Benzylic Carbon Oxidation by an in situ Formed *o*-Iodoxybenzoic Acid (IBX) Derivative

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Abstract: Benzylic C–H bonds are selectively oxidized to the corresponding carbonyl functionalities using catalytic quantities of 2-iodobenzoic acid (2IBAcid) and Oxone®. The reported procedure tolerates different functional groups and operates under mild conditions. A radical mechanism is proposed for the transformation and evidence supporting the proposed mechanism is also presented.

Key words: oxidation, *o*-iodoxybenzoic acid (IBX), single-electron transfer, rearrangement, Oxone®

Selective oxidation of activated and unactivated C–H bonds continues to interest organic chemists.[1] Growing concerns over the environmental impact of the use of transition-metal oxidants have forced chemists to develop sustainable oxidation methods using benign and user-friendly reagents.[2] The development of oxidation procedures that completely eliminate the use of transition-metal-based reagents is a desirable research objective. The hypervalent iodine reagent, *o*-iodoxybenzoic acid (IBX), has recently emerged as a reagent of choice for a plethora of unique and selective oxidative transformations including the oxidation of benzylic C–H bonds.[3] Oxidative transformations using IBX, a potentially shock-sensitive reagent,[4] are usually carried out in DMSO due to the solubility limitation of the reagent in other user-friendly solvents. Our group and others have addressed the limited solubility of IBX by functionalizing the arene moiety of IBX to impart solubility in water and to improve solubility in other solvents.[5] Catalytic protocols that involve in situ generation of IBX from 2-iodobenzoic acid (2IBAcid) in combination with co-oxidant Oxone® and its use for the

oxidation of alcohols have been reported by us[6] and others.[7] We wondered whether a similar catalytic protocol could be used for the oxidation of benzylic C–H bonds. Such a procedure would also offer a user-friendly alternative to benzylic C–H oxidation that required superstoichiometric amounts of IBX in DMSO.[3a,b] Herein, we report the first use of an in situ generated hypervalent iodine reagent for such a purpose. We also provide a plausible mechanistic rationale for the observed product distribution during the oxidation reaction.

Diphenylmethane (**1**) was chosen as our initial benzylic substrate (Scheme 1). First, we decided to ascertain the extent of background reaction of **1** with Oxone®, since it was previously reported that benzophenone (**2**), was obtained in 10% yield when the oxidation was carried out in water.[8] Our repeated attempts at oxidation of **1** in 2:1 acetonitrile–water mixture using 1.5 equivalents of Oxone® gave only a maximum of 6% isolated yield of **2**. Convinced that the extent of background oxidation by Oxone® is minimal, at best, we decided to attempt an oxidation of **1** using 0.2 equivalents of 2IBAcid and 1.2 equivalents of Oxone® as the co-oxidant[9] and observed a 50% conversion to **2**, along with trace amounts of **3**. We were, however, surprised when an attempted oxidation of **1** using IBX (preformed rather than prepared in situ) in aqueous acetonitrile failed. The encouraging result using the in situ generated reagent and the extent of oxidation beyond 20% clearly indicated that Oxone® is capable of regenerating the active catalyst by re-oxidizing the reduced form of the reagent during the reaction.
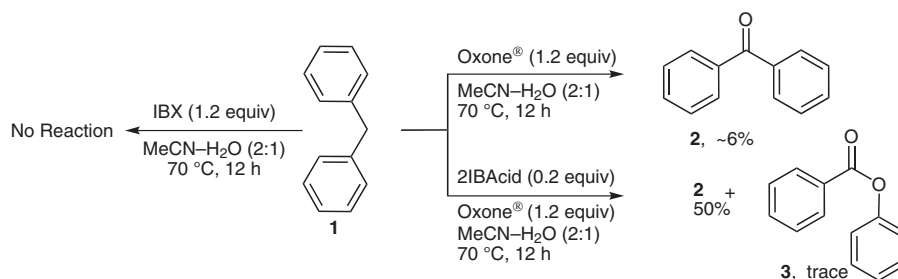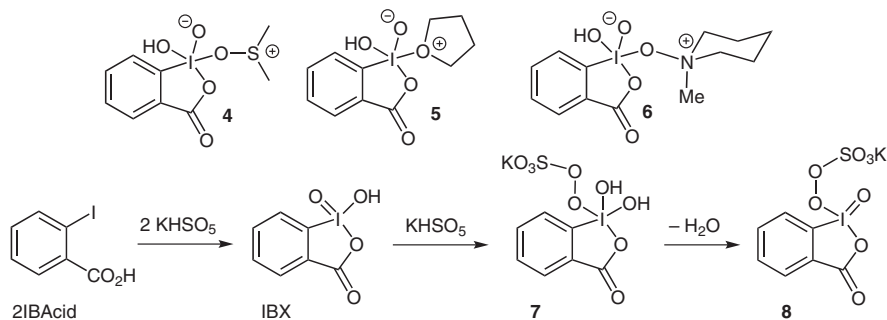

Scheme 1

Scheme 2

Considering the fact that preformed IBX does not oxidize **1** to **2** in aqueous acetonitrile and that the active catalyst prepared in situ remained soluble during the reaction, we hypothesized that the active hypervalent iodine reagent may not be IBX per se, but a soluble peroxy ligand appended (KHSO$_5$ from Oxone$^®$) derivative of IBX such as **7** or **8**. Modulation of IBX reactivity through ligand complexation is well documented by Nicolaou with the use of IBX–DMSO (**4**), IBX–THF (**5**), and IBX-*N*-oxide (**6**) for benzylic site oxidation and other unique oxidative transformations (Scheme 2).[3b]

At this juncture we set out to establish the efficiency of Oxone$^®$ as a co-oxidant for the oxidation of **1** by varying molar ratios of 2IBAcid and Oxone$^®$ and measuring the extent of oxidation by NMR methods. The results from our optimization experiments are shown in Table 1. In all cases, the Baeyer–Villiger product **3** was observed as a minor product in the product mixture. We surmised that by comparing the maximum yield of the oxidized products **2** and **3** to the maximum available oxidants in the reaction medium we would be able to shed light on the overall reaction mechanism.

Salient features of the proposed mechanism shown in Scheme 3 include: (a) initiation of the reaction via a benzylic H-atom abstraction by the I=O bond, similar to the first step in C–H oxidation by reagents that possess metal=O bonds (CrO$_3$, RuO$_2$, and MnO$_4^-$),[10] (b) a single-electron transfer (SET) from the resonance stabilized benzylic radical **9** to the odd electron iodine center in **10** producing the crucial diphenyl carbocation **11** and the peroxy-IBX anion **12**, the collapse of which regenerates IBX which can re-enter the catalytic cycle through further activation by KHSO$_5$, and (c) three plausible routes for the transformation of **11** to **2**, each requiring equal amounts of Oxone$^®$ in the overall catalytic cycle. A careful evaluation of the proposed mechanism reveals that the amount of KHSO$_5$ required to complete the first catalytic cycle of substrate oxidation is 4.0 times the molar equivalent of 2IBAcid used, and every subsequent cycle requires twice the molar equivalent of 2IBAcid employed. The overall KHSO$_5$ requirement for complete consumption of the substrate can be calculated using the formula $4y + (1/y - 1)2y$ where y is the molar equivalent of 2IBAcid employed. The amount of KHSO$_5$ needed is independent of the fate of the carbocation intermediate **11**, since transformation

Table 1 Efficacy of Oxone$^®$ as a Co-oxidant

2IBAcid (equiv)	Oxone (equiv)	Yield (%)		Theoretical yield of **2** (%)[b]
		2	**3**	
0.0	1.50	6	–	–
0.2	0.8	42	2	43
0.2	1.38	68	6	74
0.2	1.65	77	7	88
0.25	1.75	74	9	89
0.3	1.50	68	4	74
0.5	1.25	48	5	54
0.5	2.50	87	8	100
0.2[c]	1.75	ca. 5		–

[a] All reactions were carried out at 1.2 mmol scale at 70–80 °C for 48 h in 2:1 MeCN–H$_2$O.
[b] Theoretical yield of **2** based on the total consumption of available oxidants.
[c] Reaction was carried out with 1.1 equiv of the radical scavenger galvinoxyl.

of **11** to **2** either uses up IBX (reactions 2 and 3) or uses up an additional equivalent of KHSO$_5$, as a nucleophilic oxidant, in rxn 1. Subsequent catalytic cycles can only start with the regeneration of **8** from IBA (reactions 2 and 3) or **8** from IBX (reaction 1) leading to an overall consumption of equal amounts of KHSO$_5$. The theoretical yield reported in Table 1 was calculated using the formula and by noting that there is approximately a 20% loss of Oxone$^®$ due to thermal decomposition during the 48 hours reaction period.[11]

The involvement of the initial radical intermediate in the proposed mechanism is substantiated by the almost complete inhibition of the reaction with the addition of 1.0 equivalent of galvinoxyl, an effective radical scavenger (Table 1, footnote c).

We next investigated the oxidation of benzo-fused substrates **16**–**20** (Scheme 4). Except in the case of fluorene **20**, products were isolated in higher than 70% yield from the oxidation of the benzo-fused substrates. Oxidation of **16** gave the expected 1-indanone **21** in 67% isolated yield
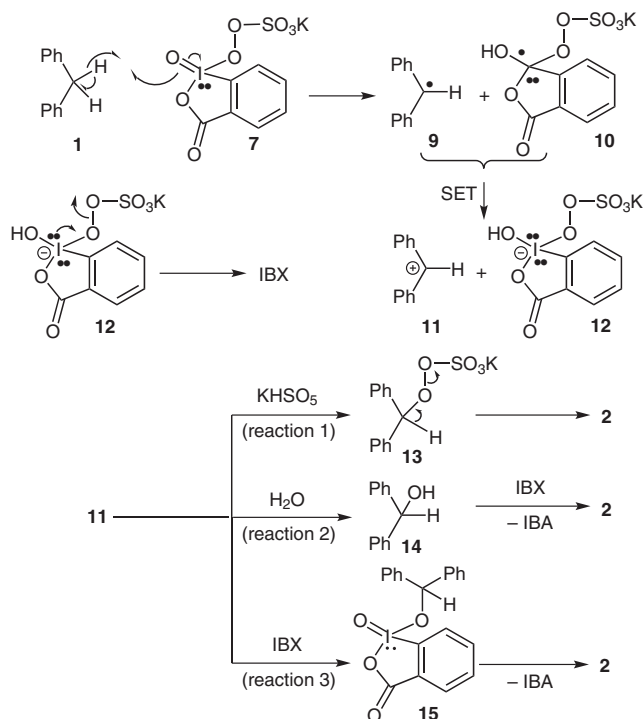
Scheme 3

Scheme 4

along with 8% of indenone **22**. Similarly oxidation of **17** yielded **23** and **24** in 60% and 12%, respectively. *o*-Iodoxybenzoic acid is known to dehydrogenate ketones and aldehydes to generate α,β-unsaturated derivatives and as such, the formation of **22** and **24** is not unexpected from these oxidations.[3a,b] Oxidation of **18** gave **25** in 93% yield by the selective oxidation of the doubly benzylic carbon, a reflection of the enhanced stability of the resulting radical. Oxidation of **19** provided phenanthrene **26** as the only product, the formation of which is explained by the loss of a proton from the carbocation intermediate (Scheme 3). The most striking support for the proposed mechanism is the complete lack of oxidation of fluorene **20**, which would necessitate the formation of the unstable anti-aromatic fluorenyl cation along the reaction path.

Interested in extending the scope of this reaction, we decided to investigate the oxidation of phenyl and diphenylalkanes. 4-Bromoethylbenzene (**28**) and 1,2-diphenylethane (**33**) were chosen as representative substrates (Scheme 5). Oxidation of **28** gave a 73% isolated yield of **29**. The ^{1}H NMR spectrum of the crude product from this attempt indicated the presence of trace amounts of 4-bromobenzoic acid (verified with GC-MS) and more importantly showed three small, overlapping quartets between δ = 4.98–4.82 ppm and three corresponding doublets between δ = 1.48–1.26 ppm. We believe that these signals indicate the presence of the intermediates **30–32**, from the capture of the benzyl carbocation by the nucleophiles in the reaction (Scheme 3). The presence of 4-bromobenzoic acid was initially not a concern until we attempted the oxidation of **33** under identical reaction conditions and recovered 70% of the starting material
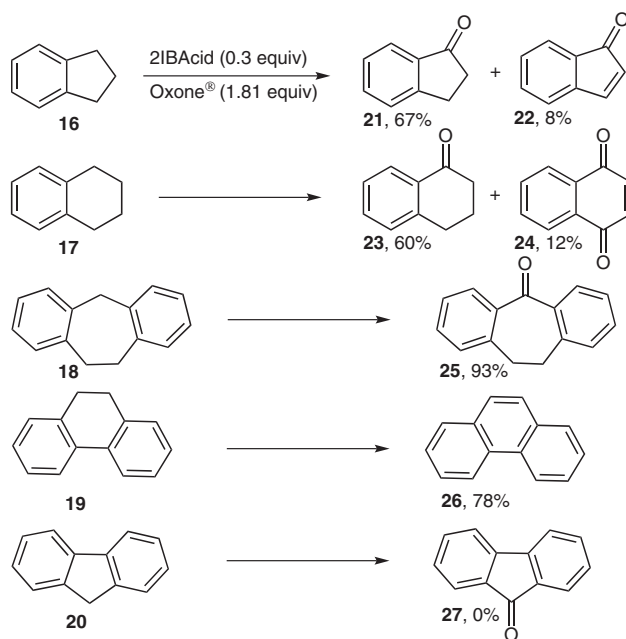
along with a complex mixture of oxygenated products including **34**, **35**, and importantly benzaldehyde (**36**) and benzoic acid (**37**). The recognition of the presence of the peroxysulfate ester intermediate **38** and the possibility of an accompanied Criegee rearrangement succinctly accounts for the cleavage of the C–C bond in the acidic reaction medium.[12] Benzaldehyde and benzyl alcohol produced from this rearrangement are further oxidized by KHSO$_5$[13] and IBX,[14] respectively, accounting for the loss of total available oxidant. Interested in establishing a substrate scope for the reaction, we oxidized a select group of phenylalkanes using excess Oxone® to compensate for the oxidation of the cleaved products formed during the reaction (Scheme 6).

The plausible mechanistic considerations discussed so far imply that phenylcycloalkanes that carry an abstractable benzylic hydrogen can lead to benzoylalkanoic acids as products (Scheme 7). As such, we hypothesized that it would be possible to synthesize benzoylalkanoic acids from the appropriate phenylcycloalkanes.
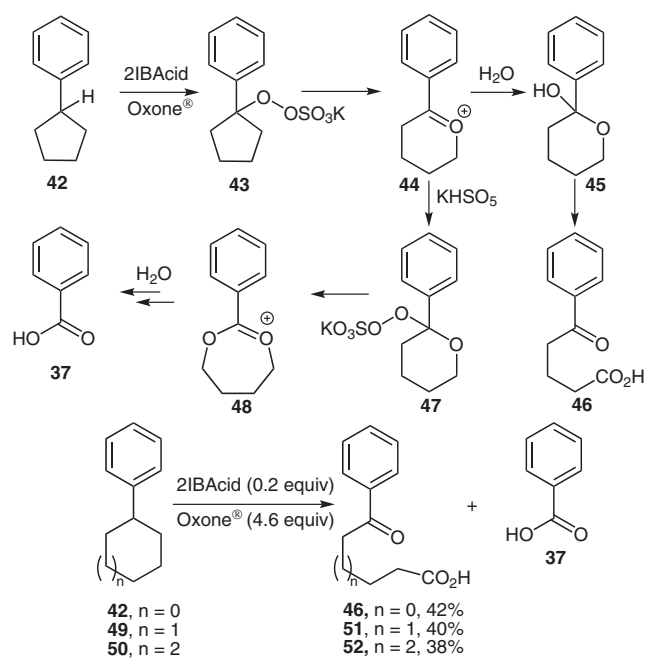
The carbocation **44** that results from a Criegee rearrangement can be trapped with water or KHSO$_5$ leading to either **45** or **47**, respectively. Decomposition of **45** in the acidic reaction medium and subsequent oxidation will lead to benzoylalkanoic acid **46**. The intermediate **47** can partake in a second Criegee rearrangement,[12c] leading to **48**, which again under the reaction conditions will hydrolyze to give benzoic acid. We tested this hypothesis with the oxidation of phenylcyclopentane (**42**), phenylcyclohexane (**49**), and phenylcycloheptane (**50**) using 0.2 equivalents of 2IBAcid and 4.6 equivalents of Oxone®. Oxidation of **42** gave 4-benzoylbutanoic acid (**46**) along with benzoic acid (**37**) in 42% and 22% yield, respectively. Oxidation of **49** and **50** provided the corresponding benzoylalkanoic acids **51** and **52** in 40% and 38% yield,
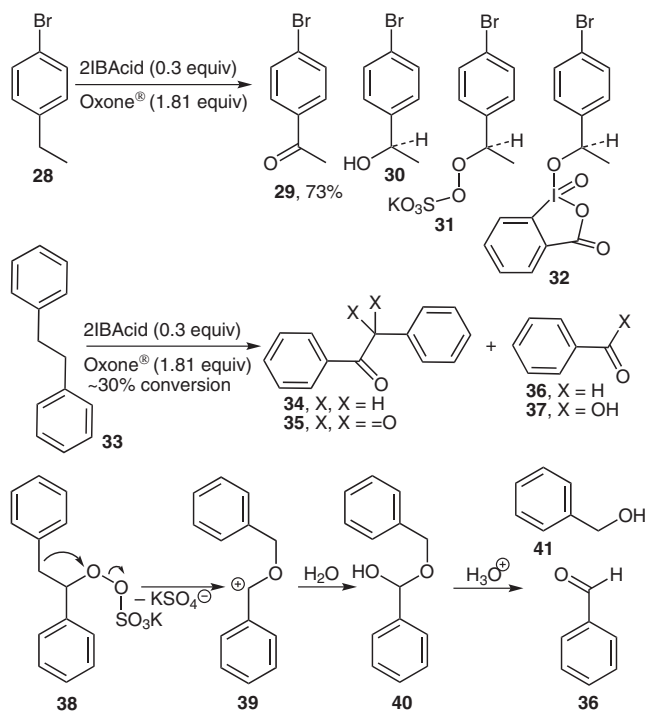
Scheme 5

Scheme 7

respectively. We are currently optimizing the reaction conditions to improve the yield of benzoylalkanoic acids products and concurrently identifying tolerance for functional groups on the cycloalkyl moiety during the oxidation.

In summary we have developed a catalytic benzylic oxidation protocol using an in situ generated hypervalent iodine reagent. Suggested mechanistic proposals account for the intermediates and explain the presence of oxida-
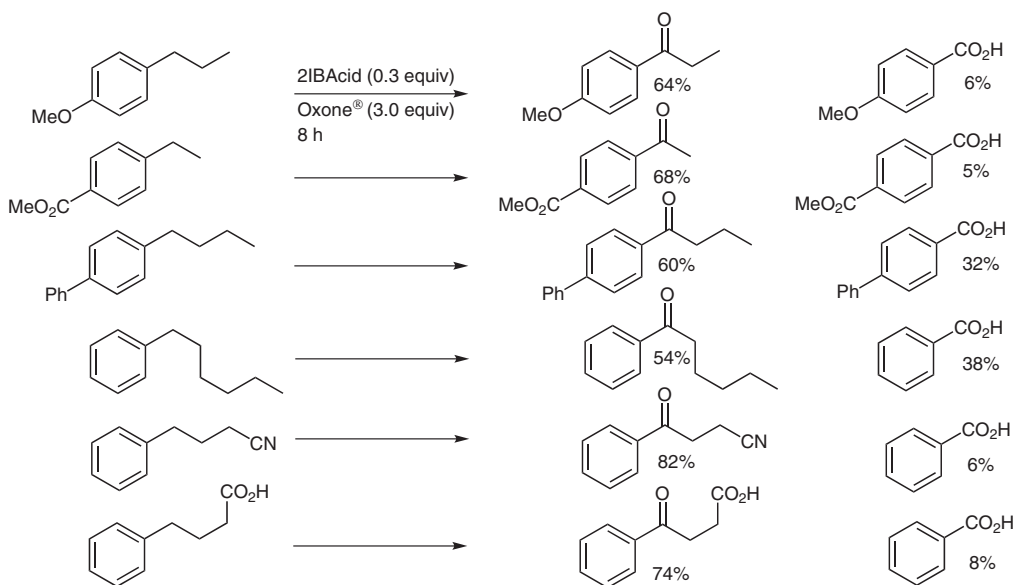
tively cleaved products. Attempts are currently under way to identify other nucleophilic oxidants which would eliminate or reduce the extent of oxidative cleavage that accompanies the benzylic site oxidation.

Acknowledgment

Scheme 6

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