A New Method for the One-Step Synthesis of α,β-Unsaturated Carbonyl Systems from Saturated Alcohols and Carbonyl Compounds

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Despite their ubiquity and utility in organic chemistry, the synthesis of α,β-unsaturated carbonyl compounds is often a tedious and sometimes challenging transformation. Several methods to effect this operation have been developed over the years.[1] Most of these protocols rely on highly toxic selenium reagents in one- or two-step procedures.[2] Another regularly employed tactic involves palladium-catalyzed oxidation of the enol-ethers derived from the carbonyl compound.[3] We surmised that the keto−enol equilibrium inherent in carbonyl systems might be exploited in a new way to selectively furnish the desired α,β-unsaturated systems if a suitably mild and stable oxidizing agent was utilized to capture the fleeting tautomeric form (see Figure 1). Our recent explorations with periodinanes[4] led us to propose the cheap and nontoxic IBX[5] (*o*-iodoxybenzoic acid) oxidizing reagent as a suitable candidate to effect this transformation. Since IBX is known to oxidize alcohols,[5] the prospect of accomplishing multiple oxidative processes in one operation was particularly enticing. Herein we present a general method for mild, swift, and highly efficient conversion of alcohols, ketones, and aldehydes to α,β-unsaturated carbonyl compounds in one pot.

We first examined the proposed reaction with cyclooctanol (**1**, Scheme 1) to determine its feasibility. To our delight, **1** was smoothly oxidized to **5** in 77% isolated yield upon exposure to 2.0 equiv of IBX at 55 °C in fluorobenzene (or toluene)−DMSO (ca. 2:1) for 3 h. Since traces of the dienone **6** were observed under these conditions, we enlisted 4.0 equiv of IBX at 85 °C and obtained an 80% isolated yield of **6**.

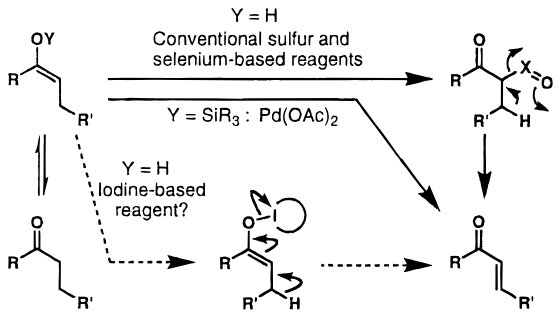
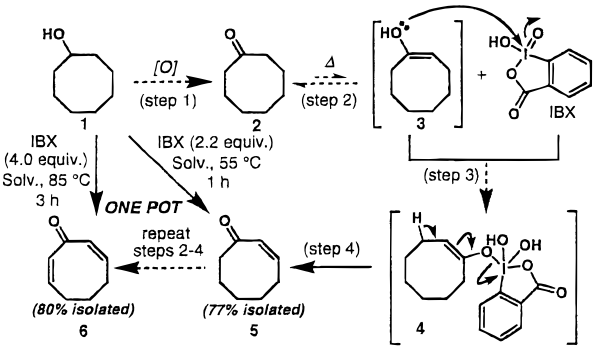


Figure 1. Mechanistically inspired design of a process for oxidation adjacent to a C=O bond.

Scheme 1. Mechanistic Rationale and Proof of Principle for the IBX-Induced Synthesis of α,β-Unsaturated Systems from Alcohols and Ketones[a]



[a] Solvent (Solv.) = fluorobenzene (or toluene)−DMSO (ca. 2:1)

This new reaction is remarkably general, high-yielding, and tolerant of a range of functionalities as demonstrated in Table 1. Thus, IBX-mediated dehydrogenated steroidal and terpenoid systems[6] (entries 1−5) are controllable for access to higher levels of unsaturation (entries 2 and 4, Table 1), react at six-membered-ring sites faster than at five-membered (entries 3 and 4, Table 1), and are amenable to oxidation cascades (entry 5, three oxidations in one pot). A range of small (Scheme 1, and entries 6−8 and 14−16, Table 1) and large (entries 9−13, Table 1) ring ketones and alcohols are easily and controllably (Scheme 1 and entries 8, 10, and 13, Table 1) oxidized. Substitution at the α- and β-sites (α, entry 14; β, entries 15 and 18) of the carbonyl system does not hinder the reaction, nor does it diminish its efficiency. The tandem oxidation of the decalin diol in entry 17 to the corresponding dienone in one pot and in 52% isolated yield is also impressive. Oxidations of complex five-membered-ring systems (entry 19) and simple acyclic substrates (entries 20−22) proceed smoothly. The reaction is easily controllable for the introduction of varying levels of unsaturation as in the case of steroids (vide supra) and as demonstrated by entries 23 and 24. Primary alcohols are also conveniently converted into the corresponding α,β-unsaturated aldehydes (entries 25−29), and in a controlled fashion (entry 26). The process works admirably well even in the presence of nitrogen-based functional groups (entries 28 and 29) and isolated alkenes (entry 27).[7]

Since IBX is itself a mild acid, we probed the effect of added base or acid on the reaction. Addition of catalytic *p*-TsOH (0.3 equiv) tended to significantly accelerate the reaction (entry 22, Table 1), while addition of pyridine (1.0 equiv) decreased the rate of the reaction (entry 12, Table 1) yet did not effect the isolated yield after extended reaction times. This feature should allow even extremely acid-labile carbonyl compounds and alcohols to enter smoothly into the process of unsaturation.

In conclusion, we have discovered a new and general synthetic reaction for the oxidation of a range of alcohols, ketones, and

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(1) For a review of halogenation−dehydrohalogenation reactions and sulfur-, selenium-, and palladium-based methods for oxidation adjacent to the C=O bond, see: Buckle, D. R.; Pinto, I. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 7, pp 119−146.

(2) For a comprehensive list of these reagents, see: Larock, R. C. *Comprehensive Organic Transformations*; John Wiley & Sons: New York, 1999; pp. 251−256. See also: Nicolaou, K. C.; Petasis, N. A. *Selenium in Natural Products Synthesis*; CIS, Inc.: Philadelphia, 1984; Chapter 3.

(3) See: (a) refs 1 and 2. (b) Ito, Y.; Hirato, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011−1013.

(4) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 622−625. Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625−628. Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Vega, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2525−2529.

(5) First preparation of IBX: Hartman, C.; Meyer, V. *Chem. Ber.* **1893**, *26*, 1727. For a superior route to IBX, see: Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537−4538. Introduction of the acronym "IBX": Katritzky, A. R.; Duell, B. L.; Gallos, J. K. *Org. Magn. Reson.* **1989**, *27*, 1007−1011. Use as a selective oxidant for alcohols: Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019−8022. Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 3485−3488.

(6) For the use of benzeneseleninic anhydride in refluxing PhCl to perform similar oxidations in steroidal systems, see: (a) Barton, D. H. R.; Brewster, A. G.; Hui, R. A. H. F.; Lester, D. J.; Ley, S. V.; Back, T. G. *J. Chem. Soc., Chem. Commun.* **1978**, 952−954. (b) Barton, D. H. R.; Godfrey, C. R. A.; Morzycki, J. W.; Motherwell, W. B.; Ley, S. V. *J. Chem. Soc., Perkin Trans 1* **1982**, 1947−1952.

(7) From our previously published work[4] with IBX reactions under similar conditions it is surmised that silyl ether, acetate, benzoate, acetal, and *p*-methoxyphenyl groups are stable under the reaction conditions employed in the present process.

(8) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44−122.

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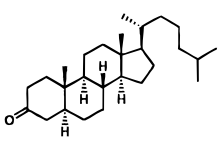
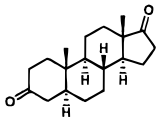
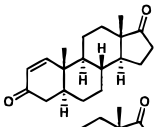
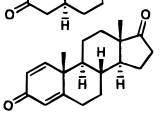
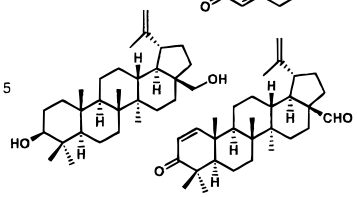
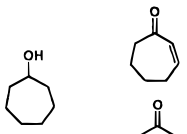
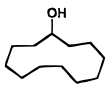
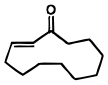
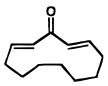
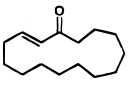
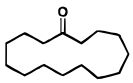
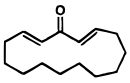
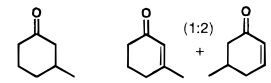
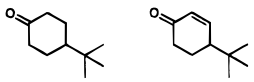
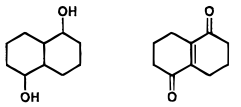
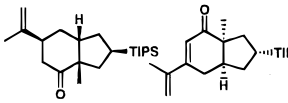
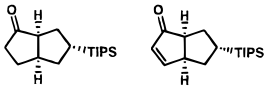
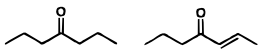
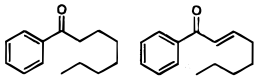
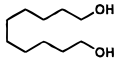
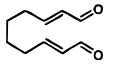
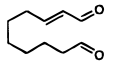
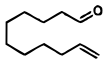
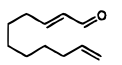
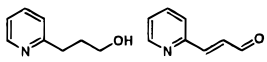
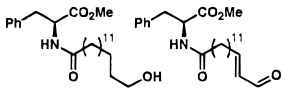
Table 1. Synthesis of α,β-Unsaturated Systems from Alcohols, Aldehydes, and Ketones

Entry	Substrate[a]	Product	Conditions[b]	Yield (%)[c]
1			24 h/65 °C 1.5 equiv	80[d]
2			48 h/85 °C 4.0 equiv	71
3			24 h/70 °C 1.5 equiv	84[e]
4			48 h/85 °C 4.0 equiv	72
5			12 h/85 °C 6.0 equiv	68
6			2 h/65 °C 2.3 equiv	88
7			4 h/60 °C 2.0 equiv	83
8			24 h/80 °C 3.0 equiv	74
9			24 h/65 °C 2.3 equiv	85
10			24 h/85 °C 4.0 equiv	71
11			24 h/65 °C 2.0 equiv	83[f]
12			60 h/65 °C 3.0 equiv *1.0 equiv py*	80[g]
13			24 h/85 °C 4.0 equiv	69
14			4 h/75 °C 2.0 equiv	85
15			10 h/65 °C 2.0 equiv	76[h]
16			2 h/70 °C 1.5 equiv	89
17			18 h/85 °C 6.0 equiv	52
18			36 h/85 °C 4.0 equiv	85
19			12 h/85 °C 2.0 equiv	87
20			3 h/65 °C 1.3 equiv	83
21			48 h/85 °C 6.0 equiv	55
22			8 h/85 °C 6.0 equiv *0.3 equiv p-TsOH*	86
23			72 h/70 °C 2.0 equiv	58
24			24 h/85 °C 4.0 equiv	60
25			24 h/85 °C 8.0 equiv	78
26			12 h/70 °C 5.0 equiv	40[i]
27			12 h/80 °C 2.0 equiv	58
28			12 h/70 °C 4.0 equiv	84
29			12 h/65 °C 2.5 equiv	86

[a] All substrates were commercially available except for those in entries 18, 19, and 29, which were prepared by standard methods. [b] For a general procedure see Supporting Information. [c] Isolated yield of spectroscopically pure compounds. For full characterization of new compounds, see Supporting Information. [d] Plus 7% of isolated dienone. [e] Plus 4% of isolated dienone. [f] Plus 8% of isolated dienone. [g] Plus 6% of isolated dienone. [h] Isolated yield of separable isomers. [i] Plus 5% of isolated di-enal. py = pyridine, TIPS = triisopropylsilyl.

aldehydes to the corresponding α,β-unsaturated species in one pot using the cheap and nontoxic IBX reagent under mild conditions. By merely adjusting the stoichiometry of IBX, temperature, and times employed, the reaction is easily programmed to provide varying degrees of unsaturation (a task not possible using existing methods). As such, this IBX-based method is expected to have widespread use in organic synthesis as a viable alternative to conventional reagents (e.g. halogen-, S-, Se-, Pd-based). Furthermore, the mild conditions involved should permit sequential reaction processes (e.g. cycloadditions) to take place in the same pot leading to rapid generation of molecular complexity. Studies along these lines, detailed mechanistic investigations, and applications to natural product synthesis[8] will be reported in due course.

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Supporting Information Available: Full experimental details and spectral data for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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