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Synthesis of α-Iodoketones from Allylic Alcohols through Aerobic Oxidative Iodination

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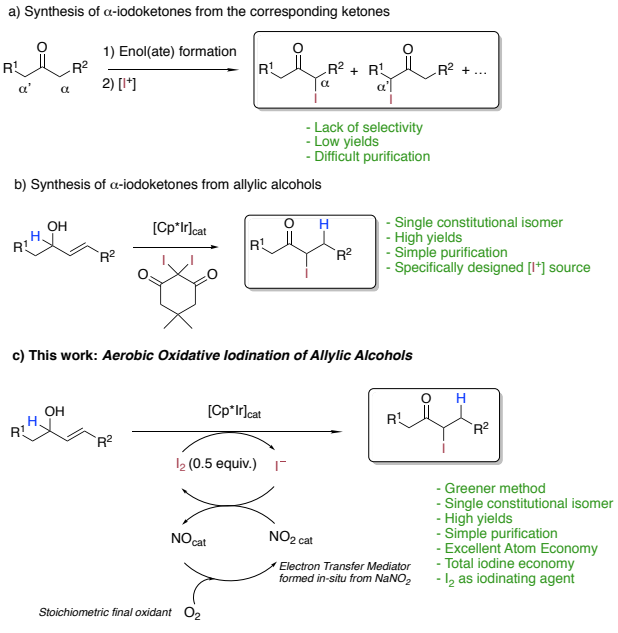
Abstract. An efficient method for the synthesis of α-iodoketones from allylic alcohols and elemental iodine is reported. We show in this paper that the isomerization of allylic alcohols catalyzed by iridium(III) complexes can be combined with an aerobic oxidative iodination protocol, resulting in a straightforward method for the synthesis of a wide range of α-iodoketones as single constitutional isomers and in high yields under mild reaction conditions.

Keywords: isomerization; aerobic oxidative iodination; α-iodoketones; α-aminoketones; allylic alcohol

Iodine is often found in molecules with important applications in industrial and medicinal chemistry.[1] Iodinated organic compounds also play a pivotal role in synthetic organic chemistry as versatile building blocks, as reflected by the vast number of derivatization procedures that have been reported in the literature.[2] At present, numerous methods are known for the synthesis of α-iodinated carbonyl compounds starting from esters,[3] ketones,[4] and even amides.[5] When it comes to the synthesis of α-iodoketones, most of the reported methods rely on the reaction of preformed enol or enolate derivatives with electrophilic iodinating agents. This approach works well when applied to ketones with only one type of enolizables carbon, such as aryl or symmetrical aliphatic ketones. From ketones with two enolizable α-carbons having a strong electronic or steric bias, excellent regiocontrol can be achieved, although often only one regiochemical outcome is viable. In most instances, however, mixtures of both regioisomers are generally obtained, leading to low yields and difficult purifications (Scheme 1a).[4c,d]

Recently, an article from one of our laboratories described an alternative procedure for the preparation of α-iodinated ketones as single constitutional isomers, starting from allylic alcohols (Scheme 1b).[6] The method relies on a 1,3-hydrogen shift catalyzed by an Ir(III) complex, carried out in the presence of an electrophilic iodinating agent. This protocol gave access to α-iodinated carbonyl compounds formally derived from unsymmetrical aliphatic ketones in excellent yields for the first time. A key aspect for obtaining high yields and minimizing unwanted iodination side reactions was the use of a new mild



Scheme 1. Synthesis of α-Iodoketones.

iodinating agent, 2,2-diiodo-5,5-dimethylcyclohexane-1,3-dione (Scheme 1b).

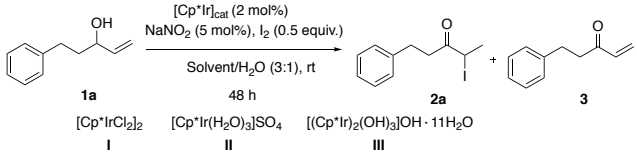
Commercially available and commonly used electrophilic iodinating agents such as I_2, ICl, or NIS (*N*-iodosuccinimide) failed to give the desired product in reasonable yield. Among these electrophilic agents, I_2 would be the most convenient option, as it has a very low toxicity, is environmentally friendly and a cheap and commercially available reagent. From an atom-economy point of view, I_2 is also the best alternative.[7]

In electrophilic monoiodination reactions that use I_2 as the halogen source, only one of the two halogen atoms can be used as electrophile (I^+); one equivalent of iodide (I^-) is formed as a by-product. The halogen atom economy can be improved through the addition of an oxidant to the reaction mixture to oxidize the iodide formed. Several oxidants, have been used in oxidative iodinations in stoichiometric amounts;[8] these include MnO_2,[8f] hypervalent iodine compounds,[8c,d,h] CuO,[8b] oxone,[8l] and H_2O_2.[8g,i,j] One of us has described the aerobic oxidative iodination of organic molecules in excellent yields, using elemental iodine together with oxygen or air as the stoichiometric oxidant.[9] The process requires the use of catalytic amounts of $NaNO_2$ as an electron-transfer mediator, and acidic conditions, and therefore involves nitrogen oxide intermediates. Although oxidative iodination protocol has been used for the α-iodination of ketones, no regiocontrol was achieved for unbiased unsymmetrical ketones (Scheme 1a).[8c,e],[9b,c]

In this paper, we report the synthesis of α-iodoketones as single constitutional isomers from readily available allylic alcohols. The method combines a 1,3-hydrogen shift mediated by iridium(III) catalysts with a C–I bond formation using 0.5 equivalents of iodine as the halogen source under aerobic oxidative conditions (Scheme 1c).

As a starting point to study this transformation, we chose to test the reaction conditions reported by one of us[9d] for oxidative iodination, i.e., I_2 (0.5 equiv.) and $NaNO_2$ (5 mol%) and applied them to allylic alcohol **1a** (Table 1). First, we tested several iridium catalysts of the general structure [Cp*Ir(III)], that we used successfully in the halogenation of allylic alcohols, and in the isomerization of allylic alcohols into carbonyl compounds in a mixture of THF and H_2O (3:1).[10,11] Catalysts **II** and **III** showed similar activities, higher to that of Ir(III) chloride complex **I**. α-Iodoketone **2a** was formed in all cases, in yields ranging from 47 to 60%. An important challenge of this chemistry is to minimize the formation of enone by-products, formed by direct oxidation of the allylic alcohols. For the three catalysts screened, only up to 8% of enone **3** was produced (Table 1, entries 1-3). Complex **II** ($[Cp^*Ir(H_2O)_3]SO_4$) was chosen to continue the optimization studies. Higher yields of **2a** were obtained when the reaction was run under an atmosphere of O_2 (70 *vs* 60%, entry 4 *vs* entry 2). Interestingly, this change also inhibited the formation of enone **3** (entry 4). When the reaction was carried out in a mixture of 2-methyltetrahydrofuran (2-MeTHF) and H_2O in a 3:1 ratio, **2a** was obtained in 72% yield (entry 5). When a mixture of acetone and H_2O (3:1) was used, **2a** was formed in only 13% yield (entry 6). 2-MeTHF/H_2O was chosen as the optimal solvent mixture being 2-MeTHF an ecofriendly alternative to THF.[12] Upon dilution of the reaction mixture (0.04 M *vs* 0.2 M), the yield of **2a** increased further to 90% (entry 7). Control experiments were also carried out (entries 8-11). Both catalysts, iridium complex **II** and $NaNO_2$, were found to be essential for the formation of the desired product (entries 8 and 9, respectively). Replacement of I_2 by NIS or KI under otherwise identical reaction conditions did not give the product either (entries 10-11). The reaction conditions of entry 7 were chosen as the optimal conditions for studying the substrate scope, i.e., 0.5 equiv. of I_2, 5 mol% of $NaNO_2$, and 2 mol% of iridium complex **II**. Remarkably, oxidation by-products, such as enone **3**, were not observed under these reaction conditions.

Table 1. Optimization of the reaction conditions.

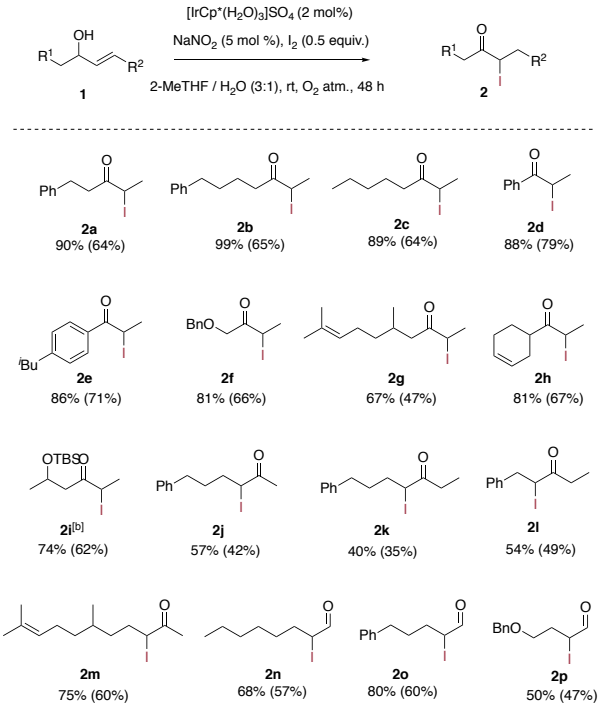


Entry[a]	[Cp*Ir]	atm.	Solvent / H_2O	**2a**/**3** (%)[b]
1	**I**	Air	THF / H_2O	47/8
2	**II**	Air	THF / H_2O	60/8
3	**III**	Air	THF / H_2O	60/8
4	**II**	O_2	THF / H_2O	70/-
5	**II**	O_2	2-MeTHF / H_2O	72/-
6	**II**	O_2	Acetone / H_2O	13/7
7[c]	**II**	O_2	2-MeTHF / H_2O	90/-
8[c]	-	O_2	2-MeTHF / H_2O	-
9[c],[d]	**II**	O_2	2-MeTHF / H_2O	32/-
10[c],[e]	**II**	O_2	2-MeTHF / H_2O	-
11[c],[f]	**II**	O_2	2-MeTHF / H_2O	-

[a] Unless otherwise noted, **1a** (0.2 mmol), solvent / H_2O (0.2 M, (3:1)), [Ir] (2 mol%), $NaNO_2$ (5 mol%), I_2 (0.5 equiv.) were used. [b] Yield determined by ^1H NMR spectroscopy against an internal standard. [c] 0.04 M. [d] Without $NaNO_2$. [e] NIS instead of I_2; a mixture of unknown byproducts was observed. [f] KI instead of I_2; after 48 h, only starting material was observed.

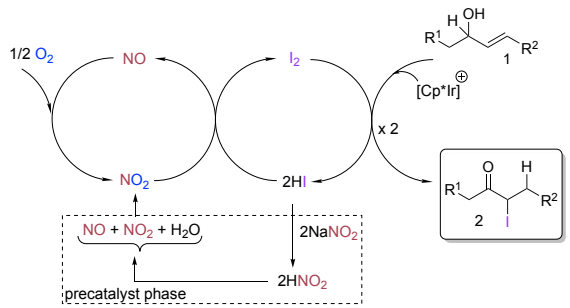
Having established these optimal conditions, the substrate scope was investigated (Scheme 2). Aliphatic allylic alcohols bearing terminal alkenes (**2a**-**2c**) gave the desired α-iodoketones in high yields (89-99%). Aromatic allylic alcohols (**2d**-**2e**) were also well tolerated. Additional functional groups in the allylic alcohols, such as benzyl-protected alcohols, additional double bonds, and silyl ethers, were well tolerated, and the corresponding α-iodinated products

were formed in high yields (**2g-2i**). Allylic alcohols bearing internal alkenes (**2j-2m**) provided the desired products in moderate to good yields (40-75%). Finally, α-iodinated aldehydes were obtained in good yields when primary allylic alcohols were subjected to the reaction conditions (**2n-2p**). In all instances, **2** obtained as single constitutional isomers.

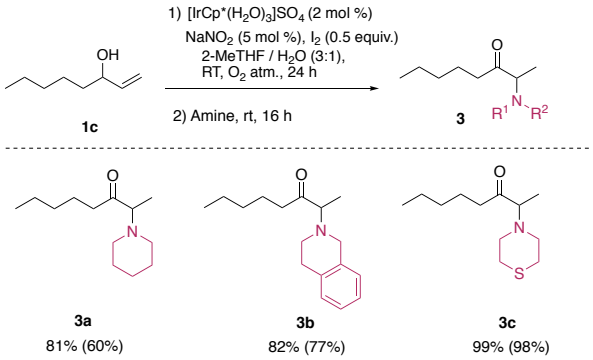


Scheme 2. Substrate scope. Yield determined by ^{1}H NMR spectroscopy against an internal standard. Isolated yields in parentheses. [b] TBS = *tert*-butyldimethylsilyl.

Remarkably, the reactions were carried out using only 5 mol% of $NaNO_2$ and 0.5 equiv. of I_2, and, in contrast to our previous reports,[9] in the absence of an acid additive. A proposed mechanism is shown in Scheme 3. The reaction of the allylic alcohol with the iridium catalyst[11,13] and molecular iodine gives the corresponding α-iodoketone.[6,10] HI is formed as a byproduct, which in turn protonates $NaNO_2$ to give nitrous acid. Rapid decomposition of HNO_2 gives NO_2, a good oxidant that acts as an electron-transfer mediator in the oxidation of iodide by oxygen, the stoichiometric oxidant.[9d]



Scheme 3. Proposed mechanism.



Scheme 4. Synthesis of α-aminoketones. Yield determined by ^{1}H NMR spectroscopy against an internal

The synthetic utility of this new method was demonstrated by taking advantage of the reactivity of α-iodoketones with nitrogen nucleophiles. Thus, α-aminoketones (**3a-3c**) were prepared from allylic alcohol **1c** in a one-pot two-step procedure (Scheme 4). Since α-aminoketones **3a-3c** are formally derived from unsymmetrical aliphatic ketones (i.e., with unbiased enolizable methylene groups), their direct preparation from these precursors would result in the formation of mixtures of α- and α'-aminoketones. In contrast, the synthetic route shown in Scheme 4 yields these compounds as single constitutional isomers in excellent yields (99-81%).

In conclusion, we have described the synthesis of α-iodoketones from the corresponding allylic alcohols and molecular iodine. The method relies on an Ir(III)-catalyzed 1,3-hydrogen shift followed by an aerobic oxidative iodination. The reaction uses just 0.5 equivalents of molecular iodine, in combination with NaNO2 as oxidation catalyst and oxygen as the final terminal oxidant. A wide range of α-iodocarbonyl compounds have been synthesized, all as single constitutional isomers. A one-pot procedure for the transformation of allylic alcohols into α-aminoketones has also been developed.

Experimental Section

General procedure for the synthesis of α-iodoketones from allylic alcohols: In a pressure tube, $NaNO_2$ (0.7 mg, 0.01 mmol, 5 mol%), $[Cp^*Ir(H_2O)_3]SO_4$ (2 mg, 0.004 mmol, 2 mol%) and I_2 (25.3 mg, 0.1 mmol, 0.5 equiv.) were added. The tube was sealed with a Teflon lined cap and the allylic alcohol **1** (0.2 mmol) dissolved in 2-MeTHF (3.75 mL) and H_2O (1.25 mL) was added to the mixture. The pressure tube was purged with oxygen (1 atm) and kept under oxygen (1 atm) by using a balloon. The reaction was stirred at room temperature for 48 h, and subsequently quenched with an aqueous solution of $Na_2S_2O_3$ (1.5 mL) and extracted with Et_2O (3 x 2 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was reduced under pressure. The final product was purified by column chromatography using petroleum ether / EtOAc (99:1) mixture as eluent.

General procedure for the synthesis of α-aminoketones from allylic alcohols: In a pressure tube, $NaNO_2$ (0.7 mg, 0.01 mmol, 5 mol%), $[Cp^*Ir(H_2O)_3]SO_4$ (2 mg, 0.004 mmol, 2 mol%) and I_2 (25.3 mg, 0.1 mmol, 0.5 equiv.) were added. The tube was sealed with a Teflon lined cap and the allylic alcohol **1c** (26 mg, 0.2 mmol) dissolved in 2-MeTHF (3.75

mL) and H_2O (1.25 mL) was added to the mixture. The pressure tube was purged with oxygen (1 atm) and kept under oxygen (1 atm) by using a balloon. The reaction was stirred at room temperature for 24 h, and the corresponding amine (0.3 mmol) was added. The mixture was stirred 16 h under air atm. and subsequently quenched with an aqueous solution of $Na_2S_2O_3$ (1.5 mL) and extracted with Et_2O (3 x 2 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was reduced under pressure. The final product was purified by column chromatography using petroleum ether / EtOAc (9:1) mixture as eluent.

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