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COMMUNICATION

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

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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.

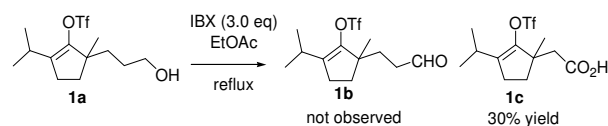
The adjustment of carbon chain length is often crucial in organic synthesis. Dehomologation, as the necessary complement to homologation, is thus regarded as a fundamental reaction. However, even the dehomologation of simple substrates sometimes requires tedious multi-step strategies. For instance, primary alcohols may be oxidized to carboxylic acids and then subjected to the Hunsdiecker reaction to obtain corresponding dehomologated alkyl halides. To the best of our knowledge, the simple dehomologation of primary alcohols has only been achieved with concentrated nitric acid¹ or Cr (VI) reagents,^{2,3} and thus, both methods have limited scope. Herein, we report a novel dehomologation of primary alcohols to corresponding one-carbon shorter carboxylic acids using *o*-iodoxybenzoic acid (IBX)⁴ as a mild oxidant.

In the course of our studies on natural product total synthesis, 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 loss⁵) were not detected. In fact, the above reaction conditions were originally reported to provide aldehydes.⁶ To the best of our knowledge, this dehomologation has 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 I₂. Because of the potential usefulness of the transformation and our interest in the reaction mechanism, we next investigated the scope of the reaction.

In an initial study, using *n*-heptanol (**2a**) as the model substrate, IBX dehomologation in the presence or absence of I₂ was explored (Table S1, ESI). When I₂ 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**) was 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, 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).

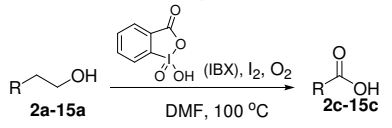


Scheme 1 Serendipitous observation of the IBX dehomologation reaction. Tf = trifluoromethanesulfonyl, IBX = *o*-iodoxybenzoic acid.

To clarify the reaction mechanism, the dehomologation of **2a** in deuterated DMF (D₇-DMF) was monitored via NMR (Scheme 2). The reaction mixture was first stirred at room temperature for 1 h, and then the temperature was raised to 100°C. The yield of **2c** in this experiment was similar to that in Table 1 (entry 1). The ¹H- and ¹³C-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** were 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-I₂

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-I₂ 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 CO₂ as a product was confirmed via ¹³C-NMR analysis of the reaction of a ¹³C-labeled substrate (Figure S3, ESI).

Table 1 IBX dehomologation with various primary alcohols^a



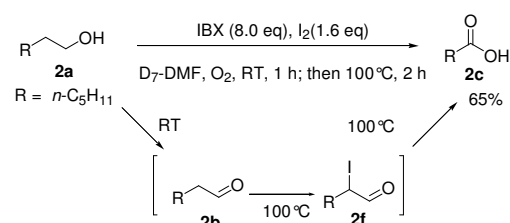
| Entry | Substrate | Time (h) | Product | Yield ^b (%) |
|-----------------|-----------|-----------------|---------|------------------------|
| 1 | | 2a , 7 | | 2c , 74 |
| 2 | | 3a , 3 | | 3c , 97 |
| 3 | | 4a , 3 | | 4c , 99 |
| 4 | | 5a , 3 | | 5c , 73 |
| 5 | | 6a , 3 | | 6c , 81 |
| 6 | | 7a , 9 | | 7c , 69 |
| 7 | | 8a , 3 | | 8c , 72 |
| 8 | | 9a , 3 | | 9c , 72 |
| 9 | | 10a , 3 | | 10c , 100 |
| 10 | | 11a , 3 | | 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 I₂ (0.40 mmol) in DMF (3.6 mL) was heated at 100 °C under an O₂ 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 I₂ (1.1 eq) were used and unhomologated carboxylic acid (41%) was also detected.

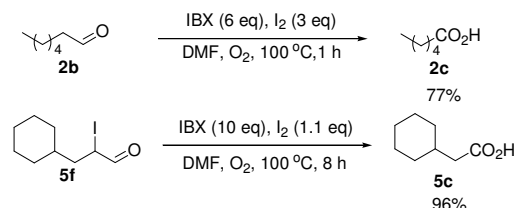
Additionally, NMR analysis of the reaction provided a clue to the active species that actually mediates dehomologation. Specifically, IBX was observed to be consumed via rapid reaction with I₂ to generate a species designated as **X**, which was the major detected hypervalent iodine species present during 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-I₂ mixture without 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 ¹H-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 I₂, and BA forms via the reduction of **X** with I₂, 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).



Scheme 2 IBX-mediated dehomologation of **2a** in D₇-DMF.



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

We next turned our attention to the role of **X** in this transformation (Scheme 4). As shown in Scheme 3, primary alcohols are oxidized to their corresponding aldehydes and then dehomologated to 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 I₂. 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 I₂, 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.

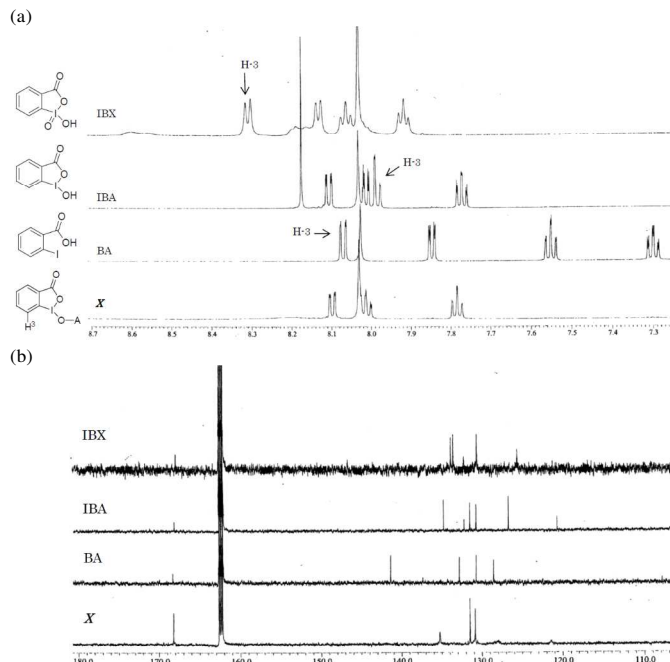
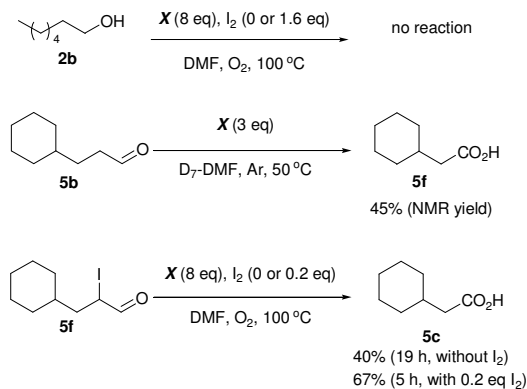


Fig. 1 Comparison of the ¹H- and ¹³C-NMR spectra of X, IBX, IBA, and BA. All spectra were measured in D₇-DMF at room temperature. (a) ¹H-NMR spectra (600 MHz, 7.3 to 8.7 ppm). (b) ¹³C-NMR spectra (150 MHz, 90 to 180 ppm). A ≠ H.



Scheme 4 Reactivity of the hypervalent iodine species X.

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

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, optimization of reaction conditions, and spectroscopic data. See DOI: 10.1039/b000000x/

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- 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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