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Harvesting short-lived hypoiodous acid for efficient diastereoselective iodohydroxylation in *Crixivan*® synthesis

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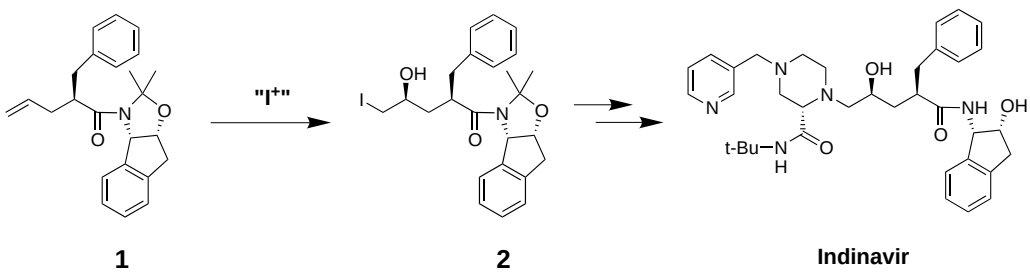
Abstract—The evasive hypoiodous acid is generated in situ from NaOCl and NaI and used efficiently for clean iodohydroxylation of **1**, producing the *Crixivan*® intermediate **2** in high yield with highly efficient 1,3-asymmetric induction. This pH-tunable process allows HOI generation at a pH optimal for supressing byproduct formation in pH-sensitive iodohydroxylation reactions. © 2001 Published by Elsevier Science Ltd.

Diasteroeselective iodohydroxylation of 2-alkyl-4-enamide **1** to iodohydrin **2** is a key step in the synthesis of Merck's HIV protease inhibitor *Crixivan*® (indinavir sulfate). The iodohydrin is converted to the corresponding epoxide and further elaborated to indinavir (Scheme 1).[1] The iodohydroxylation step has been accomplished with high diastereoselectivity and high yield using *N*-iodosuccinimide (NIS) or *N*-chlorosuccinimide (NCS) with sodium iodide in a buffered biphasic reaction system [isopropyl acetate (IPAc)/aq. $NaHCO_3$].[1a] Pathway of the reaction is pH sensitive. The amide bond cleavage reaction leading to byproduct **3** increases significantly with decreasing pH. Thus, it is desirable to conduct the reaction at high pH to minimize byproduct formation. However, NIS becomes increasingly unstable with increasing pH above 8.

It has been reported that hypoiodous acid (HOI), generated electrochemically or via iodine disproportionative hydrolysis in the presence of HgO, converts **1** to **2** with high stereoselectivity and good yield.[2] It would be of great interest to develop a practical and pH-tunable method that produces active hypoiodous acid cleanly and efficiently over a wide range of pHs, and in this case, at high pH optimal for the iodohydroxylation reaction.

Few methods of producing HOI are currently available and they either require strongly acidic conditions,[3] or utilize molecular iodine (which is either used as starting material[4] or generated in situ via oxidation of NaI[5]). Other efforts include reduction of periodic acid or sodium periodate by sodium bisulfite,[6] and oxidation of iodomethane by dimethyldioxirane.[7] Acidic conditions are incompatible with substrate **1**, while the use of iodine leads to numerous impurities including lactones **3** and oxazoline **4**.[8] We describe here a novel and practical chemical process wherein HOI is generated in



1 **2** **Indinavir**

Scheme 1.

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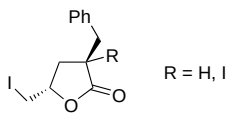
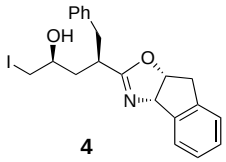
situ from readily available NaOCl and NaI at a pH optimal for selectivity and captured efficiently to convert **1** to iodohydrin **2** in excellent yield (96%) with highly efficient 1,3-asymmetric induction (96% de).

Due to its reactive nature, hypoiodous acid can not be prepared using conventional methods,[9] and its characterization has been challenging.[10] Reaction of NaOCl with NaI in aqueous phase produces hypoiodous acid, or hypoiodite depending on pH. Using this reaction, Chia and Lister produced HOI, measured its formation kinetics, and recorded its electronic spectrum.[11]



R = H, I

3



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We attempted to use this simple reaction to generate HOI in situ for iodohydroxylation of **1**. Due to the highly unstable nature of HOI under normal conditions, its clean chemical generation is challenging. Scheme 2 describes a few key pathways for HOI formation from NaOCl/NaI and its degradation. Since the reaction between NaOCl and NaI is extremely fast and exceeds the rate of HOI disproportionation,[11,12] we expect that it is possible to build up HOI in solution in significant concentrations for iodohydroxylation. However, in addition to the desired iodohydroxylation and the undesired disproportionation, HOI can also be oxidized by excess NaOCl to inactive species such as iodate, or react with excess NaI to give iodine. This implies that the outcome of using NaOCl/NaI to generate HOI for iodohydroxylation depends on the mode and ratio of NaOCl/NaI addition.

Addition of NaOCl to the reaction already containing NaI would result in reduction of HOI to iodine that is known to react with **1** to give numerous byproducts.[8] Alternatively, addition of NaI to the batch charged with NaOCl would lead to oxidation of HOI (presumably to iodate) and thus no substrate conversion. A successful experimental protocol for generating HOI in solution should employ *concurrent but separate addition* of NaOCl and NaI in nearly *equal molar ratio* to the **1**/IPAc/aq. $NaHCO_3$ biphase in order to avoid an excess of either NaOCl or NaI and thus minimize the unproductive HOI degradation. Since the rate of reaction with **1** is most likely first order in [HOI], while the rate of HOI disproportionation is second order in [HOI],[12] the concurrent addition of NaOCl and NaI should be sufficiently slow to favor iodohydroxylation over HOI disproportionation.

We found that the best iodohydroxylation results are achieved when the NaOCl (2 equiv.) and NaI (1.8 equiv.) solutions were fed concurrently but separately to the agitated **1**/IPAc/aq. $NaHCO_3$ biphase over 1 h, with the reaction pH controlled in the 8–9.5 range by on-demand addition of dilute sulfuric acid.[13] Under these reaction conditions, the iodohydroxylation of **1** was nearly complete (99.9% conversion) to give **2** in 96% de and 96% yield[13] at the end of 1 h addition of NaOCl and NaI (Fig. 1). The success of this simple NaOCl/NaI process demonstrates that highly reactive HOI generated in situ was sufficiently long-lived under these reaction conditions to convert cleanly **1** to iodohydrin **2**. The success also indicates that the reaction between HOI and **1** is much faster than HOI disproportionation. Fig. 1 shows that the rate of iodohydroxylation was so fast that it was limited by the addition rate.

Several other characteristics of this process are discussed below. Firstly, the reaction pH is a critical reaction parameter as can be seen from Fig. 2 where the conversion of **1** at the end of reagent addition is plotted

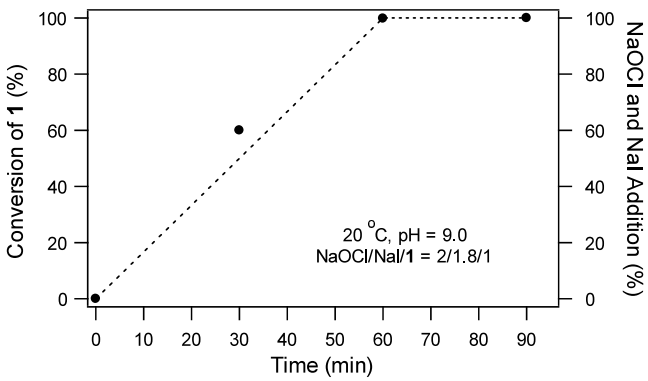
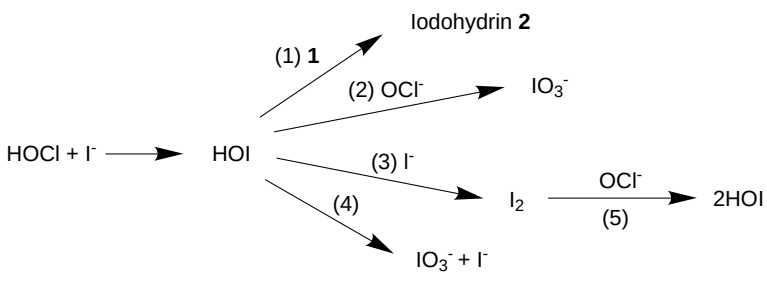


Figure 1. Conversion of **1** to **2** as a function of time during co-addition of NaOCl and NaI (dash line is the addition profile).



Scheme 2. Fate of HOI.

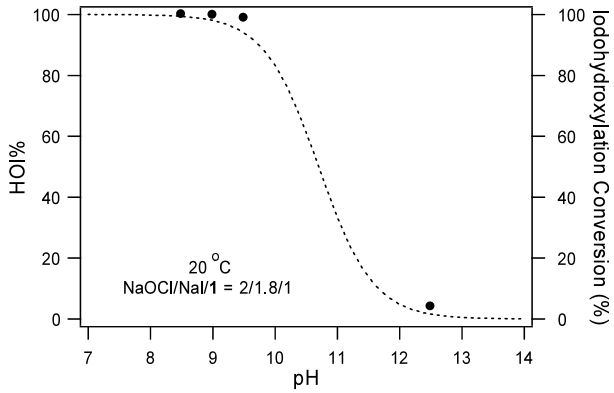


Figure 2. Effect of reaction pH on the conversion (solid circle) of iodohydroxylation of **1** to **2**, and its correlation to HOI% (HOI% = [HOI]/([HOI]+[OI^-], dashed line) as a function of pH.

versus the reaction pH. The fact that the conversion falls precipitously with pH>9.5 may result from two factors. One is related to the fact that the rate of formation of hypoiodous acid from NaOCl and NaI is inversely proportional to [OH^-].[11b,14] The slower HOI formation rate results in enhanced degradation of HOI by reacting with the unreacted NaOCl and NaI. Furthermore, HOI, instead of OI^-, is likely the principal iodination species in this biphasic system, and extraction of HOI into the organic phase is a key step. The latter is supported by the apparent correlation between conversion and the HOI percentage shown in Fig. 2. Since HOI is a weak acid ($pK_a = 10.7$),[9] at pH below 9.5, >95% of the I^{+1} species exists in the form of HOI which is extracted into organic phase where it is sheltered from degradation reactions with NaOCl and NaI in the aqueous phase. The conversion is high as a result. At high pHs, e.g. pH = 12.5, the I^{+1} species exists predominantly as hypoiodite that resides in the aqueous phase, unable to react with **1** and eventually destroyed.

Secondly, yield of iodohydroxylation of **1** to **2** using NaOCl/NaI (96%) is higher than typical yield of the NCS/NaI process (90–92%) primarily due to reduced levels of byproducts **3** and **4**. The pH-tunable nature of the NaOCl/NaI process allows the HOI generation at a reaction pH optimal for selectivity. Since low pHs favor amide bond cleavage and formation of **3**,[1,15] the ability of the NaOCl/NaI process to operate at high reaction pH (up to 9.5) strongly suppressed the amide bond cleavage pathway. The level of **3** is reduced by a factor of four compared with the NCS/NaI process (pH = 7.2–8.0). Since the commonly employed NCS and NIS are unstable at pH>8.5, the new NaOCl/NaI process should prove more beneficial in iodohydroxylation of 2-alkyl-4-enamides in general. The decrease in the amount of impurity **4** can be rationalized by the fact that in our controlled NaOCl/NaI process HOI is generated more cleanly with minimal degradation to iodine which is the principal cause behind the formation of impurity **4**.

Thirdly, we checked the other possible addition protocols that we ruled out during initial consideration. As expected, the addition of NaI to a mixture of NaOCl/**1**/IPAc/aq. $NaHCO_3$ in the pH range 9–12 gave no desired product. When NaOCl was added to the mixture NaI/**1**/IPAc/aq. $NaHCO_3$ at pH 8.0–9.5, poor conversion (11%) and a high level of impurity **4** were observed during the addition of the first half of the NaOCl solution. However, greater than 99% conversion was achieved upon addition of the second half of NaOCl. These observations were consistent with the proposed reaction pathways whereby during addition of the first half of NaOCl solution, HOI generated can not react with **1** due to its fast reaction with the excess iodide to I_2. During the second half of NaOCl addition, NaI is depleted and I_2 is oxidized by NaOCl to give two moles of HOI (step 5 in Scheme 2).[16]

Finally, the greater than 50% conversion at midpoint of NaOCl/NaI addition in Fig. 1 implies that the iodide usage (1.8 equiv.) may be reduced. Indeed, the use of 1.4 equiv. of iodide (with 1.6 equiv. NaOCl) is sufficient to reach complete conversion.

In summary, we have developed a new, efficient, and pH-tunable iodohydroxylation method. This method has been demonstrated for preparation of *Crixivan*® iodohydrin **2** in high yield with highly efficient 1,3-asymmetric induction. The key to the success of this chemistry is a carefully designed experimental protocol that minimizes side reactions and allows for clean in situ generation of reactive iodination species, hypoiodous acid, at a pH optimal for selectivity. Among the advantages of this new process are its high operating pH and minimization of iodine formation that suppress formation of byproducts, inexpensive and nontoxic reagents, fast reaction rate, simple product isolation procedure, high iodine utilization efficiency, and elimination of organics (e.g. succinimide) in the waste stream. Studies of this chemistry as a general synthetic utility for iodination are in progress.

Acknowledgements

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References

1. (a) Maligres, P. E.; Upadhyay, V.; Rossen, K.; Cianciosi, S. J.; Purick, R. M.; Eng, K. K.; Reamer, R. A.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett*. **1995**, *36*, 2195–2198; (b) Maligres, P. E.; Weissman, S. A.; Upadhyay, V.; Cianciosi, S. J.; Reamer, R. A.; Purick, R. M.; Sager, J.; Rossen, K.; Eng, K. K.; Askin, D.; Volante, R. P.; Reider, P. J. *Tetrahedron* **1996**, *52*, 3327–3338; (c) Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett*. **1996**, *37*, 6843–6846.
2. Rossen, K.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett*. **1997**, *38*, 777–778.

3. Ohta, H.; Sakata, Y.; Takeuchi, T.; Ishii, Y. *Chem. Lett.* **1990**, 733–736.
4. For examples, see: (a) Yang, S. G.; Kim, Y. H. *Tetrahedron Lett.* **1990**, *40*, 6051–6054; (b) Sanseverino, A. M.; de Mattos, M. C. S. *Synthesis* **1998**, *11*, 1584–1586.
5. Edgar, K. J.; Fallings, S. N. *J. Org. Chem.* **1990**, *55*, 5287–5291.
6. Masuda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* **1994**, *59*, 5550–5555.
7. Asensio, G.; Andreu, C.; Boix-Bernardini, C.; Mello, R.; Gonzalez-Nunez, M. E. *Org. Lett.* **1999**, *1*, 2125–2128.
8. Reaction of **1** with I_2 leads to amide bond cleavage and the formation of iodolactones **3** in un-buffered aqueous THF,[1] and to the formation of ca. 1:1 mixture of **2** and **4** in IPAc/aq. $NaHCO_3$ at pH 7–9.
9. Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th ed.; John Wiley & Sons, 1988; p. 565.
10. The first IR spectrum of HOI was obtained in 1975 after the synthesis of HOI via photolysis of iodomethane in the presence of oxygen in solid argon at 10 K (Ogilvie, J. F.; Salares, V. A.; Newlands, M. J. *Can. J. Chem.* **1975**, *53*, 269–275). Analysis of isotopic shift was used to establish the structure of hypoiodous acid as H-O-I. The first IR spectrum of gaseous HOI was obtained in 1992 (Barnes, I.; Becker, K. H.; Starcke, J. *Chem. Phys. Lett.* **1992**, *196*, 578–582). For electronic spectrum of HOI in aqueous phase, see Ref. 11 and Haimovich, O.; Treinin, A. *Nature* **1965**, *207*, 185–186.
11. (a) Chia, Y. T.; UCRL–8311, **1958**; (b) Chia, Y. T.; Connick, R. E. *J. Phys. Chem.* **1959**, *63*, 1518–1519; (c) Lister, M. W.; Rosenblum, P. *Can. J. Chem.* **1963**, *41*, 3013–3020.
12. (a) Truesdale, V. W.; Canosa-Mas, C.; Luther, G. W. *J. Chem., Soc. Faraday Trans.* **1994**, *90*, 3639–3643; (b) Lengyel, I.; Li, J.; Kustin, K.; Epstein, I. *J. Am. Chem. Soc.* **1996**, *118*, 3708–3719.
13. The experiments were carried out in Mettler's RC1 (1 L) equipped with a pH control. *Reaction procedure*: add **1** in IPAc (200 ml, 137 g/L) and H_2O (121 ml) to reactor. Add NaOCl (16 wt%) and NaI (57 wt% in water) in a molar ratio of NaOCl/NaI/**1** = 2/1.8/1 over 1 h into the reactor at 20°C as the batch pH was controlled externally to an accuracy within ±0.2 by on-demand addition of H_2SO_4 (1 M). Yield and diastereoselectivity were determined by HPLC using authentic product iodohydrins as standards.
14. HOCl is considered the active iodide oxidation reagent, see: Anbar, M.; Taube, H. *J. Am. Chem. Soc.* **1958**, *80*, 1072.
15. Tamaru, Y.; Mizutani, M.; Furukawa, Y.; Kawamura, S.; Yoshida, Z.; Yanagi, K.; Minobe, M. *J. Am. Chem. Soc.* **1984**, *106*, 1079–1085.
16. In a separate experiment, iodohydroxylation of **1** was performed by adding NaOCl (2 equiv.) to the reaction containing **1**/iodine (0.9 equiv.)/IPAc/aq. $NaHCO_3$ over 0.5 h at pH 9. Complete conversion to **2** was achieved at the end of NaOCl addition with elevated levels of **3** observed.