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IBX-Mediated α-Hydroxylation of α-Alkynyl Carbonyl Systems. A Convenient Method for the Synthesis of Tertiary Alcohols

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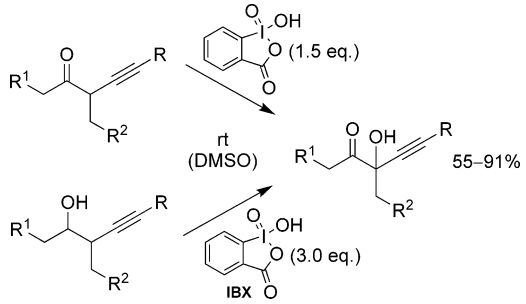
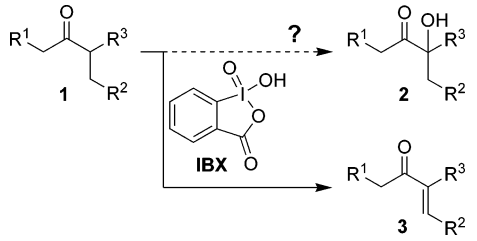


IBX (*o*-iodoxybenzoic acid) is an excellent reagent for the α-hydroxylation of α-alkynyl carbonyl compounds without giving dehydrogenation products. The convenient procedure proves to be useful for the construction of a variety of tertiary alcohols (55−91%) under mildly acidic conditions.

The synthetic use of *o*-iodoxybenzoic acid (IBX)[1] as an oxidizing agent was initially demonstrated by Frigerio and Santagostino in 1994 for the oxidation of alcohols to carbonyl compounds.[2] Since then, the synthetic value of IBX has been extended to a variety of other useful oxidative transformations.[3−5] Recently, some interesting conversions have been described which proceed probably via intramolecular delivery of oxygen and expulsion of iodosobenzoic acid (IBA) using the oxide ligand of IBX as a nucleophile.[6−9] To date, there has been no report of α-hydroxylation of carbonyl compounds through IBX-mediated oxygen transfer. Such transformations have been traditionally accomplished by the reaction of enolates and silyl enol ethers with oxygen electrophiles,[10] although its synthetic utility is somewhat depreciated by a lack of general routes to generate tertiary alcohols.[11,12] We disclose herein an efficient approach to α-substituted α-hydroxy α-alkynyl carbonyl compounds by an oxidation in the α-position of α-alkynyl carbonyl compounds and 2-alkynyl alcohols mediated by IBX.

SCHEME 1. IBX-Induced α-Hydroxylation of Carbonyl Compounds



Nicolaou and co-workers developed an excellent method for the dehydrogenation of aldehydes and ketones that provides α,β-unsaturated carbonyl compounds using IBX at elevated temperatures (**1** → **3**, Scheme 1).[5] Preliminary work has shown that reaction of 2-phenylcyclohexanone ($-R^1R^2- = -(CH_2)_2-$, R^3 = Ph) with 1.5 equiv of IBX in DMSO at 40 °C produced a mixture of 2-hydroxy-2-phenylcyclohexanone (31%), 6-phenylcyclohex-2-enone (33%), and traces of 2-phenylcyclohex-2-enone after 24 h. This result indicates that a tertiary alcohol is formed in the presence of stoichiometric amounts of IBX with the dehydrogenation between R^2 and R^3 (with R^3 = Ph) being almost suppressed. Unfortunately, the 2-position and the 6-position of 2-phenylcyclohexanone were simultaneously oxidized by IBX without favoring the 2-position. Encouraged by this result, it was planned to find suitable substrates **1** for the selective α-hydroxylation of carbonyl compounds via IBX-mediated oxygen transfer under formation of tertiary alcohol **2** (Scheme 1).

In an attempt to obtain selectivity for tertiary alcohol **2**, we explored substrates, which contain sterically less

(1) For the synthesis of IBX, see: (a) Hartmann, C.; Meyer, V. *Chem. Ber.* **1893**, *26*, 1727−1732. (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537−4538.

(2) (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019−8022. (b) De Munari, S.; Frigerio, M.; Santagostino, M. *J. Org. Chem.* **1996**, *61*, 9272−9279. For recent examples, see: (c) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001−3003. (d) Thottumkara, A. P.; Bowsher, M. S.; Vinod, T. K. *Org. Lett.* **2005**, *7*, 2933−2936.

(3) For reviews, see: (a) Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2812−2814. (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523−2584. (c) Kumar, I. *Synlett* **2005**, 1488−1489. (d) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656−3665.

(4) (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625−628. (b) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2525−2529. (c) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2001**, *123*, 3183−3185. (d) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192−5201. (e) Schulze, A.; Giannis, A. *Adv. Synth. Catal.* **2004**, *346*, 252−256.

(5) (a) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596−7597. (b) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245−2258. (c) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993−996. (d) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996−1000.

(6) Besides the more likely SET-based mechanism, an ionic mechanism was discussed for the IBX-mediated dehydrogenation of carbonyl compounds: ref 5b.

(7) The reaction of *p*-cresol with IBX gave 4-methyl-1,2-bisphenol: ref 5b.

(8) The benzylic oxidation using IBX can be explained via intramolecular oxygen transfer: ref 5b.

(9) (a) Magdziak, D.; Rodriguez, A. A.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2002**, *4*, 285−288. (b) Shibuya, M.; Ito, S.; Takahashi, M.; Iwabuchi, Y. *Org. Lett.* **2004**, *6*, 4303−4306.

(10) (a) Jones, A. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 7, pp 151−191. (b) Davis, F. A.; Chen, B.-C. In *Methods of Organic Chemistry (Houben-Weyl)*, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: New York, 1995; Vol. E21b, pp 4497−4518. (c) Chen, B.-C.; Zhou, P.; Davis, F. A.; Ciganek, E. *Org. React.* **2003**, *62*, 1−356.

(11) For selected examples for the synthesis of tertiary alcohols via α-hydroxylation of carbonyl compounds, see: (a) Davis, F. A.; Weismiller, M. C. *J. Org. Chem.* **1990**, *55*, 3715−3717. (b) Shea, K. J.; Sakata, S. T. *Tetrahedron Lett.* **1992**, *33*, 4261−4264.

(12) Christoffers, J.; Baro, A.; Werner, T. *Adv. Synth. Catal.* **2004**, *346*, 143−151.

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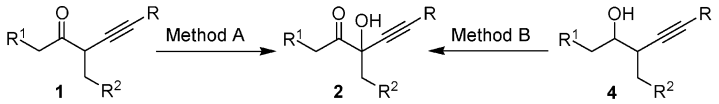
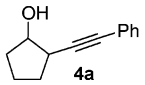
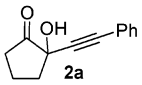
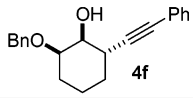
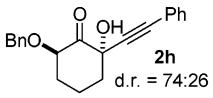
TABLE 1. IBX-Mediated Formation of 2 from 1 and 4[a]



entry	substrate[b]	product	method	time [h]	yield of **2** [%][c]
1	 **4a**	 **2a**	**B**	12	55
2	**1a**: R = Ph	**2b**	**A**	20	84
3	**1b**: R = 3-thienyl	**2c**	**A**	17	78
4[d]	**1c**: R = CH_2CH_2OTBS	**2d**	**A**	12	70
5[e]	**1d**: R = $(CH_2)_3OTHP$	**2e**	**A**	16	81
6	**4b**: R = Ph	**2b**	**B**	15	80
7	**4c**: R = 2-pyridyl	**2f**	**B**	5	73
8[f]	**4d**: R = TMS	**2g**	**B**	12	91
9[e]	**4e**: R = $(CH_2)_3OTHP$	**2e**	**B**	21	74
10[g,h]	 **4f**	 **2h** d.r. = 74:26	**B**	12	68[i,j]
11	**4g**: R = Ph	**2i**	**B**	12	77
12	**4h**: R = TMS	**2j**	**B**	14	74

[a] Conditions: (a) **Method A**: 0.64 mmol **1**, 1.5 equiv IBX, 23 °C, [substrate] = 0.5 M, DMSO; (b) **Method B**: 0.42 mmol **4**, 3.0 equiv IBX, 23 °C, [substrate] = 0.5 M, DMSO. [b] All compounds **4** are *trans* isomers. [c] Isolated yield of **2** after column chromatography. Average of two experiments. [d] TBS = *tert*-butyldimethylsilyl. [e] THP = 2-tetrahydropyranyl. [f] TMS = trimethylsilyl. [g] Bn = benzyl. [h] Diastereomeric ratio of **2h** determined by ^{1}H NMR of crude mixture. [i] Yield of the shown diastereoisomer **2h** after column chromatography (d.r. > 95:5). [j] The relative configuration of **2h** was determined by NOESY experiments.

demanding alkyne substituents for R^3 (R^3 = C≡CR). Thus, we examined initially the hydroxylation of 2-(2-phenylethynyl)cyclohexanone (**1a**) to tertiary alcohol **2b** using 1.5 equiv of IBX in DMSO. Indeed, IBX was effective, giving alcohol **2b** in 84% yield after 20 h at room temperature (Table 1, entry 2). To our delight, the formation of α,β-unsaturated carbonyl compounds through dehydrogenation was not observed under these conditions.[13] As summarized in Table 1, the conversion of various ketones **1** to the corresponding tertiary alcohols **2** can be accomplished in good yields under notably practical conditions: 1.5 equiv of IBX, DMSO (0.5 M), 23 °C, reaction times 12−20 h (method A) (entries 2−5). Since IBX is known to oxidize alcohols, it was also possible to obtain the tertiary alcohols **2** starting from 2-alkynyl alcohols **4** in the presence of 3.0 equiv of IBX (method B) (entries 1, 6−12),[14] a modification that is particularly advantageous with 2-alkynylcycloalkanones that undergo a facile isomerization to the conjugated allenones. In the case of *trans*-2-alkynylcyclopentanol **4a**, for example, clean oxidation to the corresponding five-membered ketone **1** is sometimes difficult,[15] but treatment with 3.0 equiv of IBX led to the formation of 2-hydroxycyclopentanone **2a** in moderate yield (entry 1). With these methods in hand, 2-hydroxy carbonyl compounds **2** were formed in good yields with R being aryl and heteroaryl substituents (entries 1−3, 6, 7, 10, 11). Moreover, substrates with alkyl substituents at the alkyne terminus were effectively converted into the tertiary alcohols (entries 4, 5, and 9). The reaction of substrate **4d** (R = TMS) with 3.0 equiv of IBX also took place in high yield (entry 8). Although not extensively examined at this point, functional groups such as ether (entry 10), silyl ether (entry 4), and acetal (entries 5 and 9) are well tolerated. Substrates containing a six-membered ring system gave the tertiary alcohols **2** as oxidation products in excellent regioselectivity, as did substrates containing a simple acyclic skeleton (entries 11 and 12). The oxidation of benzyl ether **4f** proceeded in moderate diastereoselectivity (dr = 74:26) with the hydroxy group favoring a position *trans* to the benzyloxy group (entry 10).

Several additional observations merit note. This method is limited to the conversion of ketones **1** and secondary alcohols **4**; aldehydes and primary alcohols were not

(13) Other hypervalent iodine compounds were not used in such α-hydroxylations.

(14) Ketone **1** was detected as the intermediary occurring species in the transformation **4** → **2** by capillary gas chromatography and by thin-layer chromatography.

(15) (a) Carlson, R. G.; Cox, W. W. *J. Org. Chem.* **1977**, *42*, 2382−2386. (b) Murray, T. F.; Samsel, E. G.; Varma, V.; Norton, J. R. *J. Am. Chem. Soc.* **1981**, *103*, 7520−7528.

transformed at room temperature or at elevated temperatures. It was not necessary to take special precautions to exclude air and moisture from the reaction mixture. To ensure reproducible yields, it was advantageous to add IBX in two portions to the reaction mixture.[16] A concentration of 0.5 M in the substrate was ideal to achieve good conversion in the oxidation of both the ketones **1** and the alcohols **4**. A too high concentration of IBX in DMSO (>2.0 M) led to solubility problems, while concentrations <0.2 M resulted in significantly lower yields due to competitive reduction of IBX by DMSO.[5b] During the reaction course, a white precipitate was formed which was mainly composed of IBA.[5b] The alkynyl moiety appears to be essential for the rapid and clean oxygen transfer from IBX at room temperature.[17] Performing the hydroxylation at 60 °C gave a significant amount of unidentified decomposition products with the tertiary alcohol **2** remaining the main product.[18] Reaction of carbonyl compounds containing alkyl substituents at C2 rather than alkynyl did not take place in the presence of IBX at room temperature. At elevated temperatures, these substrates (e.g., 2-methylcyclohexanone) did not provide the corresponding tertiary alcohols, forming instead product mixtures which mainly contained dehydrogenation products.[19]

In conclusion, a new method for the selective α-hydroxylation of α-alkynyl carbonyl compounds was developed. The IBX-mediated reaction can be conducted under convenient conditions to provide tertiary alcohols. As enolate formation by reaction with bases is not required, this mildly acidic method is a practical alternative to previously reported α-hydroxylation procedures.[10c] Further studies, including detailed investigations into mechanism and applications in total synthesis, are currently underway.

Experimental Section

General Experimental Details. Alkynyl alcohols **4** were prepared according to published procedures by alkynylation of oxiranes [LiC≡CR (1 equiv), $BF_3{\cdot}OEt_2$ (1 equiv), −78 °C, THF].[20] All α-alkynyl carbonyl compounds **1** were synthesized by the oxidation of the corresponding alkynyl alcohols **4** with PCC.[21] DMSO contained less than 0.005% of water. IBX was prepared according to a procedure developed by Santagostino and coworkers.[1b]

2-Hydroxy-2-(2-phenylethynyl)cyclohexanone (2b). General Procedure for the IBX-Mediated α-Hydroxylation of α-Alkynyl Carbonyl Compounds 1 (Method A). IBX (0.48 mmol, 134 mg) was added to a solution of ketone **1a** (82 mg, 0.64 mmol) in DMSO (1.3 mL), and the reaction vial was sealed, protected from light, and stirred at room temperature. After 3 h, additional IBX (0.48 mmol, 134 mg) was added. The reaction mixture was then stirred at room temperature for 17 h (until TLC analysis indicated complete consumption of starting material) and diluted with CH_2Cl_2 (10 mL), and stirring was continued for 30 min to precipitate the insoluble byproduct, which was removed by filtration. The precipitate was washed with CH_2Cl_2 (2 × 5 mL), and the combined filtrate was subsequently diluted with aqueous saturated $NaHCO_3$ (20 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (10% Et_2O/pentane) to afford **2b** as a pale yellow oil (115 mg, 0.54 mmol, 84%).

General Procedure for the IBX-Mediated α-Hydroxylation Starting from 2-Alkynyl Alcohols 4 (Method B). IBX (0.42 mmol, 118 mg) was added to a solution of alcohol **4b** (84 mg, 0.42 mmol) in DMSO (0.9 mL), and the reaction vial was sealed, protected from light, and stirred at room temperature. After 4 h, additional IBX (0.84 mmol, 235 mg) was added. The reaction mixture was then stirred at room temperature for 11 h (until TLC analysis indicated complete consumption of starting material) and diluted with CH_2Cl_2 (10 mL), and stirring was continued for 30 min to precipitate the insoluble byproduct, which was removed by filtration. The precipitate was washed with CH_2Cl_2 (2 × 5 mL), and the combined filtrate was subsequently diluted with aqueous saturated $NaHCO_3$ (20 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were washed with water (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography on silica (10% EtOAc/pentane) to afford **2b** as a pale yellow oil (72 mg, 0.34 mmol, 80%): R_f 0.39 (20% EtOAc/pentane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.69 (dt, J = 13.6, 3.9 Hz, 1 H), 1.76 (dt, J = 3.5, 13.1 Hz, 1 H), 1.91−1.93 (m, 1 H), 2.12 (tt, J = 13.6, 3.6 Hz, 1 H), 2.11−2.20 (m, 1 H), 2.57−2.61 (m, 2 H), 3.04 (dt, J = 6.2, 13.7 Hz, 1 H), 4.32 (s, 1 H), 7.33−7.38 (m, 3 H), 7.46 (dd, J = 7.3, 1.4 Hz, 2 H); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 22.9, 27.7, 37.3, 42.5, 74.1, 87.5, 87.8, 122.0, 128.3, 128.8, 131.8, 207.5; LRMS (EI) 214 (80) [M^+], 185 (62), 157 (58), 129 (100); HRMS 214.0993 [214.0994 calcd for $C_{14}H_{14}O_2$ (M^+)].

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Supporting Information Available: Product characterization data and copies of ^{1}H and ^{13}C NMR spectra for tertiary alcohols **2a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Adding IBX at once to the reaction mixture gave varying yields for the conversion **1a** → **2b** (51−88%).

(17) The origin of this effect remains unclear.

(18) A facile dehydration of the tertiary alcohols **2** giving α,β-unsaturated carbonyl compounds **3** was not observed under these conditions.

(19) Tertiary alcohols were not detected as intermediary species in the IBX-mediated dehydrogenation of carbonyl compounds.

(20) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391−394.

(21) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647−2650.