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Iodobenzene-Catalyzed Synthesis of α,α′-Dihydroxy Ketones: In Situ Generation of [Bis(trifluoroacetoxy)iodo]benzene

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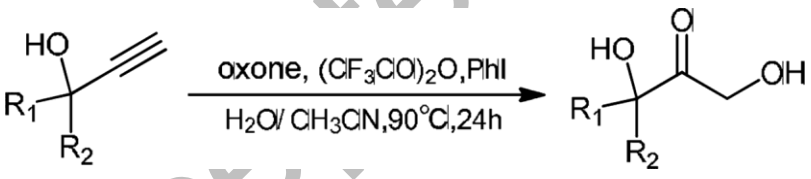
Abstract

Exposure of ethynyl carbinols to oxone / $(CF_3CO)_2O$ in the presence of a catalytic amount of iodobenzene afforded α, α′- dihydroxy ketones in good yield, which are common structural motifs in natural products and biologically active compounds. Compared with traditional methods, this method is more convenient and avoids using stoichiometric amounts of hypervalent iodine reagents.



KEYWORDS: oxone, ethynyl carbinol, iodobenzene, α, α′- dihydroxy ketones

INTRODUCTION

There is clearly significant interest in the synthesis of compounds possessing the α, α′-dihydroxy ketone functionality, which is found in several natural products and

biologically active compounds, such as pirarubicin and betamethasone.[1] α, α′- dihydroxy ketones also can be easily transferred into a range of compounds including ketosugars and 2-amino-1,3-diols.[2] α, α′- dihydroxy ketone can be prepared via various ways, including a five steps procedure to aromatic analogues and an enantioselective chiral auxiliary strategy reported by Enders *et al* ,[1, 3] but it requires many steps and suffers from environmental problems. It has also been prepared by formation of α, α′- dihydroxy ketones using Transketolase (TK) or the biomimetic TK reaction using *N*-methylmorpholine.[4] Wild-type TKs have been noted to tolerate some non-a-hydroxylated aliphatic aldehydes, but compared to a-hydroxyaldehydes lower substrate activities were reported.[4c] The biomimetic TK reaction typically used stoichiometric amounts of *N*-methylmorpholine (NMM) and yields were dependent upon the acceptor aldehyde used, but in the absence of amine the reaction did not proceed.[4a]

Therefore, a simple and efficient conversion method for preparing α, α′- dihydroxy ketones would be an important step in organic synthesis and medicinal chemistry. Meanwhile, much attention has been paid to hypervalent iodine (III) reagents in recent years due to their interesting activity, ready availability, and ease of handling.[5, 6] Hypervalent iodine(III) reagents, such as phenyliodine diacetate (PIDA) and phenyliodine di(trifluoroacetate) (PIFA), have been extensively employed in organic synthesis as popular and useful oxidants due to their unique and beneficial properties. However, stoichiometric amounts of hypervalent iodine reagents are required and

equimolecular amounts of iodobenzene are produced as a waste in the reaction. To overcome this drawback, Ochiai and co-workers have developed an efficient method for catalytic α-oxidation of ketones. The method involves in situ generation of hypervalent phenyl-λ^3-iodanes by the oxidation of a catalytic amount of iodobenzene with *m*-CPBA.[7]

In our laboratory, we have been extensively utilizing these reagents to perform a variety of organic transformations. We now report here a facile synthesis of α, α′- dihydroxy ketones by oxidizing ethynyl carbinols to oxone / $(CF_3CO)_2O$ in the presence of a catalytic amount of iodobenzene (Table 1), compared with the biomimetic TK reaction, this method is more convenient, and it also avoids using stoichiometric amounts of hypervalent iodine reagents.

RESULTS AND DISCUSSION

Exposure of ethynyl carbinols to oxone (2.7 equiv) /$(CF_3CO)_2O$ (2.0 mmol) in the presence of a catalytic amount (20 mol%) of iodobenzene at 90 ℃ for 24 hours afforded α, α′- dihydroxy ketones in 76% yield (Table 1, entry 2). The effect of temperature on the reaction was studied. As show in Table 1, raising the temperature to 100℃ resulted in a decrease in the yield to 68% (Table 1, entry 3). If 30% aq H_2O_2 was uesd instead of oxone, no reaction was observed, whereas the yield dropped sharply when CF_3COOOH or *m*-CPBA was used as oxidant (Table 1, entries 4-6). As water is stronger nucleophile than trifluoroacetic acid, α, α′-ditrifluoroacetoxy ketones would not be obtained.[8] When

acetic anhydride was used instead of trifluoroacetic anhydride, the product yield decreased from 76% to 65%, it showed that the electron-withdrawing ligand would increase the oxidative efficiency of hypervalent iodine reagents (Table 1, entries 2, 7), if there was no ligand, it gave a obvious decreased yield (26%) of 2-phenylbut-3-yn-2-ol (Table 1, entry 8).

Accordingly, substrate generality of the protocol to various α, α′- dihydroxy ketones was examined (Table 2). The reaction was observed with ethynyl carbinols in which R_1 is an aromatic group and R_2 is an aliphatic group (Table 2, entries 2−9). Oxidation reactions were observed with functionalized molecules bearing *para* substitutions on phenyl ring (Table 2, entries 2-7), that ethynyl carbinols bearing electron-donating groups on the phenyl ring were converted into the corresponding α, α′- dihydroxy ketones in good yields，whereas substrates bearing electron-withdrawing groups on the phenyl ring gave lower yields(Table 2, entry 7). ethynyl carbinols bearing *meta* substitutions on phenyl ring (Table 2, entries 8-9) as well as substrate bearing *para* substitutions were converted into the corresponding allyl alcohols in fair yields. The reaction ran smoothly to furnish the desired products in high yields when both R_1 and R_2 were aromatic substituted ethynyl carbinols (Table 2, entries 10−13). When R_1 and R_2 were acyclic aliphatic groups, there was a decrease in the yield (Table 2, entries 14−16).

To understand the mechanism better, the reaction was carried out with but-3-yn-2-ylbenzene under the standard conditions; no reaction was observed (Scheme 1-1). This result revealed that the OH group of ethynylcarbinol have participated the oxidation process. When chiral ethynylcarbinol (R)-2-phenylbut-3-yn-2-ol was subjected to the reaction conditions, only racemic product was afforded in 73% yield (Scheme 1-2).

On the basis of the experimental results and the previous reports[9] we proposed a tentative mechanism, as shown in Scheme 2. First, the alkynyliodonium salt is formed from **1** in the presence of $PhI(OCOCF_3)_2$. Then, a Michael-type addition of the *ortho*-OH group to the alkynyliodonium salt **a** provides intermediate **b**. A carbocation intermediate **c** could be obtained from the epoxide intermediate **b**. Then, intermediate **c** can be trapped by H_2O to form intermediate **d**. Reductive elimination or substitution of the phenyliodonium salt provides α, α′-dihydroxy ketone 2.

CONCLUSION

In conclusion, the conversion of ethynyl carbinols to corresponding α, α′- dihydroxy ketones using oxone and trifluoroacetic anhydride as a terminal oxidant has been accomplished in good yields. This method has some advantages such as mild reaction conditions, simple procedure and overcome this drawback that iodobenzene are produced as a waste in the reaction. Further investigation focused on expanding the scope of substrates of this method is currently in progress.

EXPERIMENTAL

All reactions were performed under an atmosphere of air. Commercially available reagents were used without further purification. NMR spectra were performed on a *Bruker* Avance III 400 spectrometer (^{1}H: 400 MHz; ^{13}C: 100 MHz). ^{1}H NMR chemical shifts were determined relative to Me_4Si (0.0 ppm) as an internal standard. ^{13}C NMR chemical shifts were determined relative to $CDCl_3$ (77.0 ppm). IR spectra recorded on Perkin-Elmer 2000 FTIR spectrometer. HRMS date were determined on a *Bruker Daltonics* APEXII 47e FT-ICR spectrometer.Mass spectra were recorded by the EI method on a HP 5998 mass spectrometer.

Typical Procedure

A solution of 3.1 g oxone, 2.0 ml trifluoroacetic anhydride and 10 ml H_2O was stirred for 4 hours at 40 °C, and then cooled to room temperature. 2-Phenylbut-3-yn-2-ol (292 mg, 2 mmol) and iodobenzene (41 mg, 0.2 mmol) in 30 ml CH_3CN were added at room temperature. The resulting solution was stirred for 24 hours at 90 °C (The progress of the reaction was monitored by TLC). 10 ml CH_2Cl_2 was added. The mixture was neutralized with a cooled 10% aqueous sodium carbonate solution and extracted with CH_2Cl_2 (100 ml × 3). The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography

[silica gel (200-300 mesh), petroleum ether-EtOAc (8:1)] to give 1, 3-dihydroxy-3-phenylbutan-2-one (273.7 mg, 76%).

ACKNOWLEDGMENTS

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher's website.

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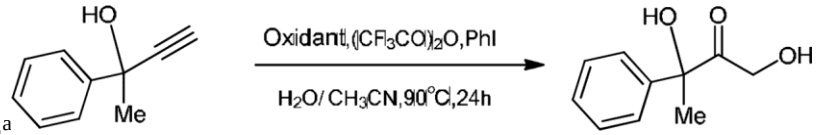
Table 1 Exposure of 2-phenylbut-3-yn-2-ol under various conditions[a]



Entry	Oxidant	Temperature/℃	Yield/% [b]
1	oxone	70	56
2	oxone	90	76
3	oxone	100	68
4	30% H_2O_2	90	NR[c]
5	CF_3COOOH	90	20
6	m-CPBA	90	43
7[d]	oxone	90	65
8[e]	oxone	90	26

[a] Reaction conditions: 2-phenylbut-3-yn-2-ol (2 mmol), oxidant (5 mmol), $(CF_3CO)_2O$(2 mL), PhI (0.2 equiv.), H_2O–CH_3CN (1 : 4, v/v) for 24 h.

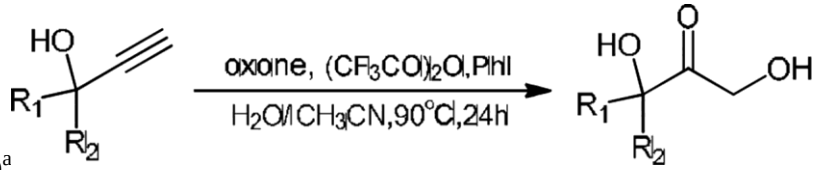
[b] Isolated yields.

[c] NR, no reaction.

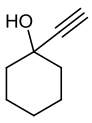
[d] Ac_2O was used instead of $(CF_3CO)_2O$.

[e] $(CF_3CO)_2O$ was not used.

Table 2 Exposure of ethynyl carbinols to oxone /



$(CF_3CO)_2O$[a]

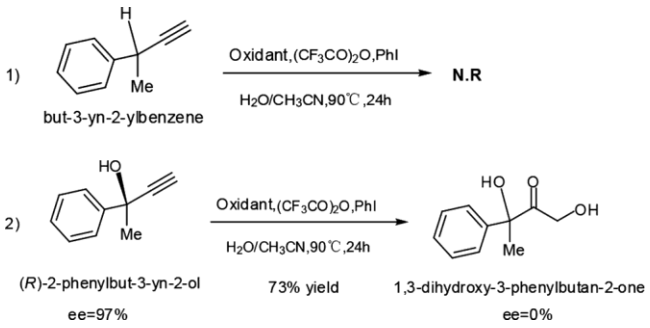
Entry	**R_1**	**R_2**	yield(%)[b]
1	Ph	Me	76
2	4-MePh	Me	75
3	4-ClPh	Me	72
4	4-BrPh	Me	82
5	4-IPh	Me	80
6	4-MeOPh	Me	86
7	4-NO_2Ph	Me	58
8	3-MePh	Me	73
9	3-BrPh	Me	81
10	Ph	Ph	86
11	4-MePh	4-MePh	62
12	4-ClPh	4-ClPh	85
13	Ph	Bn	81
14			63
15	Me	Me	71

16	Me	Et	74

[a] Reaction conditions: ethynyl carbinol (2 mmol), oxidant (5 mmol), $(CF_3CO)_2O$(2 mL), PhI (0.2 equiv.), H_2O–CH_3CN (1 : 4, v/v) for 24 h.

[b] Isolated yields.

Scheme 1. Mechanism Studies



Scheme 2. A Plausible Mechanism for the Oxidation Process