Special Topic

Iodine(III)-Mediated Oxidative Hydrolysis of Haloalkenes: Investigation of the Effect of Iodine(III) Reagents

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Abstract The iodine(III)-mediated oxidative transposition of vinyl halides to the corresponding α -halo ketones has been recently reported. The method is high yielding and offers good substrate scope. The investigation of other iodine(III) reagents to promote this reaction is described. The newly developed protocol reduces the number of waste products formed in the synthetic transformation. A structure-reactivity relationship study of numerous [hydroxy(tosyloxy)iodo]arenes toward haloalkenes is reported. The results highlight the challenge of obtaining a chemoselective reaction using these reagents.

Key words hypervalence, iodine, oxidation, vinyl halides, chemoselectivity

The development of oxidative transformations mediated by hypervalent iodine reagents has, without doubt, greatly influenced the field of synthetic chemistry. These compounds and their applications have been receiving increased attention for many years.¹ Due to their carbonbased nature, they tend to have lower environmental impact, compared with common heavy-metal-based oxidants.² Both iodine(III) and iodine(V) reagents give access to a wide diversity of synthetic transformations, such as phenolic dearomatizations³ and various other oxidative rearrangements.⁴ Of particular interest, there have been numerous reports recently concerning the development of stereoselective methods using these reagents.⁵

Our group has been involved in the development of iodine(III)-mediated methods to access functionalized ketone derivatives.⁶ This has been an active area of research in hypervalent iodine chemistry,⁷ because of the widespread presence and usefulness of α -functionalized ketones. Our approach has focused on the introduction of a leaving group α to the carbonyl, because we considered these products to be versatile synthetic precursors. In this regard, we have initially developed new chiral precatalysts for the enantioselective iodine(III)-promoted α -tosyloxylation of ketones (Scheme 1A).⁸ Selectivity issues encountered in our group and others⁹ for this transformation led us to investigate enol surrogates,¹⁰ in particular enol esters,¹¹ to access these products (Scheme 1B). From the success of this recent work, we then explored the use of haloalkenes as possible substrates to access similar α -substituted ketones (Scheme 1C).

We have recently demonstrated that chloro- and bromoalkenes could be converted in usually very high yields into their corresponding α -halo ketone products by the action of [hydroxy(tosyloxy)iodo]benzene (HTIB, 1) (Equation 1).¹² The method presents a good scope and is an attractive strategy to access α -halo ketones from non-ketonic substrates.









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Given the potential of this synthetic transformation, we envisioned that it would benefit from an improvement of its reaction conditions, and by having a better understanding of the factors governing it. Herein, we present the results of an evaluation of the efficiency of other iodine(III) reagents to promote the oxidative hydrolysis of haloalkenes, as well as an investigation of the structurereactivity relationship of various [hydroxy(tosyloxy)iodo]arenes for this transformation.



Our initial reported protocol for the direct conversion of haloalkenes into their corresponding α -halo ketone products presented unprecedented reaction scope and excellent yields with most substrates. However, in contrast to our previous work involving the conversion of enol esters to α -tosyloxy ketones, the toluenesulfonic acid (TsOH) released in the reaction, coming from HTIB, is not consumed in the process. Additionally, we have demonstrated that an excess of TsOH·H₂O is beneficial to achieve short reaction times, increasing the mass of unused acid in the reaction. These conditions thus lead to large amount of waste products. In this context, and in an effort to reduce the environmental impact of this reaction, we explored the replacement of HTIB and TsOH·H₂O to effect this transformation.

From a practical point of view, we considered (diacetoxyiodo)benzene (DIB) to be a good alternative iodine(III) reagent. It is commercially available, well-defined, and stable. It is known that this compound can be readily converted into HTIB by addition of $TsOH \cdot H_2O$,¹³ hence we envisioned that generation of a Koser like reagent in situ would be sufficient to promote the reaction. We tested various strong acids, and the results are reported in Table 1.

The first tests were made using bromoalkene **2b**. The requirement for water in the reaction was explored by using anhydrous MsOH. Treatment of the substrate with DIB and an equimolar quantity of MsOH at 60 °C for three hours resulted in only partial conversion into the desired product (Table 1, entry 1). Under the same conditions, but with the addition of an equimolar quantity of water, complete conversion was observed within 20 minutes, affording the desired product **3b** in almost quantitative yield (entry 2). SubDownloaded by: Cornell. Copyrighted material

sequent tests were performed with bromoalkene 2d. Reaction with DIB and water, without an additional acid, led to low conversion and modest yield (entry 3), confirming the requirement for a strong acid to access a Koser like reagent. To achieve rapid conversion, we tested conditions involving two equivalents of acid. Both TsOH·H₂O and MsOH led to complete conversions, albeit in lower yields than that obtained using HTIB in our previous communication.¹² The next acid we considered in an effort to improve the reaction was H₂SO₄. It has the particular advantage of being inexpensive, low-weight, and eco-friendly. To our delight, we found that this acid led to rapid and clean conversion of **2d**. with or without additional water (entries 6 and 7). An extremely fast reaction (within 5 minutes) could be achieved at 60 °C (entry 8). This protocol is particularly practical because the only waste products are water-soluble acids (H₂SO₄ and AcOH) and PhI. Following work-up, the final product can thus be obtained in pure form by simple removal of PhI under vacuum. Finally, we tested these conditions with chloroalkene 2c. Lower yields were obtained with this substrate, and addition of water to the reaction did not improve the yield (entries 9 and 10).

 Table 1
 Effect of Acid on the DIB-Mediated Oxidative Hydrolysis of Haloalkenes

	Ph R 2b-d	PhI(OAc) ₂ (1.1 equiv) acid MeCN, r.t., time	Ph Ph	N X N⊢d
Entry	Substrate	Acid (equiv)	Time (min)	Yield (%)ª
1	2b	MsOH (1.15) ^b	180	75°
2	2b	MsOH (1.15) ^{b,d}	20	99
3e	2d	-	120	17
4	2d	TsOH·H ₂ O (2.0)	120	76
5	2d	MsOH (2.0) ^d	120	75
6	2d	H ₂ SO ₄ (2.0)	120	92
7	2d	H ₂ SO ₄ (2.0) ^d	120	89
8	2d	H ₂ SO ₄ (2.0) ^b	5	95
9	2c	H ₂ SO ₄ (2.0)	120	82
10	2c	H ₂ SO ₄ (2.0) ^d	120	82

^a Isolated yield.

^b Reaction performed at 60 °C.

^c Conversion, based on ¹H NMR spectroscopic analysis.

^d One equivalent of water per acid equivalent was added.

^e Two equivalents of water was added to the reaction.

Another aspect we wanted to explore was the relative rates of reaction of haloalkenes toward HTIB, to determine whether synthetically useful selectivities could be obtained when multiple reactive sites were present in the reaction. Additionally, since the oxidative hydrolysis reaction is high yielding with no discernible side products, we decided to R. Dagenais et al.

exploit this to investigate the chemoselectivity aspect of [hydroxy(tosyloxy)iodo]arene reagents. We considered that the information obtained on this specific transformation could be, at least in part, applicable to other methodologies involving reagents such as HTIB. The selected haloalkenes **2a–e** to be used for the chemoselectivity study, as well as the selected iodine(III) reagents **4–8**, are illustrated in Figure 1. The latter were selected to evaluate both the steric and electronic parameters of these reagents.

The first chemoselectivity profile was determined for the **2b/2d** bromoalkene pair, using HTIB and its derivatives; the results are reported in Table 2. TsOH·H₂O was used as an additive in all cases to insure clean and rapid conversion of the haloalkenes. Under these conditions, the iodine(III) reagents were consumed within two hours. The results show a very small preference for the less sterically hindered substrate **2b**. Surprisingly, neither steric nor electronic factors of the iodine(III)-reagents had a noticeable effect on the chemoselectivities. For this substrate pair, it is clear that synthetically useful selectivities are not easily achievable. To evaluate whether the nature of the halogen atom could greatly influence the chemoselectivity, we performed similar competition experiments using the chloroalkene pair **2a/2c**.

Table 2	Chemoselectivity Profile of the 2b/2d Pair				
2b/2d (1:1)	reagent: TsOH:H ₂ O (1:1, 0.25 equiv) CD ₃ CN, r.t., 2 h $Ph \xrightarrow{0} f_6$ Br	+ Ph Br			
Entry	Reagent	Conv. 2b/2d ª			
1	1	1.3			
2	4	1.3			
3	5	1.2			
4	6	1.3			
5	7	1.3			
a The matic survey determined from the velocity conversions have done					

^a The ratios were determined from the relative conversions, based on ¹H NMR spectroscopic analysis.

As was shown in our previous communication,¹² in this process we added 10 equivalents of water to prevent formation of aryl migration side products. The results of the competition experiments are presented in Table 3.

In analogy to the results measured for the **2b/2d** pair, the chloroalkene pair **2a/2c** presents almost identical chemoselectivity profiles. Again, the nature of the iodine(III) reagent does not affect the selectivity obtained in any noticeable manner. We also evaluated whether the absence of additional TsOH·H₂O would change the selectivity, but found no effect (Table 3, entry 1 vs. entry 2). From these first competition experiments, it seems clear that the steric



2a/2c (1:1)	reagent: TsOH·H ₂ O (1:1, 0.25 equiv) H ₂ O (10 equiv) CD ₃ CN, r.t., 2 h Ph $\begin{pmatrix} 0 \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\$	Ph Cl
Entry	Reagent	Conv. 2a/2cª
1 ^b	1	1.2
2	1	1.2
3	4	1.3
4	5	1.3
5	6	1.3
6	7	1.2

^a The ratios were determined from the relative conversions, based on ¹H NMR spectroscopic analysis.

^b Reaction was performed without TsOH H₂O additive.

hindrance of the substrate alkyl chain has a marginal effect on reaction rate.

We next evaluated the effect of Z/E isomerism on the reactivity, using the **2b**/**2e** bromoalkene pair; the results are described in Table 4. Alkene stereochemistry was found to have a much more pronounced effect on oxidation rate, with *E* alkenes being roughly four times more reactive than their *Z* counterpart, yielding synthetically useful selectivities. Unfortunately, the steric and electronic properties of the iodine(III) reagents have again only marginal effect on the selectivities. At this point, we decided to explore the influence of the halogen atom on reaction rate, to probe the electronic effect of the substrates, since only limited selec-

Table 4 Chemoselectivity Profile of the 2b/2e Pair

2b/2e (1:1)	$\xrightarrow{\text{reagent: TsOH:H_2O}}_{(1:1, 0.25 \text{ equiv})} \xrightarrow{O}_{\text{CD}_3\text{CN, r.t., 1 h}} \xrightarrow{O}_{\text{Ph}} \xrightarrow{O}_{\text{H}} \xrightarrow{O}_{\text{Br}}$	+ Br
Entry	Reagent	Conv. 2b/2e ª
1 ^b	1	3.8
2	1	3.7
3	4	3.3
4	5	4.0
5	6	3.2
6	7	3.7
7	8	3.7

^a The ratios were determined from the relative conversions, based on ¹H NMR spectroscopic analysis.

^b Reaction was performed without TsOH·H₂O additive.

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^a The ratios were determined from the relative conversions, based on

 1 H NMR spectroscopic analysis. b Reaction was performed without TsOH·H₂O additive.

tivity could be obtained from the steric properties of the haloalkenes. The substrate pair **2a/2d** was selected, and the results are reported in Table 5.

Halogen scrambling on the final products was observed, as expected from a control experiment of our previous communication.¹² Chloroalkene **2a** was found to be roughly twice as reactive as bromoalkene **2d**. Considering the slight steric bias toward the less hindered substrate **2a**, the chloroalkene/bromoalkene preference factor is thus approximately 1.6. This preference is in line with the Hammett-Brown σ_p^+ values (0.150[Br], 0.114[Cl]), in support of the presence of a strong positive charge on the carbon bearing the halogen atom at the selectivity-determining step.¹⁷ Surprisingly, almost no influence on selectivity was observed from the different iodine(III) reagents, even for the strongly electron attracting perfluorophenyl variant **8**.

In summary, we have demonstrated that it is possible to reduce the amount of waste products of the oxidative hydrolysis of haloalkenes to their corresponding α -halo ketones by using DIB and sulfuric acid. By removing the presence of an organic sulfonic acid, this new protocol has the added advantage of simplifying access to the pure final product. On the other hand, our investigation of the chemoselectivity profiles of haloalkenes and structure-reactivity relationship investigation of numerous iodine(III) reagents has exposed a limitation of the current methodology. Except for the more important preference for *E* vs. *Z* alkenes, the selectivities measured are not synthetically useful. Moreover, it is surprising to find that modification of either the steric or electronic properties of the involved iodine(III) reagents does not lead to a noticeable enhancement of these selectivities. While this might be specific to the oxidative hydrolysis of haloalkenes, it does raise the concern that it could also be an issue for other similar iodine(III)-

mediated processes. To account for the behavior reported, one could raise the possibility that the iodine(III) reagent is not involved in the selectivity-determining step. A theoretical investigation of this transformation is under way to better understand the reaction mechanism and the requirements to achieve chemoselectivity.

CDCl₃ was dried over anhydrous K₂CO₃ but not thoroughly dried. CD₃CN was used as received. Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F₂₅₄). NMR spectra (¹H, ¹³C, DEPT) were recorded with either Avance III HD 300 (Bruker, Billerica, MA, USA) or Mercury+ 400 (Agilent Technology, Santa Clara, CA, USA) spectrometers. Chemical shifts for ¹H NMR spectra are recorded in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard. Highresolution mass spectra were recorded with a Maxis ESI-Q-Tof (Bruker, Billerica, MA, USA) at the Université de Sherbrooke. All commercial materials were used without further purification. The haloalkenes **2a–e**¹² and [hydroxy(tosyloxy)iodo]arenes **4** and **6**,¹⁴ **5** and **7**,¹⁵ and **8**¹⁶ were prepared by using reported procedures.

Oxidative Hydrolysis using DIB and $H_2SO_4;$ Typical Procedure for $\alpha\mathchar`-Bromoisovalerophenone (3d)$

To a reaction flask were added haloalkene **2d** (56.3 mg, 0.250 mmol), MeCN (1.33 mL, 0.2 M), concentrated (98%) H₂SO₄ (27 μ L, 0.50 mmol, 2.0 equiv) and (diacetoxyiodo)benzene (88.6 mg, 0.275 mmol, 1.1 equiv). The suspension was stirred at r.t. for 2 h, then the solution was diluted with water (1:1) and extracted with three portions of Et₂O. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and concentrated by rotatory evaporation. The crude material was purified by flash chromatography (1% Et₂O/pentane) to obtain the pure α -halo ketone **3d** (57.3 mg, 95%). Alternatively, pure **3d** can be obtained by removal of PhI under vacuum. The analytical and spectral data for this compound were consistent with reported data.¹²

Chemoselectivity Experiments; Typical Procedure

Reagent **1** (6.2 mg, 0.0157 mmol, 0.25 equiv) was added to a small vial. To the solid was added a stock solution containing TsOH·H₂O (2.7 mg, 0.0157 mmol, 0.25 equiv) in CD₃CN (100 µL). To this suspension was then added a stock solution containing bromoalkene **2b** (16.8 mg, 0.0629 mmol) and bromoalkene **2d** (14.2 mg, 0.0629 mmol) in CD₃CN (500 µL). The resulting suspension was stirred at r.t. for 2 h, at which point the reaction mixture was now a clear solution. The whole reaction mixture was filtered over a small quantity of solid NaHCO₃ directly into an NMR tube. ¹H NMR spectroscopic analysis (8 s relaxation time) was performed and conversions were determined by integration of the vinylic protons of the remaining starting materials and protons α to the carbonyl of the products. Reference ¹H NMR spectra for all substrates and final products were obtained from the literature.¹²

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