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Chemoselective Oxidation and Deprotection of *para*-Methoxybenzylic Position with (Diacetoxyiodo)benzene in Acetic-Trifluoroacetic Acid

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ABSTRACT

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1. Introduction

The direct functionalization of the benzylic C-H bond is an important toolbox for the synthesis of versatile new building blocks in organic synthesis. Benzylic C-H oxidation to carbonyl group is consider as one of the most important transformations in which transitional metals have play a key role.¹ Recently, hypervalent iodine reagents have emerged as a new environmental friendly metal-free condition to facilitate numerous organic transformations, such as oxidation, carboncarbon bonds formation, and carbon-heteroatom bonds formation.² Nicolaou et al. reported the first use of hypervalent iodine (V) reagent (IBX in wet DMSO) for the hitherto unknown benzylic C-H oxidation of arylmethylenes to provide the corresponding carbonyl compounds for use as versatile building blocks in organic synthesis.³ The hypervalent iodine (III) is more stable and safer as compared to hypervalent iodine (V) reagents. Consequently, Kita et al. utilized polymeric iodobenzene with KBr with the presence of montmorillonite-K10 in water at 80 °C for the efficient benzylic C-H bond oxidation.4 Recently, Telvekar et al. used the commercially available (diacetoxyiodo)benzene in the presence of a catalytic amount of sodium azide at room temperature for the benzylic C-H oxidation.5

A drawback of these reported hypervalent iodine reagents for the benzylic C-H oxidation is the low chemo- and regioselectivity that often resulted in a mixture of products. Herein, we report our new findings whereby *para*-methoxy substituent on the aryl ring can have a directing effect on the chemo- and regioselective benzylic C-H oxidation to aryl carbonyl compounds using (diacetoxyiodo)benzene (DAIB) in the presence of acetic –

(Diacetoxyiodo)benzene in the presence of acetic - trifluoroacetic acid in THF has been developed for the chemoselective *para*-methoxybenzylic C-H bond oxidation to provide aryl carbonyl compounds at room temperature. The reaction condition is also applicable for the chemoselective deprotection of *para*-methoxybenzyl (PMB) ether in the presence of benzyl ether.

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trifluoroacetic acid mixture with THF as solvent at room temperature.

2. Results and discussion

For our initial studies, we explored the reaction of *para*methoxytoluene as the substrate with (diacetoxyiodo)benzene (DAIB) under various conditions (Table 1). In the absence of acetic or trifluoroacetic acid, the reaction does not take place.

Table 1.

Reaction conditions for DAIB mediated benzylic C-H oxidation of *para*-methoxytoluene.



Entry	Reaction conditions	Yield
1	DAIB(1 equiv), DMSO, 80°C, 2 days	no reaction
2	DAIB(1 equiv), THF, rt (or reflux)	no reaction
3	DAIB(1 equiv), AcOH(1 equiv), THF, rt	traces
4	DAIB(1 equiv), TFA(1 equiv), THF, rt	5%
5	DAIB(1 equiv), TFA(1 equiv), AcOH(1 equiv), THF, rt	30%
6	DAIB(6 equiv), TFA(4 equiv), AcOH(1 equiv), THF, rt	80%
7	DAIB(6 equiv), TFA(4 equiv), AcOH(2 equiv), THF, rt	93%
8	DAIB(6 equiv), TFA(4 equiv), AcOH(4 equiv), THF, rt	85%
9	DAIB(1 equiv), TFA(1 equiv), AcOH(6 equiv), THF, rt	20%
10	DAIB(3 equiv), TFA(2 equiv), AcOH(1 equiv), THF, rt	50%

It was found that treatment of *para*-methoxytoluene with DAIB in the presence of trifluoroacetic acid (TFA)/acetic acid (AcOH)

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(1:1) in THF at room temperature give the benzylic C-H oxidation product, *para*-methoxybenzaldehye, in 30% yield (Table 1, entry 5). Next, we systematically examined the influence on the amount of DAIB, TFA and AcOH to optimize the reaction conditions. To our delight, the reaction condition with 6 equiv of DAIB, 4 equiv TFA and 2 equiv AcOH in tetrahydrofuran at room temperature (Table 1, entry 7) dramatically improved the yield to 93% and all further reactions were carried out using these optimized condition. It is noteworthy that the oxidation of *para*-methoxytoluene selectively stopped at the aldehyde without any over-oxidation to the acid.

With these results in hand, we first investigated the electronic influence of the aryl ring and scope of the reactions (Table 2). Our results show that the benzylic C-H oxidation can be very sensitive to the nature and position of the substituents. Toluene, para-nitrotoluene, para-bromotoluene did not undergo benzylic C-H oxidation under the optimized reaction condition (Table 2, entries 1-3). This is in stark contrasts to the previously reported benzylic C-H oxidation using hypervalent iodine reagents that showed only slight dependency on the electronics nature of the substituents on the aryl containing substrates.^{3,4} On the other hand, our reagent with DAIB/TFA/AcOH at room temperature preferred the benzylic C-H oxidation of para-methoxytoluene over that of ortho-methoxytoluene (Table 2, entries 4, 5) The meta-methoxytoluene did not undergo benzylic C-H oxidation. The electronic properties of additional substituents on paramethoxytoluene may also influence the reaction. Electron donating group such as methoxy moiety at the ortho-positions of para-methoxytoluene was successfully converted into the corresponding aldehydes, while electron withdrawing group (ortho-nitro) hampered the reaction (Table 2, entries 7 and 8). This clearly indicates that the inductive effect of the substituents on the aryl ring also plays an important role during benzylic C-H oxidation. In addition, 1-ethyl-4-methoxy benzene was successfully oxidized to the corresponding ketone under the same reaction condition (Table 2, entry 9).

The selective mono-oxidation of aromatic rings with more than one benzylic positions can be somewhat challenging. This result prompted us to investigate further the chemoselective oxidation of the para-methoxybenzylic position. As anticipated, our condition gave site selective para-benzylic mono-oxidation product of 6-methoxy-1,2,3,4-tetrahydronaphthalene and 4methoxy-1,2-dimethylbenzene in good yield (Table 2, entry 10, 11, 73-75%). It has been reported that TiO_2 -sensitized photooxidation of 4-methoxy-1,2-dimethylbenzene gave the 1methyl group mono-oxidation product in very low yield (20%).⁶ Furthermore it is extremely interesting to note that in the case of 1-methoxy-4-(para-tolyloxy-methyl)benzene, selective oxidation at the para-methyl position is favored over the para-benzylic ether position (Table 2, entry 12). The oxidation of the 4allyloxytoulene also proceeded selectively at the benzylic position (Table 2, entry 13). To our delight, our reaction condition can be used for the selective cleavage of paramethoxybenzyl (PMB) ether in the presence of benzyl ethers in good yield (Table 2, entry 14). This new method can complement the existing strategy of utilization DDQ (2,3-dichloro-5,6dicyanobenzoquinone) for the fast and selective removal of PMB-ether to regenerate alcohol in organic synthesis.⁷

A study on hypervalent iodine(III) reactive intermediates in solutions using electrospray ionization mass spectrometry has been reported.⁸ The reactive iodine (III) species present in solutions of DAIB are highly dependent on the solvent utilized. The ESI-MS spectrum without matrix using DAIB (6 equiv) in TFA (4 equiv) and AcOH (2 equiv) in THF solution for our optimized reaction condition showed two most abundant peaks of nearly equal intensity at m/z 440.8 and 482.8 that correspond to

Table 2.

Chemo- and regio-selective benzylic C-H oxidation directed by the aromatic substitutions with DAIB (6 equiv)/TFA (4 equiv)/AcOH (2 equiv).



the reported dioxo-bis(iodobenzene) species **I**, $[Ph_2I_2O_2Ac]^+$, and **II**, $[Ph_2I_2O_2H]^+$ respectively (Fig. 1). The formation of **I** and **II** from the reactions of PhIO, $[PhIOAc]^+$ and $[PhIOH]^+$ during

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DAIB disproportionate were previously discussed in the literature (Scheme 1).⁸ However, this is in contrast to the reported most abundant peak corresponding to $[PhIOAc]^+$ observed for DAIB in AcOH as solvent.⁸ Our reaction condition has attenuated the formation of I and II and can also be envisage to simultaneously exist in the form of zwitterions.

In this regard, it is most likely that the dioxo-bis(iodobenzene) derivatives I and II act as the reactive species, rather than DAIB. Although at present a detailed understanding of the reaction mechanism must await further study, our results indicate a conventional electrophilic-like reactivity pattern for the benzylic C-H oxidation reaction using DAIB/AcOH/TEA at ambient temperature in THF. As such, the chemoselective benzylic C-H oxidation arises from the electrophilic nature of the observed hypervalent iodine species. The use of highly electrophilic iodonium species for numerous C-H functionalization have also been reported and found useful applications in organic synthesis. Our reaction condition thus complement the highly electrophilic nature of the iodine atom that has been reported for hypervalent (III) reagents.¹⁰⁻¹² The hypervalent iodine mediated benzylic C-H oxidation generally proceeded through a SET from the aromatic ring. Thus, we sought evidence for the intermediacy of a radical species under our reaction condition by carrying out the reaction of para-methoxytoluene with the radical scavengers, 2,2,6,6tetramethylpiperidine-N-oxyl radical (TEMPO) and 2,4,6-tri-tertbutylphenol, and no aldehyde product was detected.



Fig. 1. ESI-MS spectrum of Dioxo-bisiodobenzene intermediate.



Scheme 1. Proposed mechanism for the formation of I and II.

3. Conclusion

In summary, we have discovered a new condition to generate iodonium-oxo dimer species I and II from DAIB/AcOH/TFA for the efficient chemo- and regio-selective *para*-methoxybenzylic C-H oxidation at room temperature. We demonstrate that selective reaction at the *para*-methoxybenzylic position is favored over that of benzyl and allyl ether. Furthermore, this can be an expedient mild method for selective deprotection of the *para*-methoxybenzyl ether group during organic synthesis. Further studies on the mechanism and applications are now in progress.

4. Experimental Section

General Procedure for the Benzylic C-H Oxidation:

To a solvent of (bisacetoxyliodo)benzene (DAIB) (4.75 g, 14.75 mmol) in dry THF (20-30 mL) was added trifluoroacetic acid (1.12 g, 9.83 mmol) and acetic acid (0.29 g, 4.92 mmol). The mixture stirred for 30 minutes, after which the compound added for benzylic C-H oxidation (2.46 mmol) and further reacted for 24 hours. The progress of the chemical reaction was monitored using thin-layer chromatography with pre-coated silica gel 60 (0.25 mm thickness) plates. The reaction was quenched with 1 mL of sat. NaHCO₃ (aq), and the solvent removed *in vacuo* on a rotatory evaporator. The residue was extracted with ethyl acetate (30 mL×2) and water (20 mL). The combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered, and concentrated *in vacuo*.

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Supplementary Data

Supplementary data for the ¹H, ¹³C NMR and Mass spectra of products in Table 2 associated with this article are available online.

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