Selective Oxidation at Carbon Adjacent to Aromatic Systems with IBX

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A number of new synthetic technologies based on the reactivity of the periodinane reagents DMP and IBX have recently been reported from these laboratories.[1] These reactions include the IBX-induced cyclization of unsaturated anilides (Figure 1A),[1b] whose single-electron transfer (SET) mechanism was recently elucidated,[2] and the introduction of unsaturation next to carbonyl groups,[1d] now also believed to proceed, by analogy, via a SET mechanism (Figure 1B). On the basis of these mechanistic rationales, we hypothesized that benzylic positions could be oxidized by IBX via a SET mechanism as postulated in Figure 1C. If selective and easily controllable, such a process could be a valuable tool in organic synthesis in view of the ready availability and robustness of the potential substrates and widespread utility of the corresponding oxidized products.[4] Herein, we report the realization, scope, and generality of such a process, and demonstrate the remarkable chemoselectivity of IBX-mediated processes based on simple modification of reaction conditions.

As shown in Table 1, the IBX-induced oxidation of benzylic positions is quite general and proceeds efficiently in fluorobenzene/DMSO (2:1) or DMSO at 80−90 °C. The reaction is not affected by the presence of water (entry 3), *o*-substituents (entries 4, 9, 11, 14, 17), or the presence of halogens (entries 5, 6). Over-oxidation to the corresponding carboxylic acid was not observed even in the presence of electron-rich substrates (entry 7). *n*-Butylbenzene enters the reaction smoothly, furnishing *n*-butyrophenone, and so do methylnaphthalenes (entry 7) and tetrahydronaphthalenes (entries 9, 22), furnishing the corresponding ketones. The expected retardation of the reaction by electron-withdrawing substituents (*vide infra*) (entries 23, 24) allows selective oxidation of xylenes and tetrahydronaphthalenes to mono-carbonyl systems (entries 11, 12, 9, 22). Noteworthy is the observation that whereas the presence of olefins, *N*-heterocycles, amides, and aldehydes would ordinarily interfere with such benzylic oxidations by a variety of reagents the present IBX-based method performs admirably in such circumstances. Thus, oxidation of the unsaturated substituted toluenes in entries 13 and 14 with IBX proceeds smoothly as compared to the use of DDQ, PDC, or CAN, all of which led to low conversion or decomposition.[5] It was also interesting to observe the stepwise oxidation of the substrate of entry 15 leading, at 65 °C (2.5 equiv IBX), to the α,β-unsaturated aldehyde[1d] and, under more forcing conditions (85 °C, 4.0 equiv IBX), to the bis-aldehyde shown in entry 16. In an intermolecular competition experiment, cyclodecanol and *p-tert*-butyltoluene were allowed to react with IBX (2.5 equiv, 65 °C, fluorobenzene/DMSO 2:1) leading only to 2-cyclodecen-1-one and no aromatic aldehyde. While slightly longer times or higher temperatures were necessary for the oxidation of *N*-containing aromatic systems, it is noteworthy that no *N*-oxidation was observed in such cases (entries 17, 18). The amide functionality did not hamper the oxidation reaction as demonstrated in entries 19 and 20, but remarkably, the reaction could be turned toward the oxazolidinone pathway by modulating the reactivity of the reagent simply by switching from fluorobenzene/DMSO to THF/DMSO as solvent (entry 21).[2,6]

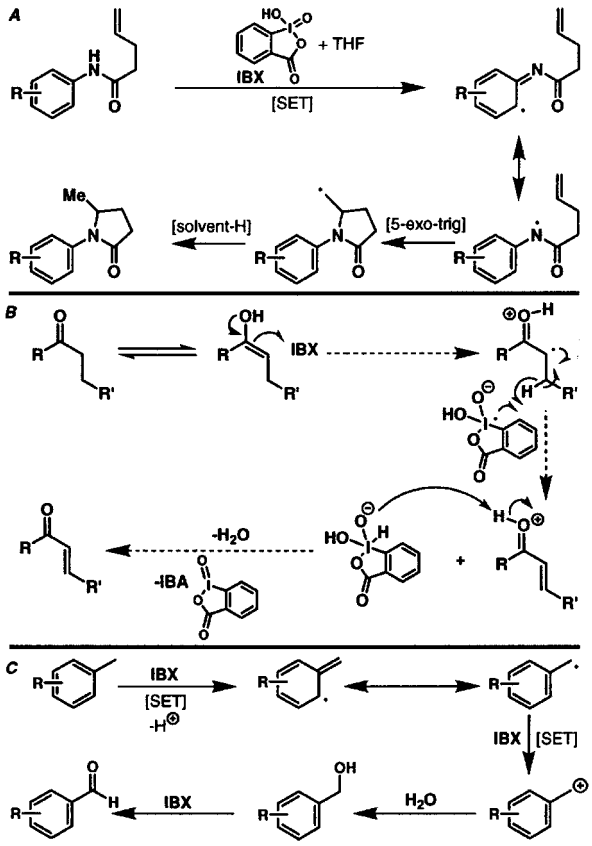

Figure 1. Mechanistic blueprints for IBX-mediated SET oxidation adjacent to carbonyl groups (B) and aromatic systems (C), inspired by the recently elucidated mechanism of the IBX-cyclization (A). SET = single electron transfer; IBX = *o*-iodoxy benzoic acid.

On the basis of mechanistic insights gained during these studies, a number of observations could be rationalized. Thus, we have previously found that the generality of the IBX-mediated cyclization depicted in Figure 1A is highly dependent on the oxidation potential of the substrate involved.[2] Anilides with higher oxidation potentials (electron-donating substituents) were found to cyclize faster than those with lower oxidation potentials (electron-withdrawing substituents). Since the present reaction is also believed to be a SET process, the same correlation should be operative. Here, therefore, may lie the explanation for the failure of the substituted toluenes shown in entries 23 and 24 (electron-poor) to enter the reaction. The clean mono-oxidation of xylenes in entries 11 and 12 can also be attributed to the inability of the

(1) (a) Nicolaou, K. C.; Zhong, Y.-L. Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 622−625. (b) Nicolaou, K. C.; Zhong, Y.-L. Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 625−628. (c) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Vega, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 2525−2529. (d) Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596−7597. (e) Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y.-L. *Angew. Chem., Int. Ed.* **2001**, *40*, 207−210.

(2) Nicolaou, K. C.; Baran, P. S.; Kranich, R.; Zhong, Y.-L.; Sugita, K.; Zou, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 202−206.

(3) The originally postulated ionic mechanism[1d] is less favored in view of the findings reported in ref 2.

(4) Franz, G.; Sheldon, R. A. In *Ullmann's Encyclopedia of Industrial Chemistry*, 5th ed.; Wolfgang, G., Yamamoto, Y. S., Campbell, F. T., Pfefferkorn, R., Rounsaville, J. F.; VCH: Weinheim, 1991.

(5) Larock, R. C. *Comprehensive Organic Transformations*; John Wiley & Sons: New York, 1999; pp 1205−1207.

(6) Although it was not necessary, dry solvents (Aldrich, EM Science) were employed in these reactions; thus, the oxygen may be derived from IBX itself. Labeling studies to determine the origin of oxygen in the products will be reported in due course.

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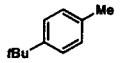
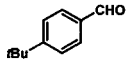
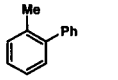
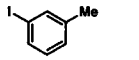
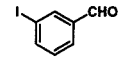
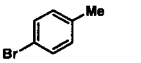
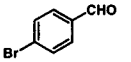
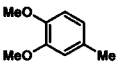
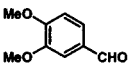
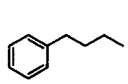
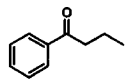
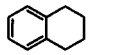
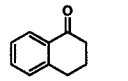
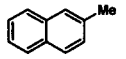
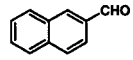
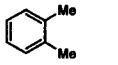
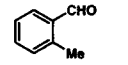
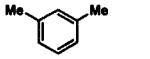
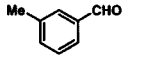
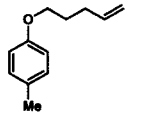
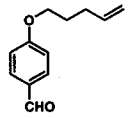
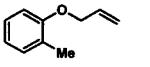
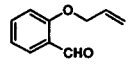
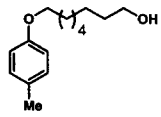
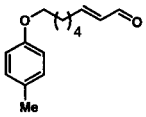
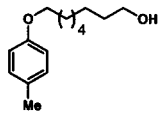
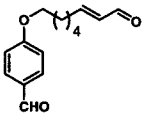
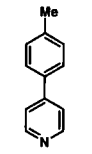
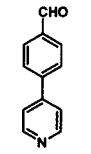
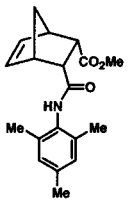
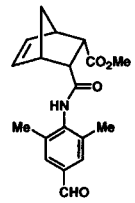
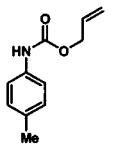
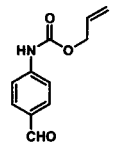
Table 1. Oxidation of Benzylic Positions Using IBX

Entry	Substrate[a]	Product	Conditions[b]	Yield (%)[c]
1			12 h/85 °C 3.0 equiv	85
2			8 h/80 °C 3.0 equiv	95
3			8 h/80 °C 3.0 equiv 100 equiv H_2O	90
4			24 h/90 °C 3.0 equiv	78
5			16 h/85 °C 4.0 equiv	72
6			16 h/80 °C 3.0 equiv	73
7			5 h/75 °C 3.0 equiv	80
8			8 h/80 °C 3.0 equiv	72
9			12 h/80 °C 3.0 equiv	70
10			20 h/80 °C 3.0 equiv	90
11			16 h/85 °C 3.0 equiv	82
12			16 h/85 °C 3.0 equiv	85
13			8 h/80 °C 3.0 equiv	88
14			12 h/80 °C 3.0 equiv	80
15			8 h/65 °C 2.5 equiv	75
16			12 h/85 °C 4.0 equiv	62
17			24 h/85 °C 3.0 equiv	70
18			36 h/90 °C 4.0 equiv	52
19			24 h/90 °C 3.0 equiv	75
20			12 h/85 °C 3.0 equiv	60
21			12 h/85 °C 4.0 equiv THF/DMSO solvent	89
22		(1:1)	24 h/85 °C 3.0 equiv	70
23		—	24 h/90 °C 3.0 equiv	NR
24		—	24 h/90 °C 3.0 equiv	NR
25		—	24 h/90 °C 3.0 equiv	NR

[a] All substrates were commercially available except for those in entries 13−16 and 19−21 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.

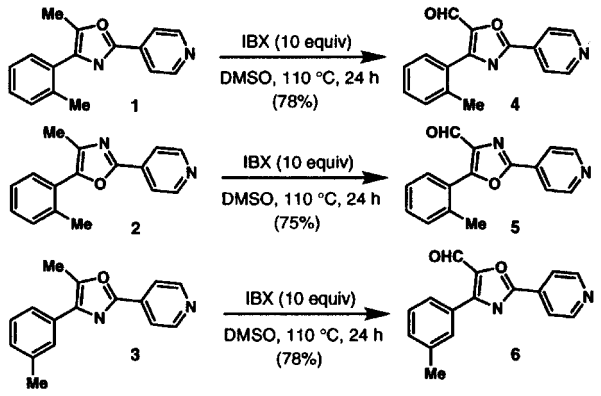
electron-poor monoaldehyde products to participate in further oxidation.[7] On the other hand, the failure of 2,4,6-trimethoxytoluene (entry 25) to yield the corresponding aldehyde (starting material recovered) can be explained by the requirement of a free *o*-position for benzylic oxidation just as it is the case for anilide cyclization (see Figure 1 C and A).[2]

Armed with important information regarding the limitations of the methodology, we then turned our attention to more complex substrates in which more than one aromatic position had the potential to be oxidized. The bis-methyl substituted pyridyl oxazoles **1**−**3** (Scheme 1) were chosen for their resistance to undergo oxidation at either methyl group with a variety of known oxidants.[8] In the event, compounds **1**−**3** were oxidized at 110 °C employing 10 equiv of IBX in DMSO, furnishing aldehydes **4**−**6** in 75−78% isolated yield along with ∼20% recovered starting material. HMQC and HMBC NMR experiments con-

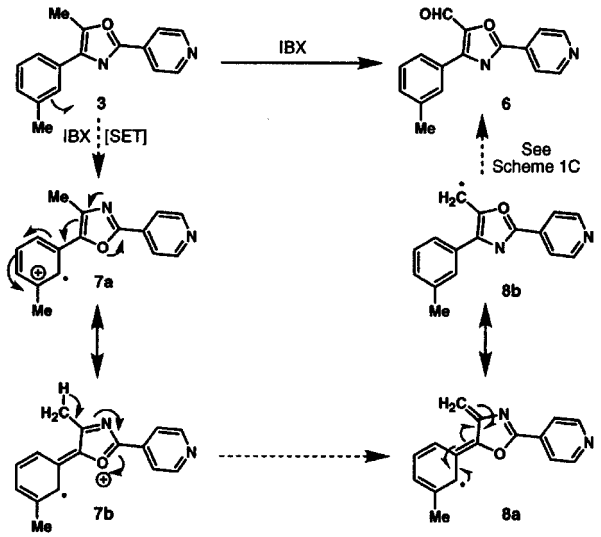
(7) Selectivity in the mono-oxidation of xylenes is often a challenging problem; see, for example: Ohkubo, K.; Fukuzumi, S. *Org. Lett.* **2000**, *2*, 3647−3650.

(8) Finney, N.; Fang, A. Department of Chemistry, University of California, San Diego, unpublished results. Professor N. Finney is gratefully acknowledged for generous samples of oxazoles **1**−**3**.

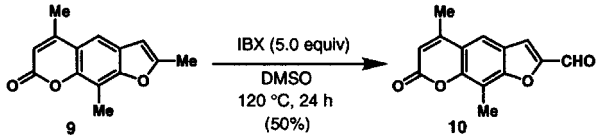
Scheme 1. Selective Oxidation of Substituted Oxazoles with IBX



Scheme 2. Postulated Mechanistic Rationale for the Selective Oxidation of 2-Methyl-3-tolyl-5-pyridyl Oxazoles to 2-Formyl-3-tolyl-5-pyridyl Oxazoles



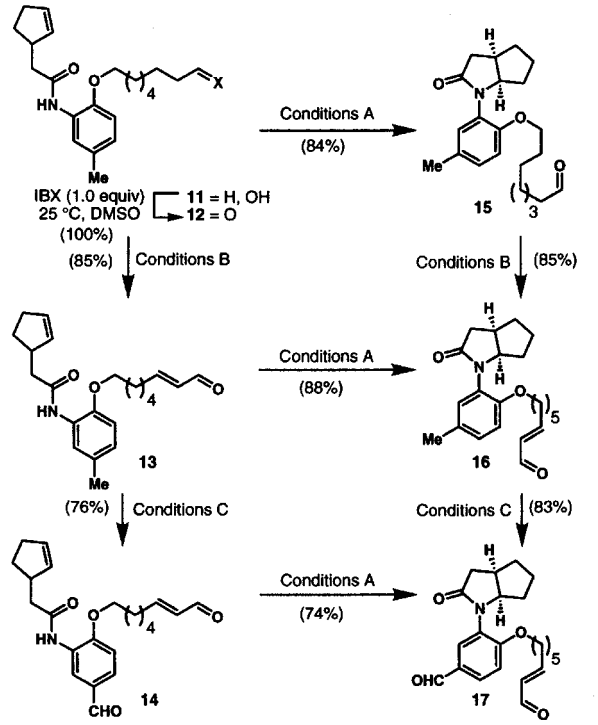
Scheme 3. Chemoselective Oxidation of Trioxsalen (**9**) to Furanaldehyde **10** Using IBX



firmed that the oxazole-bearing methyl group had been oxidized rather than the benzylic methyl group. When trimethyl oxazole was submitted to the same conditions, none of the corresponding aldehyde was detected, and more forcing conditions led only to traces of aldehyde accompanied by several unidentified products. The intriguing mechanistic rationale presented in Scheme 2 (which seemingly contradicts the observations, *vide supra*, that a free *o*-position is required for oxidation) may explain this transformation. Specifically, it is postulated that the aryl system of 2-methyl-3-tolyl-5-pyridyl oxazoles such as **3** initiates the reaction by transferring one electron to IBX, leading to species **7a** which is simply a resonance structure of **7b**. Loss of a proton from **7b** leads to **8a** which, in resonance form **8b**, leads to 2-formyl-3-tolyl-5-pyridyl oxazoles such as **6** via the mechanism depicted in Figure 1C.

The above results and mechanistic considerations led us to speculate on the IBX-mediated oxidation product of 5,5′,8-trimethylpsoralen (trioxsalen) **9** (Scheme 3). All evidence and mechanistic insights pointed to the furanaldehyde **10** as the most logical outcome, and indeed, treatment of **9** with IBX (5.0 equiv)

Scheme 4. Selective Chemical Transformations with IBX



at 120 °C for 24 h in DMSO led to this compound as the sole aldehyde (50% yield).

Finally, to probe the selectivity and controllability of the recently discovered IBX-based oxidations, we designed and synthesized compound **11** (Scheme 4) to be used as a substrate. Using only three standard conditions, **11** could be easily converted into **12**−**17**. Thus, treatment of **11** with 2.0 equiv of IBX at 65 °C in fluorobenzene/DMSO (2:1) in the presence of catalytic amounts of TsOH (conditions B, Scheme 4) led to α,β-unsaturated aldehyde **13** in 85% isolated yield. Further oxidation of **13** with 3.0 equiv of IBX in DMSO at 90 °C (conditions C) furnished fully oxidized compound **14** in 76% isolated yield. Compounds **11**−**14** could be converted to **15**−**17** simply by employing IBX and THF/DMSO as the solvent system (conditions A). Alternatively, **15** could also be cleanly converted to **16** by conditions B, which, in turn, was smoothly transformed to **17** by conditions C.

In conclusion, we have developed, on the basis of mechanistic rationale, a selective oxidation reaction of benzylic and other similarly activated positions based on IBX and demonstrated its scope, generality, and usefulness in organic synthesis. Most significantly, this reaction appears to fit well as a chemospecific tool within the family of IBX-mediated reactions recently reported from these laboratories.[1b−d] It is expected that applications of this process to the construction of building blocks will facilitate molecular diversity construction and provide further enabling technologies for biology and medicine.

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Supporting Information Available: Experimental procedures 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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