

N-Iodosaccharin - a New Reagent for Iodination of Alkenes and Activated Aromatics¹

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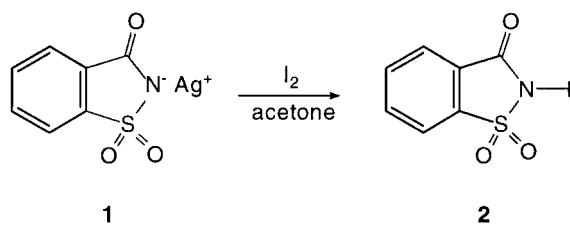
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Abstract: A mild and efficient iodination reagent, *N*-iodosaccharin was prepared. Iodination of activated aromatics and alkenes with the reagent takes place fast and under very mild conditions, without the aid of strong acids or heavy metals. The reagent does not affect oxidizable groups, such as hydroxyl or aldehyde.

Key words: iodine, halogenation, electrophilic additions, electrophilic aromatic substitutions

Introduction of an iodine atom into organic molecules is frequently an important step in organic synthesis since the iodine atom can easily be replaced by another group in a nucleophilic or free radical substitution or transition metal catalyzed condensation. As the carbon iodine bond is weak, the iodination reactions are often sluggish. However, they can be facilitated by the use of reagents in which the iodine is rendered more electrophilic, i.e. bound to an electron-attracting fragment. A variety of iodination reagents have been introduced in the last decades,² many of their reactions are catalyzed by Brønsted or Lewis acids.³ *N*-haloamides represent a class of moderately electrophilic halogenating agents which can be used under neutral conditions. The most well known and commercially available reagents of this class are derivatives of succinimide.⁴ Similar compounds, in which one carbonyl group is replaced with a more electronegative sulfone group, are derivatives of saccharin. Chloro-⁵ and bromosaccharin⁶ are very easily prepared in pure form. Although they are more electrophilic than the corresponding succinimides they have found little use.⁷ *N*-Iodosaccharin has appeared in the literature twice only,⁸ more or less not as a goal product (with no characterization, except mp.) and its iodination abilities are hitherto unexplored.



Scheme 1

The synthesis of *N*-iodosaccharin (NISac) was achieved following the classical procedure for the preparation of *N*-haloamides, the reaction of a silver salt of saccharin

with iodine.^{8a,9,10} Interestingly, the compound crystallizes as a crystalhydrate with one equivalent of water (iodometric titration, thermogravimetric analysis, IR, elemental analysis), which was gained presumably from the air moisture. Under very dry conditions the product may contain less than one equivalent of water but the exact composition can be easily determined by iodometric titration. *N*-Iodosaccharin is a stable compound which can be stored at room temperature, it is soluble in common organic solvents (better in more polar ones, such as acetone or acetonitrile) and insoluble in water.

N-Iodosaccharin (2) reacts smoothly with activated aromatics such as anilines and phenols (Table 1).¹² Thus, after 6 hours reaction with acetanilide at room temperature complete conversion of the starting compound with exclusive formation of 4-iodoacetanilide was observed.

Table 1 Iodination of Aromatic Compounds with 2^a

Entry	Substrate	Product	Time (h)	Yield (%) ^b
1			6	80
2			0.5	92
3			2	83 ^c
4			2	81 ^d
5			12	92
6			5	53 ^e

^a All experiments were carried out at r.t. (unless otherwise indicated) on 1 mmol scale in 1-2 mL of acetonitrile.

^b Isolated yields. ^c 2 equiv. of NISac. ^d *o* : *p* ratio = 7 : 93.

^e Conversion, determined by GC; *o* : *p* ratio 1 : 1.5, toluene in 3-fold excess, reflux.


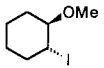

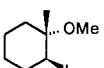

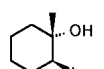

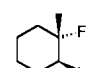
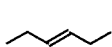
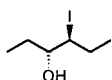
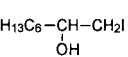

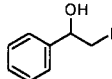
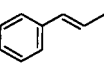
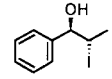
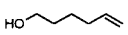
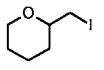

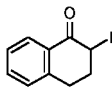
Iodination of aniline resulted in formation of tarry products, while deactivated aniline, 2-(2-amino-5-methylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol, yielded the monoiodo derivative in high yield. Phenols are iodinated to diiodo derivatives rather than to monoiodo compounds. A less reactive substrate, toluene, was only partly iodinated even at elevated temperature, with substantial decomposition of the reagent. Hydroxyl groups and aldehydes do not react under the reaction conditions.

In the presence of NISac alkenes are rapidly transformed to the corresponding adducts of iodine and nucleophile (Table 2), depending on the solvent used.¹² In comparison with the commercially available *N*-iodosuccinimide it was found that the reaction of cyclohexene with NISac in aqueous acetonitrile is approximately 500-times faster. Reactions are generally clean, only in few cases traces of by-products were formed, presumably the adducts of iodine and weakly nucleophilic saccharin. Additions follow the Markovnikov rule with very high regioselectivity, since no detectable amounts of regioisomers were found. The exception was 1-octene, where 1-iodo-2-octanol and 2-iodo-1-octanol were formed in the ratio of 3: 1. The iodohydrins synthesized from asymmetric alkenes with NISac have the opposite regiochemistry as those formed by opening of epoxides with hydrogen iodide and also the regioselectivity is higher. In any case, as a result of exclusive *anti* addition, only one diastereomer was formed.

References and Notes

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- Typical procedure: 8.50 g (50 mmol) of silver nitrate was dissolved in 50 mL of water, heated to ca. 80 °C and a solution of 10.5 g (51 mmol) of a sodium salt of saccharin in 50 mL of water was added dropwise with stirring. The white precipitate was filtered, washed with water and acetone, dried in air and 14.3 g (99%) of silver salt of saccharin **1** was obtained as fine crystals.
5.80 g (20 mmol) of the dry silver salt **1** and 5.21 (20.5 mmol) of iodine were stirred in 50 mL of acetone at r.t. in dark. After

Table 2 Iodination of Alkenes^a

Entry	Alkene	Product	Reaction conditions	Yield (%)
1			MeOH, 10 min	96 ^b
2			MeOH, 10 min	89 ^b
3			acetone-H ₂ O (3:1), 15 min	90 ^b
4			HF/pyridine-Et ₂ O, 10 min	89 ^c
5			acetone-H ₂ O (3:1), 10 min	74 ^c
6	1-octene		acetone-H ₂ O (3:1), 2 h	34 ^{c,d}
7			acetone-H ₂ O (3:1), 10 min	97 ^b
8			acetone-H ₂ O (3:1), 10 min	94 ^b
9			acetone 2 h	30 ^c
10			AcOH 24 h	86 ^b

^a All experiments were carried out at 0 °C or r.t. on 1 mmol scale in 1-2 mL of solvent. ^b Crude yield (min 95% purity). ^c Isolated yield after chromatographic separation. ^d Main product, see text.

5 h, precipitated AgI was filtered off and the filtrate was evaporated under reduced pressure. Crude product **2** (6.30 g, 96%) was pure enough for most purposes (98-99% NISac × H₂O - iodometric titration). Analytical samples were recrystallized from THF - hexane and pale yellow small crystals (mp. 206-208 °C, lit.^{8b} 205-207 °C) were obtained. ¹H NMR (300 MHz, acetone d₆) δ/ppm: 7.9-8.15 (m), ¹³C NMR (75 MHz, acetone d₆) δ/ppm: 122.2, 126.0, 128.4, 135.2, 135.6, 140.3, 162.5. IR (nujol, cm⁻¹): 3524 and 3384 (broad, OH), 1701(CO). MS (m/z (%)), FAB: 310 (100), EI: 183 (97), 128 (56), 127 (31), 120 (52), 104 (26), 92 (36), 76 (100). Anal. calcd for C₇H₄INO₃S: C 25.70, H 1.85, N 4.28, found C 25.67, H 1.61, N 4.19.

- All products have been adequately characterized on the basis of their NMR and mass spectra. 2-(2-Amino-3-iodo-5-methylphenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol: Light brown crystals, mp. 122-124 °C, ¹H NMR (CDCl₃, 300 MHz)

δ /ppm: 2.32 (3H, s), 3.7 (2H, br s), 7.38 (1H, br s), 7.76 (1H, m), 10.4 (1H, br s). ^{13}C NMR (CDCl_3 , 75 MHz) δ /ppm: 20.6, 79.9 (septet, $^2J(\text{F}-\text{C}) = 29.7$ Hz), 100.8, 123.2 (q, $^1J(\text{F}-\text{C}) = 289$ Hz), 123.5, 129.7, 136.4, 139.7, 141.2. MS (EI, m/z, (%)): 399 (42), 330 (33), 162 (23), 149 (36), 128 (100), 105 (45), 91 (55). Anal. calcd for $\text{C}_{10}\text{H}_8\text{F}_6\text{INO}$: C 30.10, H 2.02, N 3.51, found: C 30.38, H 1.78, N 3.47.

- (12) The reactions were performed typically on a 1 mmol scale by adding NISac to a stirred solution of a substrate in 1 mL of solvent at r.t. or 0 °C. Reaction mixtures were, after complete

consumption of the starting materials, diluted with ether and washed with aqueous $\text{NaHCO}_3 + \text{Na}_2\text{SO}_3$ to remove saccharin and an eventual excess of NISac. After normal work-up the products were purified if necessary and characterized.¹¹ The 5% excess of NISac was usually used, except for reactions with volatile alkenes, where alkenes were in 5-10% excess.

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