ORGANIC LETTERS

2009
Vol. 11, No. 16
3578−3581

Iodoxolone-Based Hypervalent Iodine Reagents

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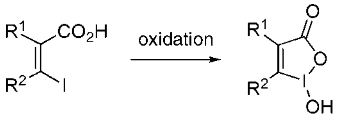
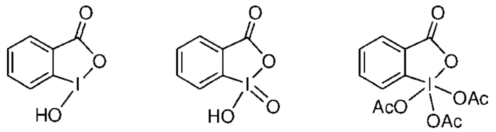
Received June 10, 2009

ABSTRACT



The fast access to simple (*Z*)-3-iodo acrylic acid derivatives which can be easily oxidized to the corresponding hypervalent iodine(III) reagents is described. They can be used for various reactions with superior or similar reactivity as conventional hypervalent iodine(III) reagents.

The past decades have revealed the use of hypervalent iodine compounds as very versatile and mild oxidation and oxygenation reagents[1] replacing toxic and heavy metal-containing reagents, thus providing more environmental friendly reaction conditions. Especially cyclic iodanes and periodanes, such as IBA **1**, IBX **2**, and DMP **3**[2] (Figure 1) are frequently used reagents which have found wide applications in synthesis.[3] IBX **2** can mediate many useful transformations[3b] such as the α,β-unsaturation of carbonyl compounds,[4] oxidation of benzylic methylene, and methyl groups or cyclizations by single electron transfer-based processes.[5] The Dess−Martin periodane **3** has shown great use in selective oxidation of alcohols to carbonyl compounds and in cascade reactions.[6]



1 (IBA) **2** (IBX) **3** (DMP)

Figure 1. Cyclic iodanes IBA **1**, IBX **2** and DMP **3**.

Herein we report the synthesis of new and simple hypervalent iodine(III) reagents, which can be regarded as simplified IBA analogues. The aryl moiety of IBA has been replaced by a substituted double bond. The synthesis of (*Z*)-3-iodo acrylic acid derivatives is straightforward and iodinations of the corresponding alkyne compounds have been performed according to literature procedures.

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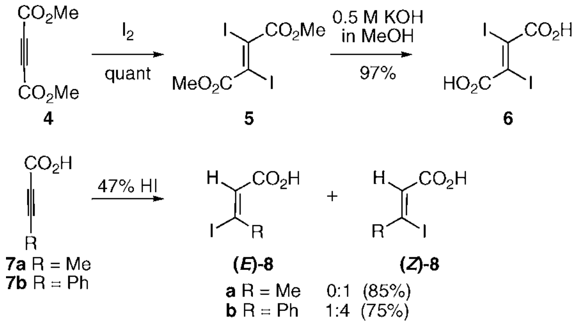
10.1021/ol9014688 CCC: $40.75
Published on Web 07/17/2009

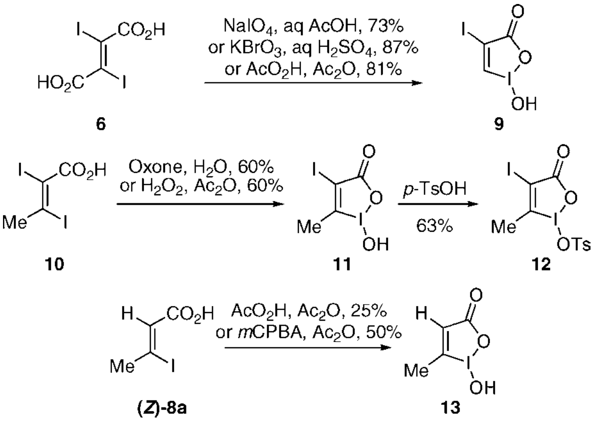
The iodination of **4** proceeded quantitatively to **5**, which was subsequently hydrolyzed to **6**.[7] The synthesis of **8** also followed literature procedures.[8] While **8a** was obtained as a single (*Z*)-stereoisomer, the addition of HI to phenylpropiolic acid resulted in a mixture of (*E*)- and (*Z*)-isomers **8b** in a ratio of 1:4 in 75% yield (Scheme 1), which is in contrast to the literature where it has been described that only the (*Z*)-isomer was obtained in 70% yield.[8] By varying the reaction conditions 1:1 (*E*:*Z*) ratios could be obtained. The NMR data reported were also not conclusive with other references.[9] After recrystallization of the product mixture we were able to separate the differently colored crystals of the two isomers manually. X-ray structural analysis of (*E*)-**8b** and (*Z*)-**8b** allowed us to assign unambiguously the ^{1}H NMR data.[10] The desired isomer (*Z*)-**8b** can be prepared exclusively by the reaction of **7b** with sodium iodide in acetic acid.[11]

Scheme 1. Synthesis of (*Z*)-3-Iodo Acrylic Acid Derivatives **6** and **8** by Iodination of Alkynes



The (*Z*)-3-iodo acrylic acid derivatives **6** and **8** were then oxidized to λ^3-iodanes by using different reagents as shown in Scheme 2. Depending on the reagents and the reaction conditions usually moderate to good yields are obtained and different oxidants can be used for these transformations.

Scheme 2. Synthesis of λ^3-Iodanes



In case of substrate **6** we were expecting that both iodide moieties would become oxidized, but under various reaction conditions as shown in Scheme 2 decarboxylation occurred, resulting in λ^3-iodane **9** in good yields. After having performed the synthesis we found that this compound has already been described in the literature.[12] A similar decarboxylation has been observed upon heating although a different oxidant (chlorine) has been used. Other compounds such as diiodomethane and diiodoethene containing two iodine atoms could also only be oxidized at one iodine atom.[13] When diiodide **10**, prepared from **7a** by reaction with iodine,[14] is oxidized, no decarboxylation occurred and hypervalent compound **11** was obtained. Further ligand substitution resulted in the tosylate derivative **12**.

Similar routes have been used previously by Moss et al. for the synthesis of closely related organoiodanes, which have been investigated as nucleophilic reagents for phosphate cleavage reactions,[15] These authors have performed mechanistic investigations[16] and also calculations on the iodoxolone moiety and their results regarding angles and distances closely match our X-ray structural data.[10,17]

Different oxidants can also be employed for the synthesis of the λ^3-iodane derivative **13** from precursor (*Z*)-**8a**. Interestingly, oxidation of (*Z*)-**8b** always led to decomposition of the starting material under various reaction conditions successful for the other substrates ($NaBrO_3$, $NaIO_4$, AcO_2H). Interestingly, we were also unable to oxidize the diiodo derivative obtained by iodination of **7b** under various conditions.

We have obtained X-ray analyses for some of the hypervalent iodine compounds (**9**, **13**).[17] The angles and distances found in the five-membered-ring system containing the iodine(III) moiety are very similar in structures **9** and **13** and directly comparable to the X-ray structure of IBA[18] or FIBA (FIBA: 3,4,5,6-F_4-IBA).[19] As an example, the X-ray structure of **9** is shown in Figure 2.

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(17) CCDC 718611 (**9**) and CCDC 718613 (**13**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033 or e-mail deposit@ccdc.cam.ac.uk).

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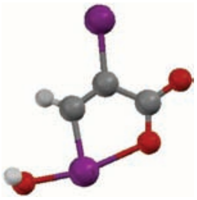
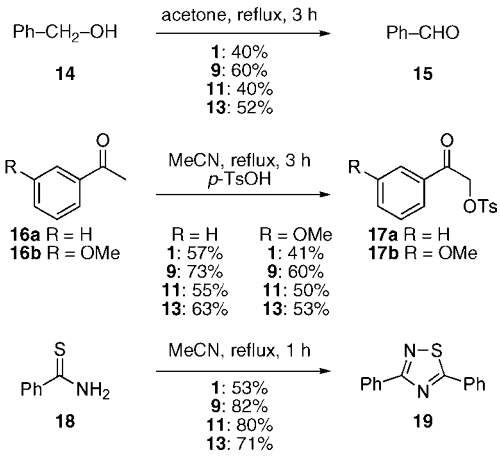


Figure 2. X-ray structure of compound **9**.

Similarities were also found in the corresponding NMR data.[20] Upon oxidation from iodine(I) to iodine(III) the *ipso*-carbon atom attached to the iodine undergoes a downfield shift of approximately 25 ppm. The same is observed for **13** ($\Delta\delta = 23.7$ ppm), whereas the other two hypervalent derivatives **9** and **11**, which contain an additional iodine substituent, show downfield shifts of $\Delta\delta = 40.5$ ppm for **9** and $\Delta\delta = 47.7$ ppm for **11** compared to their iodine(I) counterparts. Although downfield shifts of 40−50 ppm relative to the iodine(I) have previously been assigned to the corresponding iodine(V) compounds, we have not formed such derivatives as clearly shown by X-ray analysis. The larger downfield shifts might be due to the additional iodine substituent adjacent to the carboxylic acid moiety. The hypervalent iodine compounds **9**, **11**, **12**, and **13** are stable at room temperature without exclusion of oxygen as are IBA **1**, IBX **2**, and DMP **3**.

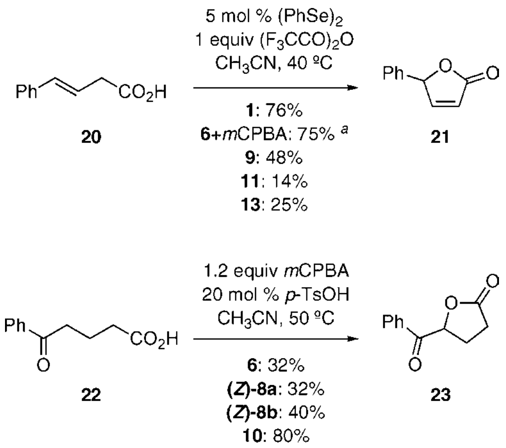
Different oxidative transformations have been performed with these new hypervalent iodine reagents. Simple oxidation reactions such as benzyl alcohol **14** to benzaldehyde **15**, α-oxytosylations of acetophenone derivatives **16** to compounds **17a** and **17b**, as well as the synthesis of heterocyclic compounds such as thiadiazole **19** from thioamide **18** have been investigated and are summarized in Scheme 3. In almost all cases the yields obtained with the new hypervalent compounds **9**, **11**, and **13** are similar or better than the yields with IBA **1**. This might be due to the complete solubility of the new reagents in acetone and acetonitrile as opposed to IBA, as this reagent has only limited solubility under the reaction conditions.

Scheme 3. Reactions with Hypervalent Iodine Compounds IBA **1**, **9**, **11**, and **13**



The novel reagents can also be used as stoichiometric oxidants for the selenium-catalyzed cyclization of the unsaturated acid **20** to butenolide **21** as shown in Scheme 4.[21] It was found that the addition of trifluoroacetic anhydride increases their reactivity in this reaction probably via a ligand exchange reaction to the corresponding trifluoroacetoxy derivatives. Even an in situ generation of the hypervalent iodine species from **6** and *m*CPBA was sufficient for a successful reaction to **21** (Scheme 4, footnote a).

Scheme 4. Synthesis of Lactones from Carboxylic Acid Derivatives **20** and **22**



[a] The hypervalent iodine compound was prepared in situ from **6**, *m*CPBA, and $(F_3CCO)_2O$ before addition of $(PhSe)_2$ and **20**.

Oxyfunctionalizations of ketones in the α-position with use of hypervalent iodine compounds as stoichiometric reagents are known[22]—very recently a catalytic procedure has been published.[23] The iodine derivatives **6**, (*Z*)-**8a**, (*Z*)-**8b**, and **10** have been successfully used as catalysts in the synthesis of ketolactone **23** from acid **22**, and yields up to 80% have been obtained.

In conclusion, these hypervalent iodine(III) reagents are novel oxidants for the facile oxidation of various substrates. They are rapidly prepared from easily accessible starting materials and offer similar reactivities to known derivatives.

Acknowledgment. We thank the Higher Education Commission (HEC), Pakistan (A.A.S., Z.A.K., U.F.), and the

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Deutsche Forschungsgemeinschaft, Germany (S.S.) for fellowships, Cardiff University, The Royal Society (S.S., B.W., T.W.), the University of Bonn, Germany (C.L.), the Ecole Supérieure de Chimie Organique et Minérale (ESCOM), France (N.C.), and the University of Nantes, France (G.M.) for support and the National Mass Spectrometry Service Centre, Swansea, for mass spectrometric data.

Supporting Information Available: Experimental procedures for the synthesis of compounds **5**,**6**, (*Z*)-**8a**, (*E*)-**8b**, (*Z*)-**8b**, **9**, **11**, **12**, **13**, **15**, **17a**, **17b**, **19**, **21**, and **23** and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9014688