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An improved synthesis of iodohydrins from alkenes

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Abstract

A series of iodohydrins was prepared in excellent yields in a one-step procedure by treating the corresponding alkenes at −20°C with NIS in a mixture of H_2O and DME.

Keywords: iodohydrins; *N*-iodosuccinimide.

The formation of halohydrins from alkenes is a well-established procedure.[1] However, in contrast to the direct preparation of bromohydrins and chlorohydrins from reaction of dilute aqueous solutions of halogens with alkenes, the formation of iodohydrins is usually difficult to achieve using the same procedure because of the ready reversibility of the addition of IOH. Indeed, in most cases, the formation of iodohydrins cannot be obtained in satisfactory yields without the presence of an iodide ion scavenger.[2] More recently, new methods for the formation of iodohydrins from alkenes were developed, based on the in situ generation of hypoiodous acid from H_5IO_6 in the presence of $NaHSO_3$.[3] Alternatively, iodohydrins are accessible from the epoxides using iodine in the presence of crown ethers as catalyst,[4] hydroiodic acid[5] or a metal iodide.[6] Iodohydrins could also be prepared by iodomethylation of carbonyl compounds with CH_2I_2 in the presence of SmI_2[7] or halogen exchange reaction of chlorohydrins or bromohydrins with sodium iodide.[8]

The use of *N*-iodosuccinimide (NIS) has been reported for several transformations including iodination[9] and oxidation.[10] As an electrophilic iodination reagent, it has been mainly used for the iodoetherification of alkenes[11] and for the acetoxyiodination of olefins[12] but, to our knowledge, its use in the synthesis of iodohydrins remains unexplored.[13] This paper describes the conversion at low temperature of a set of differently substituted alkenes into the corresponding iodohydrins using NIS in a mixture of DME and water (Table 1).

In a typical procedure, NIS (1.5 equiv.) was added at −20°C over 30 min to a solution (0.1 M) of the alkene in a 2:1 mixture of DME and water. The reactions were completed in less than 2 h. After addition

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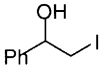
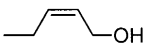
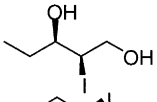
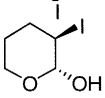
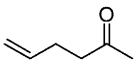
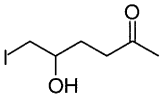
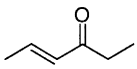
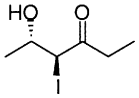
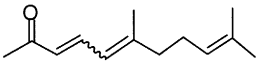
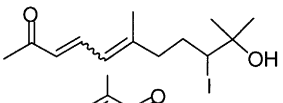
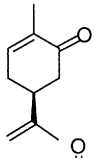
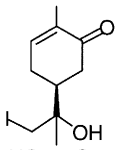
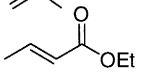
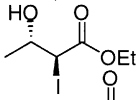
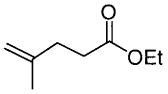
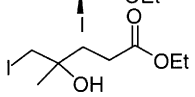
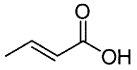
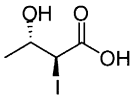
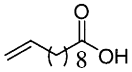
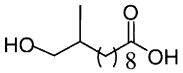
Table 1
Iodohydroxylation of differently substituted olefins

Entry	Substrates	Products	Yield[a](%)
1			95
2			98
3			80
4			96
5			95
6			100[b]
7			86
8			95
9			0[c]
10			85
11			0[c]
12			92

a: isolated yields, all products were characterised by ^{1}H, ^{13}C NMR, IR spectroscopy and mass spectrometry; b:this reaction was performed at rt; c: at -20°C, no reaction with 100% recovered starting material and, at rt, degradation

of a saturated solution of NaCl, the reaction mixture was extracted with ether. Evaporation of the solvent and purification by column chromatography furnished the desired iodohydrins in excellent yields.

This method appears to be quite general for the synthesis of iodohydrins. The iodohydroxylation of cyclohexene proceeded in high yield with *trans* stereoselectivity (entry 1). It is interesting to note that the primary allylic alcohol *cis*-2-hexen-1-ol reacted regio- and stereoselectively to give the corresponding *threo*-2-iodo-1,3-hexanediol in good yield (entries 3). A similar observation was made by Ishii et al. who used $H_5IO_6/NaHSO_3$ for the in situ generation of IOH.[3] The regioselectivity of this reaction is of

particular interest as the ring opening of allylic epoxy alcohols gives the 3-iodo 1,2-diols. Enol ethers are also excellent substrates for iodohydroxylation using NIS as exemplified by entry 4. Indeed, dihydropyran reacted readily at −20°C to give the desired product as a single regio- and *trans*-stereoisomer. The non-conjugated unsaturated ketone hex-5-en-2-one reacted in a Markownikov fashion in high yield (entry 5). The less reactive conjugated ketone, hex-4-en-3-one remained unchanged under standard conditions. However, at room temperature, the reaction proceeded slowly to give quantitatively after 12 h the *erythro* 3-hydroxy-2-iodo-hexanone (entry 6). The regioselectivity for this reaction can be rationalised by attack of H_2O on the iodonium intermediate at the β-carbon and not at the α-carbon which is deactivated by the presence of the electron-withdrawing carbonyl group. When pseudo-ionone or carvone were subjected to iodohydroxylation, in both cases, the reactions were chemoselective with only the more reactive non-conjugated double bond being converted into the corresponding iodohydrin (entries 7 and 8). The less reactive α,β-unsaturated esters and acids could not be transformed into the desired iodohydrins. Indeed, at −20°C, no reaction occurred and 100% of the starting material was recovered. However, in contrast to an α,β-unsaturated conjugated ketone (entry 6), when the reaction was carried out at room temperature, only unidentified products were formed (entries 9 and 11). The non-conjugated unsaturated esters and acids did react smoothly under standard conditions to give the expected iodohydrins in a Markownikov fashion and in high yields (entries 10 and 12).

In summary, this paper describes a very simple route to iodohydrins. Our methodology presents several advantages including mild reaction conditions, short reaction times, high chemo-, and regio-stereoselectivities as well as very high yields.

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