halohydrin formation from alkenes. When using *N*-haloimides as the electrophilic species, the reaction can be accelerated by adding

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Keywords: Alkenes; Selenium; Iodohydroxylation; Stereoselectivity; Halohydrins.

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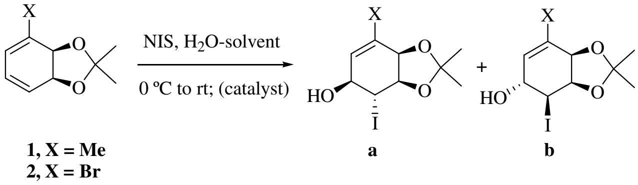
Bronsted or Lewis acids in stoichiometric or catalytic amounts, since acids enhance the heterolytic cleavage of *N*-haloimides.[22] Unfortunately, this method lacks generality since it cannot be used on acid labile substrates, such as diols **1** and **2**.[23]

Recently, Tunge and Mellegaard[24] reported on the selenium-catalyzed bromolactonization of unsaturated acids. The neutral conditions used and the resemblance between both mechanisms attracted our attention and thus we decided to study the ability of selenium reagents to catalyze halohydrin formation. Herein, we report on the catalyzed formation of iodohydrins from alkenes using stoichiometric amounts of water, under neutral conditions.

(1*S*,2*R*)-1,2-*O*-Isopropylidene-3-methylcyclohexa-3,5-diene-1,2-diol, **1**,[25] was used as a model alkene (Scheme 1). This chiral diene, readily available in our laboratory by the biotransformation of toluene,[26] presents interesting features for this study. The protected *cis*-diol functionality and the presence of di- and trisubstituted conjugated double bonds allow for taking into account both the stereo- and regioselectivity of the reaction, respectively.

In our preliminary efforts the iodohydroxylations were carried out following a slight modification of a reported procedure,[5] using 1.1 equiv of *N*-iodosuccinimide (NIS) in mixtures of DME and decreasing amounts of water, from 0 °C to ambient temperature. In addition, acetonitrile was also used in order to address the effect of changing the polarity of the solvent mixture (Table 1). The selectivity of the reaction was determined by the integration of the corresponding NMR signals of the products, the spectra being taken upon disappearance of the starting material. In all cases, the reaction showed a complete regioselectivity toward the less hindered disubstituted double bond and obeyed the generalized Markownikoff's rule, regardless of the solvent system used (Scheme 1).



Scheme 1. Iodohydroxylations of model alkenes.

The stereoselectivity was good, giving a higher than 5:1 ratio for the electrophilic attack anti to the bulky protecting group, **1a**. The modest enhancement of stereoselectivity observed with decreasing amounts of water could be ascribed to the diminished polarity of the solvent system (vide infra).

Next, the catalytic reaction was investigated using diphenyl diselenide as the catalyst. Specifically, diene **1** was treated with 5 mol % of PhSeSePh, 1.1 equiv of NIS and variable amounts of water in different solvent systems, from 0 °C to ambient temperature (Table 2).

The addition of PhSeSePh significantly improved the reaction rate, since the time needed for the complete consumption of the starting 1 mmol of olefin diminished in all conditions tried. However, the effect of the catalyst on the selectivity was not significant. The selectivities afforded by the catalyzed and uncatalyzed reactions in otherwise similar conditions (see Tables 1 and 2) were nearly the same, considering the experimental error (integration of NMR signals).

The amount of water used has a profound effect on the kinetics and a much smaller effect on the selectivity of iodohydrin formation. Given its high dielectric constant (for water, $\varepsilon_T = 78.30$; for DME, $\varepsilon_T = 7.20$; for MeCN, $\varepsilon_T = 35.94$),[27] the amount of water in the mixture dramatically affects the polarity of the system, which influences the kinetics of this reaction. An inspection of Tables 1 and 2 shows that for large amounts of water the reaction rate is almost independent of the co-solvent used (Table 1, entries 1 and 4, and Table 2, entries 1 and 3). However, if water is used in small amounts the polarity of the system is mainly determined for the organic solvent and, therefore, significant differences in reaction

Table 1. Iodohydroxylation of diene **1** in different solvent systems[a]

Entry	Solvent/H_2O	equiv H_2O/ equiv Olefin	Time[b] (h)	Selectivity[c]	Yield[d] (%)
1	1:1 DME/H_2O	140	1	84:16	94
2	25:1 DME/H_2O	10	9	92:8	60
3	140:1 DME/H_2O	2	40	97:3	75
4	1:1 MeCN/H_2O	140	0.7	86:14	60
5	140:1 MeCN/H_2O	2	15	95:5	72

[a] Reaction conditions: 1 mmol of olefin and 1.1 equiv of NIS in 5 mL of H_2O-solvent as specified, from 0 °C to rt.

[b] Time for the disappearance of 1 mmol of olefin. Conversion data points were determined by TLC, every 10 min during the first 2 h of reaction; and every 30 min over that time.

[c] **1a**:**1b**.

[d] Combined yields.

Table 2. Catalyzed iodohydroxylation of diene **1** in different solvent systems[a]

Entry	Solvent/H_2O	equiv H_2O/ equiv Olefin	Time[b] (h)	Selectivity[c]	Yield[d] (%)
1	1:1 DME/H_2O	140	0.5	82:18	72
2	140:1 DME/H_2O	2	7	96:4	50
3	1:1 MeCN/H_2O	140	0.5	80:20	60
4	140:1 MeCN/H_2O	2	4	95:5	81

[a] Reaction conditions: 1 mmol of olefin, 5 mol % of PhSeSePh and 1.1 equiv of NIS in 5 mL of H_2O-solvent as specified, from 0 °C to rt.

[b] Time for the disappearance of 1 mmol of olefin. Conversion data points were determined by TLC, every 10 min during the first 2 h of reaction; and every 30 min over that time.

[c] **1a**:**1b**.

[d] Combined yields.

rates are observed in both solvent systems, favoring the reactions run in the more polar acetonitrile (Table 1 entries 3 and 5 and Table 2 entries 2 and 4). In addition, the difference is more pronounced for the uncatalyzed reaction, in agreement with the suggested role of the selenium catalyst assisting the heterolytic cleavage of *N*-haloimides[24,28] and thus making it less dependent on the polarity of the system. Regarding the stereoselectivity the effect of water is smaller, although noticeable when used in small amounts. In this case, the lower polarity of the reaction medium increases the selectivity for an electrophilic attack anti to the protecting group (entries 1–3, and 4–5 of Table 1 and entries 1–2 and 3–4 of Table 2). This observation agrees with the presence of a less dissociated and thus more hindered electrophilic species in less polar media. The effective size of the electrophile is dependent on the polarity of the medium, which governs its dissociation, and thus a less polar system favors the electrophilic attack from the less hindered face. Since the best selectivity is obtained with either solvent system when using 2 equiv of water, we chose to carry out the reaction in acetonitrile because of the higher yield and reaction rate (Table 2, entry 4).

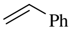
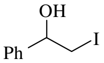
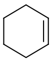
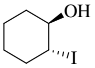
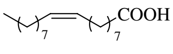
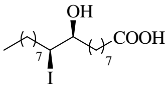
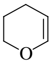
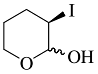
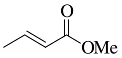
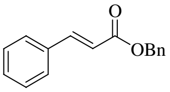
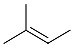
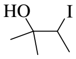
Once the optimal conditions for the catalyzed iodohydroxylation of diene **1** were defined,[†] an array of representative olefins was submitted to them. In most cases the corresponding iodohydrins were obtained in good yields (Table 3).

As expected, the iodohydroxylation of diene **2**[29] took place with total regioselectivity. The stereoselectivity was excellent, similar to the one obtained for model diene **1**, giving a 94:6 ratio of iodohydrins in a good yield (78%, entry 2). Some β-epoxide, resulting from iodide intramolecular displacement on the major isomer, was also isolated (6%). The reactions on styrene and cyclohexene proceeded cleanly in good isolated yields, even though small amounts of styrene oxide were isolated in the reaction of styrene. For oleic acid a single iodohydrin is obtained in a high yield. This remarkable regioselectivity during iodohydrin formation was reported previously by Song et al.[30]

Dihydropyran, which contains a very sensitive electron-rich double bond, decomposes at 0 °C under the reaction conditions. However, when the reaction was carried out at −20 °C an anomeric 1:1 mixture of iodohydrins was isolated in a very good yield.

For the conjugated acid derivatives (entries 7 and 8) no reaction was observed at an ambient temperature and bringing the reaction to reflux caused an extensive decomposition. The low reactivity of these systems toward iodohydrin formation is known.[3d,5]

Table 3. Selenium catalyzed iodohydroxylation of representative alkenes[a]

Entry	Substrate	Products	Time (h)	Yield[b] (%)
1	**1**	**1a:1b** 95:5	4	81
2	**2**	**2a:2b** 94:6	30	78[c]
3			1	77[d]
4			5	65
5			3	81
6			3	70[f]
7		—	—	0[e]
8		—	—	0[e]
9			10	40[g]

[a] Reactions were run with 1.1 equiv of NIS, 2 equiv of H_2O, 5 mol % of PhSePh, MeCN at 0 °C to rt.

[b] Isolated yields.

[c] Plus 6% of β-epoxide.

[d] Plus 4% of epoxide.

[e] No reaction, 100% of recovered starting material.

[f] Carried out at −20 °C. 1:1 mixture of epimers.

[g] Losses due to volatility.

Trisubstituted alkenes, such as 2-methyl-2-butene, took longer to react but still gave the desired iodohydrin. The reaction was clean, showing a complete conversion to the desired product when monitored by NMR. The modest yield reported in entry 9 was due to the difficulties during the isolation of the very volatile halohydrin. According to entries 1 and 9, it is possible to achieve a complete regioselectivity toward the reaction of a disubstituted alkene when both di- and trisubstituted double bonds are present in the same molecule.

In summary, this letter describes the use of diphenyl diselenide as an efficient catalyst for a simple iodohydroxylation of alkenes using stoichiometric amounts of water. This feature is of interest in synthetic schemes where the amount of water needs to be controlled, for example, in the preparation of oxygen-labeled compounds. The results in this area will be reported in due course. Moreover, the lower polarity associated with this solvent system allows for a moderate increase in the stereoselectivity of iodohydrin formation. The addition of PhSeSePh only affects the time and/or the conditions needed to react, with no effects on the selectivity.

[†] General synthetic procedure: PhSeSePh (5 mol %) was added at 0 °C to a stirred solution of the alkene in MeCN (5 mL/mmol of alkene). Next was added NIS (1.1 equiv) and distilled water (2 equiv), and the reaction was let to warm up to ambient temperature. After the specified time, it was diluted with saturated solution of $NaHSO_3$ and extracted with methylene chloride. The combined organic layers were washed with saturated NaCl, dried over $MgSO_4$ and then the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel using hexanes/ethyl acetate as eluant.

Nonetheless, given the diminished polarity of the reaction medium, the use of the catalyst is imperative to achieve the desired reaction in acceptable times.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.024.

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