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New reactions in water: metal-free conversion of alcohols and ketones into α-iodoketones†

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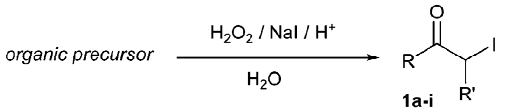
Received (in Cambridge, UK) 23rd July 2004, Accepted 6th September 2004
First published as an Advance Article on the web 4th October 2004

Using water as the reaction medium, ketones can be transformed into α-iodoketones upon treatment with sodium iodide, hydrogen peroxide and an acid; interestingly, α-iodoketones can be also obtained from secondary alcohols through a metal-free tandem oxidation–iodination approach.

The successful completion of organic reactions in water using simple starting materials and generating easily removable by-products of low toxicity is a major task,[1] and a current subject of prime interest in chemistry.[2] On the other hand, α-haloketones are versatile compounds for synthetic purposes.[3] Most methods to transform ketones in their related α-iodo-derivatives in a straightforward manner rely on an activation step of iodine, either by the addition of a stoichiometric amount of a metal salt[4] or, more recently, by that of a reagent containing reactive N–F bonds.[5] To overcome intrinsic limitations associated with the iodination reaction of ketones the use of related masked forms, such as the corresponding enols, became popular from an early stage. Their reactions towards several iodinating agents and conditions were studied[6] and often utilized, even at the expense of a lengthy overall sequence. Furthermore, the consideration of iodide as the iodine source has been scarcely investigated,[7] and is routinely associated with those iodination processes based on exchange reactions of previously α-functionalized precursors.[8] Recently, we have established a robust synthetic alternative for the preparation of iodohydrins by means of an interesting reaction that involves the treatment of an alkene with sodium iodide in the presence of hydrogen peroxide in an acid medium, a process that stems from biomimetic considerations.[9] In keeping with this, we have been interested in the search for new processes that gain access to useful building blocks using conditions that would cope with the current demand for environmentally benign chemical synthesis. Herein, we present an efficient and clean entry to α-iodoketones that offers unprecedented features, among them the manifold of valuable precursors that include not only the corresponding ketone but also the related secondary alcohol. This metal-free transformation is conducted in water as a convenient reaction medium,[10] uses inexpensive and easy to handle precursors, such as sodium iodide and hydrogen peroxide (33% aqueous solutions), and water is the by-product being formed along the reaction path. An overall view of this new process is outlined in Scheme 1.



1a-i

Scheme 1 Access to α-iodoketones from a new reaction of either ketones or alcohols with iodide and hydrogen peroxide in an aqueous acid medium.

As the starting organic compound, ketones were clearly the first to be tested, searching for a direct entry to α-iodoketones. Our approach is simply based on the incorporation of iodide into the organic skeleton (1 : 1 molar ratio) upon treatment with an excess of hydrogen peroxide in an acid medium. After the initial trials, the use of NaI, H_2O_2, and the addition of acids having a pK_a value at or below 3 was found valuable to produce nicely the iodination of cycloheptanone. Several protic acids were screened and found useful to trigger the iodination reaction, among them a simple ion-exchange resin (see Table 1).

Table 1 Effect of acid on the iodination of cycloheptanone[a]

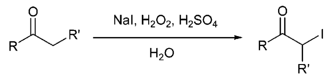
Entry	Acid	Conversion[b]
1	H_2SO_4	98 (92)[c]
2	H_3PO_4	80[d]
3	CF_3CO_2H	81
4	CH_3CO_2H	5
5	Amberlyst®-wet-15[e]	65

[a] Experiments conducted with the following stoichiometry: NaI (1 equiv.), H_2O_2 33% solution (6 equiv.), acid (8 equiv.), 40 °C, 7 h. [b] Determined by GC. [c] Within brackets, isolated yield of the iodoketone after purification by column chromatography. [d] Extending the reaction time up to 14 h. [e] Amberlyst®-wet-15 is a registered trade mark by Rohm&Haas Co., and was purchased from Aldrich.

The reactions were conducted using 5 mmol of cycloheptanone and 15 mL of water. Sulfuric acid provided best results and was routinely used for the iodination of the different ketones that were further assayed, as depicted in Table 2.

Acyclic ketones, which are elusive substrates under many of the iodination conditions previously reported, can be properly halogenated using this protocol. In this sense, higher reaction temperature (60 °C) and larger amounts of reagents were required to achieve comparable results compared with iodination of more reactive cyclic ketones. Alkylarylketones react in a more sluggish form, although giving rise to the corresponding iodinated-derivatives in good yields under optimized conditions (Table 2).

Table 2 Synthesis of α-iodoketones by reaction in water of ketones with sodium iodide, hydrogen peroxide and sulfuric acid[a]



Ketone	H_2O_2/ equiv.	H_2SO_4/ equiv.	*t*/h	α-Iodoketone yield (%)[b]
Cycloheptanone	6	8	7	**1a** (92)[c]
4-Heptanone	12	10	14	**1b** (93)[d]
Cyclooctanone	6	8	3	**1c** (91)[c]
2-Octanone	12	10	14	**1d** (90)[d,e]
p-Methoxyacetophenone	6	16	21	**1e** (94)[c]
Acetophenone	20	16	15	**1f** (85)[d]
p-Nitroacetophenone	20	16	16	**1g** (92)[d]

[a] 5 mmol (1 equiv.) of the corresponding ketone, 33% solutions of H_2O_2 and 15 mL of water were employed. [b] Yield of isolated product. [c] Oil bath at 40 °C. [d] Oil bath at 60 °C. [e] Mixture 1:1.9 (GC) of 1-iodo-2-octanone and 3-iodo-2-octanone

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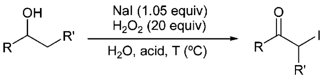
† Electronic supplementary information (ESI) available: experimental details for the iodination of cycloheptanone and the oxidation–halogenation of cyclododecanol. See http://www.rsc.org/suppdata/cc/b4/b411227j/

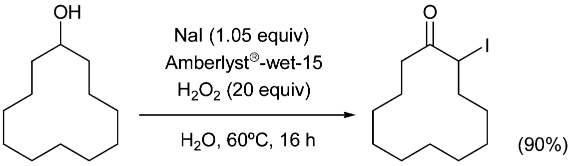
DOI: 10.1039/b411227j

Table 3 Synthesis of α-iodoketones by reaction in water of alcohols with sodium iodide, hydrogen peroxide and an acid[a]



Alcohol	T/°C[b]	Acid/equiv.	t/h	α-Iodoketone yield (%)[c]
Cycloheptanol	50	H_3PO_4 (3)	18	**1a** (71)
4-Heptanol	60	H_2SO_4 (4)	20	**1b** (85)
Cyclooctanol	40	H_2SO_4 (1.25)	16	**1c** (90)
2-Octanol	60	H_3PO_4 (6)	24	**1d** (83)[d]
Cyclododecanol	60	H_2SO_4 (1.25)	16	**1h** (90)[c]
1-Phenylbutan-1-ol	60	H_2SO_4 (6)	72	**1i** (60)[e]

[a] 5 mmol (1 equiv.) of the alcohol, 33% solutions of H_2O_2 and 40 mL of water were employed. [b] Bath temperature. [c] Yield of isolated product. [d] Mixture 1 : 1.5 (GC) of 1-iodo-2-octanone and 3-iodo-2-octanone. [e] 2 equiv. of NaI and 30 equiv. of H_2O_2 were used.



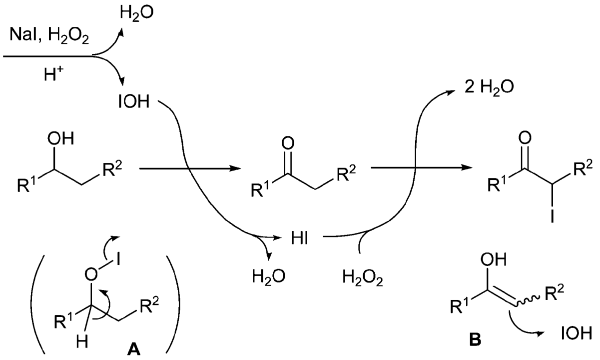
Scheme 2 A new, efficient and green tandem oxidation–iodination reaction of cyclododecanol affording 2-iodocyclododecanone.

Based on our own work on the oxidation of alcohols using stoichiometric amounts of iodine-containing oxidants[11] we became interested in exploring the feasibility of a new tandem process, namely an oxidation–halogenation sequence, starting from a secondary alcohol which would render the target α-iodoketones in a new one-pot operation.[12] After optimization studies, the first successful realization of this synthetic goal is summarized in Table 3. The reaction requires high dilution and a large excess of H_2O_2.

This new process implies more careful optimization of the experimental conditions. Interestingly, the acid, the reaction temperature and the reaction time provide a simple way to control the process. Exploring the viability of a green approach to this new transformation in water, we have gathered interesting preliminary results. Therefore, the outcome of the reaction using a recoverable source of acidity,[13] such as Amberlyst®-wet-15,[14] proved the validity of this notion, as depicted in Scheme 2.

A plausible mechanism to explain the formation of the observed iodoketones from the starting alcohols might reasonably invoke two different steps. Firstly, the alcohol can be readily oxidized upon reaction with IOH[9,15] involving intermediates such as **A**[16] leading to the formation of the corresponding carbonyl group, which then will undergo further iodination in acid media *via* enol **B**. This sequence would require the regeneration of electrophilic iodine that should be formed *in situ* upon reaction of iodide with H_2O_2. An overall view of the process is outlined in Scheme 3.

In summary, a smooth entry to α-iodoketones is reported by reaction of different types of organic precursors with sodium iodide and hydrogen peroxide, a truly convenient oxidant, in the presence of an acid. Surprisingly, though different organic compounds had been previously considered as starting materials, the herein described oxidation–iodination sequence from secondary alcohols is unprecedented. Remarkably, the process is conducted in water and represents an organic solvent and metal-free transformation that can be adapted to work using recyclable acid sources.



Scheme 3 Proposed key steps and tentative intermediates for the one-pot conversion of alcohols to α-iodoketones, comprising oxidation and further iodination.

This research was supported by Principado de Asturias (Grant PR-01-GE-9) and Spanish DGI (Grant BQU-2001-3853). F. G.-B. is grateful to the Principado de Asturias for a fellowship. Generous financial support from Merck Sharp & Dohme is gratefully acknowledged

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