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# Unexpected dehomologation of primary alcohols to one-carbon shorter carboxylic acids using *o*-iodoxybenzoic acid (IBX)†

Cite this: *Chem. Commun.*, 2014, **50**, 2758

Received 2nd December 2013,
Accepted 21st January 2014

DOI: 10.1039/c3cc49160a

www.rsc.org/chemcomm

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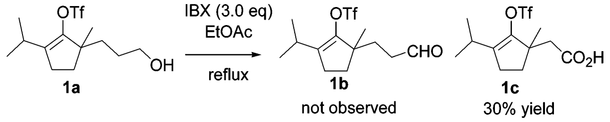
**A novel and efficient transformation of primary alcohols to one-carbon shorter carboxylic acids using IBX is reported. Mechanistic studies revealed that the combination of IBX and molecular iodine produces a different active hypervalent iodine species.**

The adjustment of carbon chain length is often crucial in organic synthesis. Dehomologation, as the necessary complement to homologation, is thus regarded as a fundamental reaction. However, even the dehomologation of simple substrates sometimes requires tedious multi-step strategies. For instance, primary alcohols may be oxidized to carboxylic acids and then subjected to the Hunsdiecker reaction to obtain the corresponding dehomologated alkyl halides. To the best of our knowledge, the simple dehomologation of primary alcohols has only been achieved using concentrated nitric acid[1] or Cr(VI) reagents,[2,3] and thus, both methods have limited scope. Herein, we report a novel dehomologation of primary alcohols to the corresponding one-carbon shorter carboxylic acids using *o*-iodoxybenzoic acid (IBX)[4] as a mild oxidant.

In the course of our studies on total synthesis of natural products, we attempted to prepare aldehyde **1b** *via* oxidation of precursor alcohol **1a** with IBX in refluxing EtOAc (Scheme 1). Surprisingly, the major product was one-carbon shorter carboxylic acid **1c**, albeit in modest yield. The expected product **1b** and its overoxidized product (carboxylic acid without carbon loss[5]) were not detected. In fact, the above reaction conditions were originally reported to provide aldehydes.[6] To the best of our knowledge, this dehomologation is yet to be reported under similar conditions. It was thought that the partial decomposition of IBX to a lower valent iodine species may affect this surprising and interesting dehomologation, because a light red color was observed as the reaction progressed, suggesting the generation of $I_2$. Because of the potential usefulness of the transformation and our interest in the reaction mechanism, we next investigated the scope of the reaction.



Scheme 1 Serendipitous observation of the IBX dehomologation reaction. Tf = trifluoromethanesulfonyl, IBX = *o*-iodoxybenzoic acid.

In an initial study, using *n*-heptanol (**2a**) as the model substrate, IBX dehomologation in the presence or absence of $I_2$ was explored (Table S1, ESI†). When $I_2$ was added to the reaction system, a shorter reaction time and a higher dehomologation ratio of *n*-hexanoic acid (**2c**) to *n*-heptanoic acid (**2d**) were observed. Solvent screening then disclosed that DMF yielded the best selectivity and the shortest reaction time. While an oxygen atmosphere provided a better yield, excellent **2c**/**2d** selectivity was retained even under an Ar atmosphere.

With the optimized conditions in hand, we then investigated the scope of the dehomologation reaction (Table 1). In all cases, little, if any, unhomologated carboxylic acid was obtained, demonstrating the high selectivity of the established conditions. Substituents including alkyl chloride (entry 2), cyclopropane (entry 3), aryl bromide (entry 8), nitrile (entry 9), anisole (entry 10), naphthalene (entry 11), phenyl ether (entry 12), benzyl ether (entry 13), and benzoate (entry 14) groups were tolerated in the reaction. Even 3-branched alcohols, including an adamantane subunit, gave good yields. Thus, the bulkiness of neighboring groups had only a limited effect on the rate and yield of the reaction (entries 4–6). In addition, both electron-donating and -withdrawing groups on the benzene ring in aromatic substrates did not alter the yield (entries 8–10). However, in contrast to the results with 3-branched alcohols (entries 5, 6 and 8–11), 2-branched alcohol **16a** gave the dehomologated ketone **16c** in only 5.5% yield,[7] together with unhomologated carboxylic acid as the major product (entry 15).

To clarify the reaction mechanism, the dehomologation of **2a** in deuterated DMF ($D_7$-DMF) was monitored *via* NMR analysis (Scheme 2). The reaction mixture was first stirred at room temperature for 1 h, and then the temperature was raised to 100 °C.

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† Electronic supplementary information (ESI) available: Experimental procedures, optimization of reaction conditions, and spectroscopic data. See DOI: 10.1039/c3cc49160a

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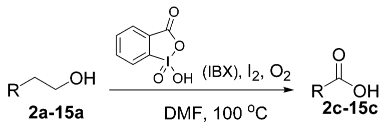
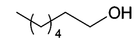
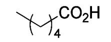
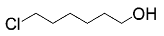
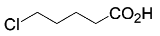
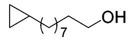
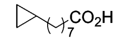
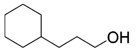
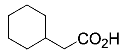
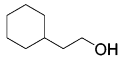
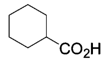
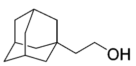
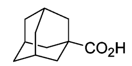
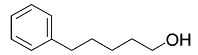
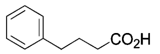
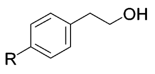
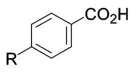
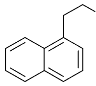
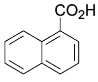
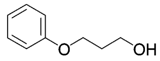
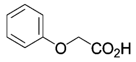
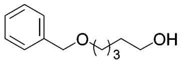
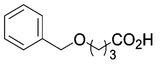
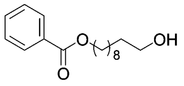
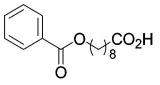
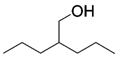
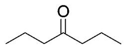
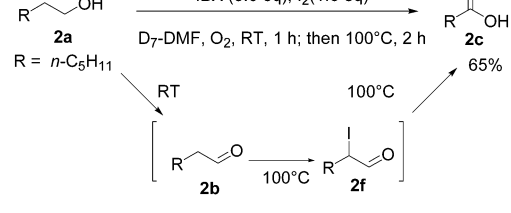
Table 1 IBX dehomologation with various primary alcohols[a]



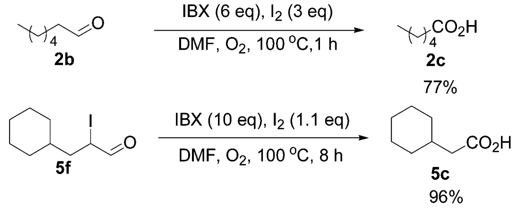
| Entry | Substrate | | Time (h) | Product | | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 |  | 2a | 7 |  | 2c | 74 |
| 2 |  | 3a | 3 |  | 3c | 97 |
| 3 |  | 4a | 3 |  | 4c | 99 |
| 4 |  | 5a | 3 |  | 5c | 73 |
| 5 |  | 6a | 3 |  | 6c | 81 |
| 6 |  | 7a | 9 |  | 7c | 69 |
| 7 |  | 8a | 3 |  | 8c | 72 |
| 8 |  R = Br | 9a | 3 |  R = Br | 9c | 100 |
| 9 | CN | 10a | 3 | CN | 10c | 100 |
| 10 | OMe | 11a | 3 | OMe | 11c | 90 |
| 11 |  | 12a | 3 |  | 12c | 99 |
| 12 |  | 13a | 18 |  | 13c | 82 |
| 13 |  | 14a | 4 |  | 14c | 57 |
| 14 |  | 15a | 21 |  | 15c | 91 |
| 15[c] |  | 16a | 3 |  | 16c | 5.5 |

[a] Reaction conditions: a mixture of alcohol **a** (0.25 mmol), IBX (2.0 mmol), and $I_2$ (0.40 mmol) in DMF (3.6 mL) was heated at 100 °C under an $O_2$ atmosphere for the indicated time. [b] The yield was determined by GC-MS with *n*-nonanoic acid as the internal standard. [c] IBX (10 eq.) and $I_2$ (1.1 eq.) were used and unhomologated carboxylic acid (41%) was also detected.

The yield of **2c** in this experiment was similar to that in Table 1 (entry 1). The $^1$H- and $^{13}$C-NMR analyses for the first 1 h indicated the oxidation of **2a** to aldehyde **2b** and formation of a small amount of 2-iodoaldehyde **2f**. Formation of **2b** and **2f** was also confirmed *via* GC-MS analysis using authentic samples.[8] After the reaction temperature was raised to 100 °C, **2b** was converted to **2f** and then further dehomologated to the carboxylic acid **2c**. In independent experiments (Scheme 3), aldehyde **2b** and iodoaldehyde **5f** were treated under IBX–$I_2$ conditions to afford the corresponding dehomologated carboxylic acids **2c** and **5c**, respectively, in good yields.[9] These observations suggest the intermediacy of the aldehyde and iodoaldehyde in the dehomologation of primary alcohols. Moreover, the reaction of *n*-heptanoic acid (**2d**) under optimal IBX–$I_2$ conditions did not lead to the formation of *n*-hexanoic acid, thus excluding the possibility of the generation of unhomologated carboxylic acid as an intermediate. In addition, the generation of $CO_2$ as a product was confirmed *via* $^{13}$C-NMR analysis of the reaction of a $^{13}$C-labeled substrate (Fig. S3, ESI†).



Scheme 2 IBX-mediated dehomologation of **2a** in $D_7$-DMF.



Scheme 3 IBX-mediated dehomologation of reaction intermediates **2b** and **5f**.

Additionally, NMR analysis of the reaction provided a clue to the active species that actually mediates dehomologation. Specifically, IBX was observed to be consumed *via* rapid reaction with $I_2$ to generate a species designated as **X**, which was the major detected hypervalent iodine species present during the conversion of the aldehyde **2b** to the carboxylic acid **2c**. Therefore, it is assumed that the newly formed compound **X** plays a key role in the novel dehomologation process. **X** was isolated in a nearly pure form as a colorless solid *via* filtration of an IBX–$I_2$ mixture without the added substrate alcohol. The NMR spectra of **X** are shown along with those of IBX, *o*-iodosobenzoic acid (IBA), and *o*-iodobenzoic acid (BA)[10] in Fig. 1 (for IR spectra, see ESI†). Notably, the aromatic H-3 proton in **X** is not observed in the $^1$H-NMR spectrum at room temperature, but can be seen in the spectrum obtained at 80 °C.[11] In addition, the melting point of **X** was observed to be 238–240 °C (dec.) and is also different from that of IBX (233 °C),[4a] IBA (234 °C),[12a] and BA (161.6–163 °C).[12b]

However, X-ray crystallographic analysis of **X** was not possible, and therefore, its structure remains unclear at this time. A tentative structure (Fig. 1a) is proposed based on the following evidence: (1) **X** forms *via* the reduction of IBX with $I_2$, and BA forms *via* the reduction of **X** with $I_2$, suggesting that the valence of the iodine atom in **X** is lower than that in IBX and higher than that in BA; (2) hydrolysis of **X** in aqueous DMF provided IBA at room temperature. This observation suggests that the iodine atoms in **X** and IBA may have the same oxidation level (data not shown); and (3) the NMR spectra of **X** are very different from those of IBX and BA but similar to those of IBA (Fig. 1).

We next turned our attention to the role of **X** in this transformation (Scheme 4). As shown in Scheme 2, primary alcohols

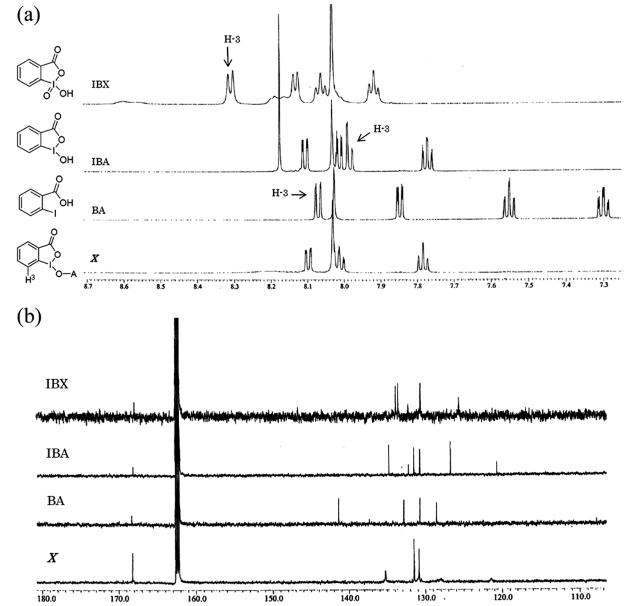
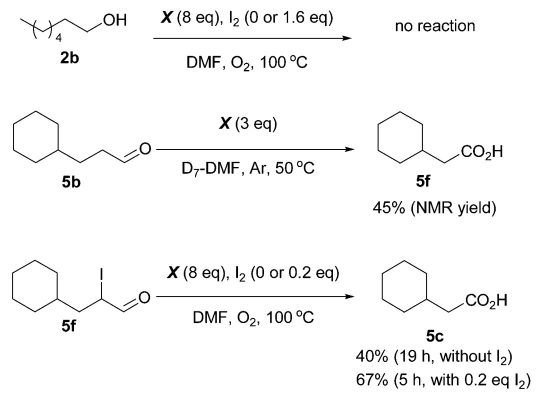


Fig. 1 Comparison of the $^{1}$H- and $^{13}$C-NMR spectra of **X**, IBX, IBA, and BA. All spectra were recorded in $D_7$-DMF at room temperature. (a) $^{1}$H-NMR spectra (600 MHz, 7.3 to 8.7 ppm). (b) $^{13}$C-NMR spectra (150 MHz, 90 to 180 ppm). A ≠ H.



Scheme 4 Reactivity of the hypervalent iodine species **X**.

are oxidized to their corresponding aldehydes and then dehomologated to the corresponding carboxylic acids. First, it was determined that the addition of **X** to alcohol **2a** did not provide the corresponding aldehyde in the presence or absence of $I_2$. This implies that the aldehyde intermediate is generated *via* IBX oxidation. On the other hand, aldehydes (*e.g.*, **5b**) react smoothly with **X** to afford the corresponding 2-iodoaldehydes (*e.g.*, **5f**), which are dehomologated to the corresponding carboxylic acids at 100 °C. Notably, in the presence of a catalytic amount of $I_2$, the dehomologation with **X** is accelerated and proceeds in higher yield. These results suggest that both **X** and some inorganic iodine species may work together during the carbon–carbon bond cleavage step. For comparison, the combination of molecular iodine with Dess–Martin periodinane (DMP) or (diacetoxyiodo)benzene ($PhI(OAc)_2$) was investigated using *n*-heptanal (**2b**) as the dehomologation substrate. Neither alternative hypervalent iodine species yielded results comparable to those obtained with IBX or species **X**. In fact, the desired dehomologated product **2c** was obtained in less than 20% yield with DMP and was not detected with $PhI(OAc)_2$.

During the last decade, IBX has attracted intense interest,[13] not only as a reagent for the oxidation of alcohols to aldehydes and ketones,[4b] but also as a mild and selective reagent in other surprisingly versatile transformations.[13c–j] Therefore, it has been widely applied in the total synthesis of complex natural products.[13f] The novel dehomologation of primary alcohols conducted by us stands as a new member of this class of reactions and will also be useful for the synthesis of functional molecules.

In summary, a novel, highly selective dehomologation of primary alcohols to their corresponding one-carbon shorter carboxylic acids using the mild, hypervalent iodine reagent IBX was developed. A stable hypervalent iodine species was isolated and shown to be crucial for the dehomologation. Further study of the reaction mechanism is currently underway.[14]

K. Itto thanks JSPS for a Research Fellowship for Young Scientists. We thank Professor Yasunori Ohba and the late Professor Seigo Yamauchi (Institute of Multidisciplinary Research for Advanced Materials, Tohoku University) for helpful discussions.

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8 Aldehydes and alpha-iodoaldehydes were characterized as key intermediates *via* GC-MS and NMR analyses. The characterization of other reaction intermediates and the examination of their possible involvement in this dehomologation are underway.
9 This result implied that our reaction conditions were also effective for the dehomologation of aldehydes, and may be a promising supplemental method for the Norrish I photocleavage and the transition-metal catalyzed deformylation of aldehydes, while the latter two methods usually could only produce the unfunctionalized dehomologated alkanes.
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