



Microwave-assisted, solvent-free oxidative cleavage of α -hydroxyketones

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ABSTRACT

The oxidative C–C cleavage of α -hydroxy ketones was found to proceed smoothly in solvent-free, silica-supported sodium metaperiodate, under microwave irradiation. This provides a useful and green synthetic procedure to form the corresponding carboxylic acid and aldehyde in good yields, avoiding the solubility problems of the sodium metaperiodate in organic solvents.

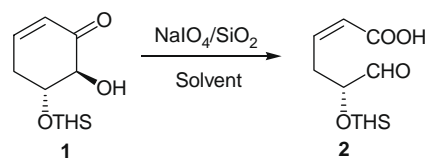
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The oxidative cleavage of vicinal diols, α -hydroxyketones, and related functionalities is a common synthetic procedure and various reagents are available to perform this reaction, such as sodium bismuthate,¹ iodo triacetate,² manganic pyrophosphate,³ KHSO_5 ,⁴ calcium hypochlorite,⁵ basic hydrogen peroxide,⁶ methylrhodium trioxide,⁷ Bi/O_2 ,⁸ sodium percarbonate,⁹ and vanadium-based HPA and dioxygen.¹⁰ However, the most versatile reagents for this purpose are sodium metaperiodate,¹¹ and lead tetraacetate.^{12–14} Usually sodium metaperiodate is used in aqueous solutions, because the effectiveness of this oxidant in organic solvents is very limited due to its insolubility.¹⁵ Lead tetraacetate has been used in non-aqueous media to accomplish the same types of reactions effected by periodates with water-soluble compounds.¹⁵ On the other hand, this reagent is difficult to store and handle, non-environmentally friendly and, being more reactive, can afford undesired oxidation byproducts.

Aiming to expand the versatility of sodium metaperiodate as an oxidizing reagent in organic media, and to overcome the solubility issues, variations of a silica gel-supported sodium metaperiodate reagent have been disclosed, to promote oxidative cleavage of 1,2 diols, and oxidation of hydroquinones and sulfur-containing compounds.^{16–18} Usually the sodium periodate is adsorbed on silica gel, and stirred with the starting material in dichloromethane, ether, or benzene. To our knowledge, no applications of this silica-supported reagent for the oxidation α -hydroxyketones have been reported.

In the course of our studies toward the synthesis of isolaulimide, we needed to effect the oxidative cleavage of acyloin **1** to the formylacid **2**, Scheme 1. Because of the insolubility of **1** in water, the oxidation was first tried with lead tetraacetate,¹⁴ giving mainly products resulting from over-oxidation, along with trace amounts of the desired oxoacid. Thus, we tried the milder metaperiodate to achieve the desired cleavage. Initial attempts using sodium metaperiodate in several acetonitrile/ H_2O and THF/ H_2O mixtures met with failure, with the starting material being recovered unchanged. To overcome the solubility issues, a supported reagent was considered, in order to achieve a greener and more versatile method to promote the cleavage of α -hydroxyketones. Since we were not aware of the use of silica-supported metaperiodate to produce formylacids by cleavage of acyloins we decided to undertake a study of this reaction.

Following the protocol described by Shing,¹⁶ a wet silica-supported metaperiodate reagent was prepared, which also supplies the moisture needed to accelerate the reaction.¹⁸ Initially, α -hydroxyketone **1** (Scheme 1) was subjected to oxidative conditions using 3.0 equiv of sodium periodate in silica gel, at ambient temperature for 24 h in the solvent indicated (Table 1).



Scheme 1. Oxidation of acyloin 1.

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Table 1
Solvent effect in oxidative cleavage of **1**^a

| Entry | Solvent | p^b | ϵ^c | 1:2 ratio ^d |
|-------|-----------------|-------|--------------|------------------------|
| 1 | Ethyl acetate | 4.3 | 6.0 | 85:15 |
| 2 | Tetrahydrofuran | 4.2 | 7.4 | 87:13 |
| 3 | Dichloromethane | 3.4 | 9.1 | 80:20 |
| 4 | Toluene | 2.3 | 2.4 | 12:88 |
| 5 | No solvent | — | — | 0:100 |

^a Reactions were carried out with 0.11 mmol of **1** in 1.5 mL of solvent and 3 equiv of NaIO₄/SiO₂, at ambient temperature for 24 h.

^b Solvent eluotropic strength parameter for silica gel, according to Halpaap.¹⁹

^c Dielectric constant at 20 °C.

^d All ratios were determined by ¹H NMR of the crude reaction mixture.

As can be seen from Table 1, the solvent has a profound effect on the reaction conversion. The data show that the eluotropic strength of the solvent is more related than its polarity to the conversion. This seems to indicate that higher conversions are obtained when the substrate is more retained to the surface of the silica, in agreement with the fact that best results were found using no solvent (entry 5), where complete conversion was achieved upon 24 h.

Given the long reaction time needed for full conversion, the possibility of accelerating the reaction by microwave irradiation on a monomode microwave reactor (CEM corporation, model Discover) was considered (representative results are shown in Table 2).

This was indeed the case, although the effects were dependent on the solvent used. For ethyl acetate and dichloromethane (entries 1 and 3), 10 min of irradiation at 80 °C was enough to produce a conversion similar to that of the non-irradiated experiment run for 24 h at ambient temperature. Unfortunately, irradiation at higher temperature (110 °C) or for longer periods (up to 20 min, data not shown) did not result in improvement of the yield. Irradiation of the tetrahydrofuran suspension (entry 2) for 10 min afforded a higher conversion than that at ambient temperature. However, similar to the previous results, upon further irradiation the conversion did not improve significantly (reaching a maximum near 70%, data not shown). On the other hand, toluene (entry 4) showed a good initial conversion in the first 10 min at 80 °C, but further irradiation at this temperature resulted in decomposition, which also occurred after 10 min at 110 °C. Likewise, irradiation of the sample without solvent at 80 °C resulted in decomposition.

The results are in agreement with an acceleration of the reaction induced by microwave irradiation, despite the different solvent-dependent outcomes. Considering that a solvent-free approach was desirable, we searched for a temperature where no decomposition of the sample in the solid support occurred. After some experimentation, it was found that at 50 °C the reaction proceeded smoothly (entry 5), giving no decomposition products through a very clean reaction. Moreover, upon 2 h of irradiation,

Table 2
Oxidative cleavage of **1** under microwave irradiation^a

| Entry | Solvent | 1:2 ratio 80 °C/10 min | 1:2 ratio 110 °C/10 min | 1:2 ratio 50 °C/1 h |
|-------|---------------------------------|---------------------------|----------------------------|------------------------|
| 1 | EtOAc | 85:15 | 80:20 | No reaction |
| 2 | THF | 70:30 | 40:60 | No reaction |
| 3 | CH ₂ Cl ₂ | 72:28 | 66:34 | 84:16 |
| 4 | Toluene | 44:56 | Decompose | 80:20 |
| 5 | No solvent | Decompose | Decompose | 21:79 |

^a All reactions were carried out with 0.11 mmol of **1** in 1.5 mL of solvent and 3 equiv of NaIO₄/SiO₂ and irradiated at 200 W, at the temperature and time specified in the table.

Table 3
Periodate:acyloin ratio for cleavage of **1** under microwave irradiation

| Entry | Periodate equivalents | Conversion at 60 min, 50 °C |
|-------|-----------------------|-----------------------------|
| 1 | 1.5 | 50:50 |
| 2 | 3.0 | 21:79 |
| 3 | 4.5 | 16:84 |

the conversion was complete (100%) and the product was isolated with an excellent yield of 90%.

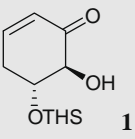
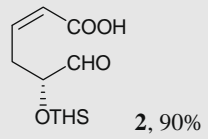
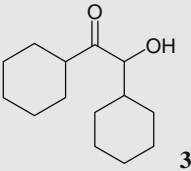
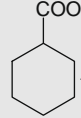
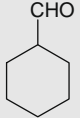
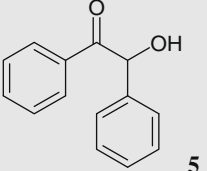
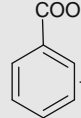
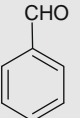
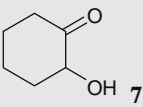
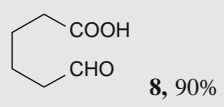
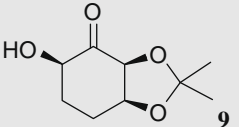
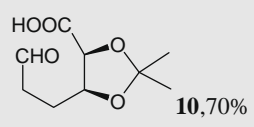
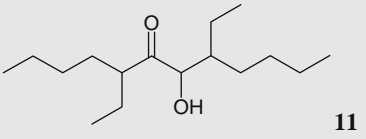
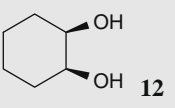
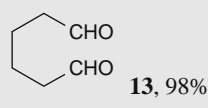
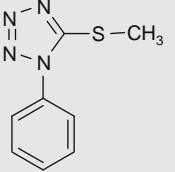
Having these conditions at hand, the optimum NaIO₄/substrate ratio was determined (Table 3). Given the non-significant difference in conversion achieved with 3.0 and 4.5 equiv, the use of a 3:1 ratio was chosen as the optimum.

Once optimal conditions for the oxidative cleavage of α -hydroxy ketone **1** were defined (3 equiv of sodium metaperiodate, solvent-free, 50 °C, 200 W)[†], an array of representative acyloins, diols, and sulfides was subjected to them. As can be seen from Table 4, most α -hydroxyketones gave the expected products in good to excellent isolated yields. For entries 2 and 3, the yields were calculated based on the carboxylic acids since the resulting aldehydes were volatile. The mild conditions of this method allowed performing the oxidation on sensitive compounds such as acyloin **9**, which rapidly afforded the labile formylacid **10** in good isolated yield (entry 5). Conversely, this mildness could also explain the lack of reactivity of compound **11**, which was recovered unchanged even after 4 h of irradiation (entry 6). As expected, diols were more reactive than acyloins, giving the dicarbonyl compounds in a fast and clean reaction (entry 7). In the conditions tested, sulfides were reluctant to react, affording less than 10% of oxidized products after 4 h of irradiation (entry 8). This observation could lead to a selective method for cleavage of acyloins and/or vic-diols in the presence of sulfur-containing compounds.^{20,21} Further studies in this direction are under way. Finally, the reaction was performed in a 1 mmol scale (the maximum capacity of the microwave reactor used), obtaining the same clean conversions and isolated yields, although in a consistently 20–25% longer reaction time.

In summary, the facile oxidative cleavage of acyloins with wet silica-supported sodium metaperiodate under microwave irradiation has the advantages of manipulative convenience, excellent yield, and wide application. This protocol is attractive for vicinal diols, α -hydroxyketones that are not soluble in polar media, and for aldehydes and acids that are water soluble (where the product recovery from an aqueous solvent is difficult). It is worth mentioning the mildness of the method which allows its use with sensitive compounds, and probably produces selective oxidative cleavage in the presence of sulfur functionalities.

[†] In a typical procedure, silica gel-supported sodium metaperiodate is prepared according to the procedure described by Shing.¹⁶ NaIO₄ (2.57 g, 12.0 mmol) was dissolved in 5 mL of hot water (70 °C) in a 25 mL round-bottomed flask. To the hot solution silica gel (230–400 mesh, 10 g) was added with vigorous swirling and shaking. The resultant silica gel coated with NaIO₄ was in a powder form and was free-flowing, with a concentration of approximately 15% in NaIO₄. The reagent can be kept in a bottle for 1 month with negligible loss of activity. The oxidative cleavage is carried out in the following manner. The α -hydroxyketone (0.11 mmol) is dissolved in a round-bottomed flask and silica-supported sodium metaperiodate (3.0 equiv in NaIO₄) is added. Solvent is evaporated and the free-flowing silica is placed in a proper microwave test tube (sure sealed 10 mL test tubes with magnetic stirring). After the indicated time of irradiation at 200 W, 50 °C, in a monomode microwave reactor from CEM corporation, model Discover, ethyl acetate is added and the silica is filtered off. Solvent is evaporated and the reaction crude is purified by column chromatography if needed.

Table 4
Solvent-free oxidative cleavage of representative substrates^a

| o | Substrate | Time (h) | Product (%) ^b |
|---|---|----------|---|
| 1 |  1 | 2 |  2 , 90% |
| 2 |  3 | 1 |  +  4a + 4b , 97% |
| 3 |  5 | 3.5 |  +  6a + 6b , 70% |
| 4 |  7 | 0.7 |  8 , 90% |
| 5 |  9 | 0.1 |  10 , 70% |
| 6 |  11 | 4 | No reaction |
| 7 |  12 | 0.1 |  13 , 98% |
| 8 |  14 | 4 | <10% of sulfone and sulfoxide |

^a All reactions were carried out with 0.11 mmol of substrate and 3 equiv of NaIO₄/SiO₂ and irradiated at 50 °C with 200 W, for the time specified in the table.

^b Isolated yield.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2009.07.048](https://doi.org/10.1016/j.tetlet.2009.07.048).

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