SHORT PAPER

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A novel catalytic role of molecular iodine in the oxidation of benzylic alcohols: microwave-assisted reaction

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Molecular iodine was used to catalyse the oxidation of several benzylic alcohols to the corresponding ketones under the microwave-irradiated method, and the role of iodine was explored.

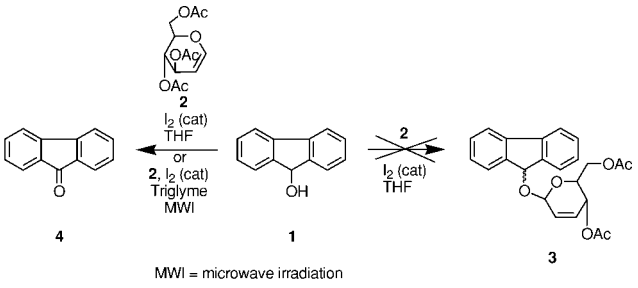
Keywords: molecular iodine, benzylic alcohols

The oxidation of alcohols to aldehydes and ketones is a very common reaction in organic synthesis, both in regular laboratory experiments and in process research in the pharmaceutical industry.[1] For many of the methods reported for this transformation, it has been found that a majority of the common oxidizing agents require a molar or higher proportion of the reagents. As a result, large amounts of hazardous and toxic chemicals may be formed, creating a severe disposal problem. For this reason, ecologically friendly[2,3] methods are desirable.

Results and discussion

In continuation of our program on the synthesis and biological evaluation of polycyclic aromatic compounds as anticancer agents,[4] we required several optically active polycyclic benzyl alcohol derivatives. A number of methods are known for the synthesis of optically active alcohols via the resolution of racemic alcohols. One attractive method is the Lewis acid-mediated glycosylation reaction.[5] It has been found that racemic alcohols with diverse functionalities can react with tri-O-acetyl D-glucal (**2**) in the presence of molecular iodine to give separable diastereomeric glycosides, and on mild acid-mediated cleavage, these glycosides generate the corresponding chiral alcohols.[6] In contrast to our expectations, treatment of 9-fluorenol (**1**) (Table 1, entry 1) with the tri-O-acetyl D-glucal (**2**) in the presence of 20 mol% iodine at room temperature using dry tetrahydrofuran as the solvent did not produce any glycoside **3**; instead the product was 9-fluorenone (**4**) (Scheme 1).

At reflux temperature, the product was also the ketone **4**, though the reaction time was shorter. This result is interesting since only 20 mol% of iodine was used. To be successful in this type of reaction one would expect to need a molar ratio of the reagents.



Scheme 1

The oxidising power of several iodine salts has been reported.[7] Oxidation studies of phenolic derivatives in the presence of strong alkali with molecular bromine[8] and iodine[9] are also known. In many cases, however, this type of oxidation produces a mixture of products because drastic conditions and excess reagents are used.

Efforts to reduce the number of by-products has led to a growing tendency to utilise the benefits of microwave irradiation in organic synthesis,[10] because of its convenient nature. Therefore, we treated alcohol **1** (entry 1) with tri-O-acetyl D-glucal (**2**) in the presence of 20 mol% iodine using triglyme as the energy transfer medium using microwave irradiation (see below). The product of this reaction was found to be the ketone **4**.

As a result, we became interested in comparing the molecular iodine-catalysed oxidation reactions in other systems using conventional heating and microwave irradiation. To our knowledge, a study of the oxidation of organic molecules by molecular iodine under neutral conditions has never been explored.

We selected several alcohols for the study. From Table 1, it appears that dibenzylic alcohols (entries 1–7) are the most suitable substrates, although benzylic alcohols can be used with success (entries 8 and 9). A wide range of dibenzylic alcohols (open chain, tricyclic, and pentacyclic) can be oxidised readily by 20 mol% molecular iodine using tetrahydrofuran as the solvent at room temperature or at reflux temperature in excellent yield. Recently, we[4b] have demonstrated the use of a substituted dibenzofluorenone as an antitumor agent *in vitro*.

The oxidation of a substrate containing an amido group (Table 1, entry 7), using catalytic amounts of iodine, to the ketone under these conditions, is of special interest. Under strong alkali and with a molar proportion of iodine, no defined product from this reaction could be isolated. Under microwave irradiation, tetrahydrofuran (b.p. 66°C) is not the solvent of choice because of its relatively low boiling point compared to the other higher boiling ether-like solvents, such as diglyme (b.p. 162°C) and triglyme (b.p. 216°C). We considered a number of parameters in selecting the solvent for microwave irradiation.[11] For the microwave irradiation method, we required solvent with a much higher boiling point than the required temperature of the reaction and a high dipole moment. We found triglyme to be the best microwave energy transfer agent for these oxidations. Irradiation of a suspension of the alcohol (entry 1) in triglyme using 20 mol% iodine for a few minutes under medium power level afforded the ketone. The same reaction outside the microwave oven at room temperature to 120°C required 2 h for completion. Using a preheated oil-bath (at 120°C, inside temperature), the reaction was complete within 30 min.

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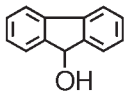
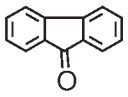
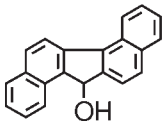
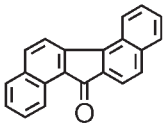
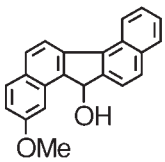
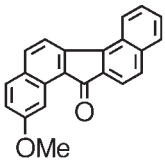
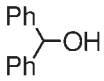
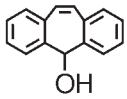
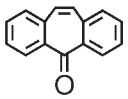
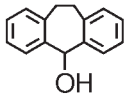
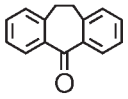
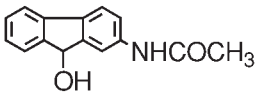
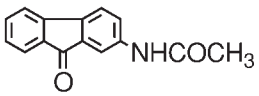
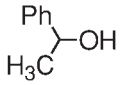
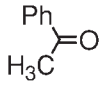
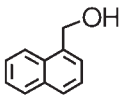
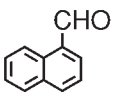
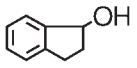
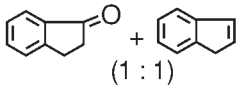
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Molecular iodine-catalysed oxidation of alcohols under microwave irradiation

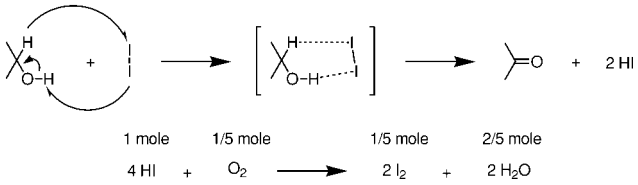
Entry	Starting Material	Product	Power level	Reaction time (min)[a,b]	Yield (%)	mp (°C) (crystalising solvent)
1			5	6	81	80–82 (CH_2Cl_2/hexanes) lit[17]: 82–85
2			5	8	76	162–164 (acetone) lit[17]: 175
3			5	8	72	(benzene) 180–182 (acetone/hexanes)
4			5	8	90	48–50 (CH_2Cl_2/hexanes) lit[17]: 48–49
5			5	8	85	86–88 (CH_2Cl_2/hexanes) lit[17]: 88–89
6			5	8	82	32–34 (CH_2Cl_2/hexanes) lit[17]: 32–34
7			5	8	75	224–226 (CH_2Cl_2/hexanes)
8			5	7	50	Oil
9			5	8	50	Oil
10			5	8	60	Did not isolate

[a] Reaction time under conventional method 12–24h; 6h (THF, reflux), 1.5–2h (triglyme, RT to 125°C), 30 min (triglyme, preheated oil bath, 120–125°C).
[b]The approximate average temperature of the reaction mixture was estimated by turning off the oven. A direct comparison[11a] with known authentic samples kept in a sealed capillary tube next to the reaction mixture was done.

No reaction was observed in the absence of iodine indicating that dissolved oxygen is not the catalysing agent responsible, although we believe that it has a significant role (see below). That this reaction required catalytic amounts of iodine was demonstrated by a titration experiment with standard sodium thiosulfate solution. The amount of sodium thiosulfate solution consumed after the completion of the experiment was identical to the amount needed to neutralise the same amount of iodine used separately.

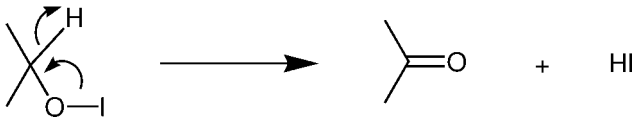
The mechanism of iodine-catalysed reaction has been studied by some investigators.[9,12] Notably, with a molar proportion of iodine, two mechanisms were advanced based on the kinetics of the experiment and the nature of the solvents. The striking differences between those conditions and the present study is the use of one-fifth mole of iodine and the absence of any alkali. It is most probable that the oxidation of alcohol under the present conditions involved a cyclic transition state[13, 14] and the oxidative transfer of a hydride ion from an α-carbon. As the reaction proceeded with catalytic amounts of iodine, regeneration of iodine must have occurred.

Very recently, Koreeda *et al.*[12] demonstrated the generation of anhydrous hydrogen iodide by the reaction of catalytic amounts of solid iodine and a thiol. Since we used one-fifth mole of iodine, we expected the formation of one-fifth mole of the ketone and two-fifth mole of hydroiodic acid, assuming complete consumption of iodine. We believe that hydroiodic acid generated in the presence of oxygen liberates free iodine. This was verified by treatment of the alcohol with hydroiodic acid in tetrahydrofuran, which led to the formation of the ketone. The colour of the reaction mixture was turned reddish indicating the liberation of iodine in the media. A slow bubbling of oxygen into the reaction medium enhanced the speed of the reaction, whereas conducting the reaction in dry anhydrous solvent (THF or triglyme) under inert conditions drastically slowed the reaction. By considering the above facts and by following the mechanism postulated by Kaplan,[8a, b] we suggest an equation (equation (1)) whereby one mole of the alcohol and one mole of iodine generate one mole of the ketone and two moles of hydroiodic acid. Equation (1) shows the catalytic role of iodine in the present oxidation.



Equation (1) Mechanism of molecular iodine-catalysed benzylic alcohol through cyclic transition-state.

Alternatively, we suggest the formation of a hypoiodite intermediate even though it may form slowly in the absence of a base.[13,15] This hypoiodite intermediate can eliminate hydroiodic acid at high temperature and/or under microwave irradiation (equation (2)).



Equation (2) Mechanism of molecualr iodine-catalysed benzylic alcohols through the formation of hypoiodite.

In conclusion, we have developed a simple molecular iodine-catalysed oxidation method for the rapid synthesis of several polycyclic aromatic ketones under microwave irradiation. The catalytic role of iodine has also been advanced. The characteristic features of this procedure are operational simplicity, very simple glass apparatus, no stirrers, no oil-bath or heating mantle, and excellent yield with catalytic amounts of the reagents. The application of this method will be reported in due course.

Experimental

General experimental procedure for microwave irradiation: In a 125 ml Erlenmeyer flask, hydroxy compound (entry 7, 2.75 mmol) was taken in triglyme (2 ml) and iodine (0.55 mmol). The mixture was irradiated in a domestic microwave oven (2450 MHz) for 6–8 min at medium power level (Kenmore Model 565.69580890, 600-1200W of 2450MHz microwave beam). The temperature was kept under 130°C.[16] The reaction mixture was diluted with water (10 ml) and extracted with dichloromethane (50 ml), washed with saturated sodium thiosulfate solution, brine, dried with anhydrous sodium sulfate, and evaporated. The pure product[17] was isolated after column chromatography over silica gel using ethyl acetate-hexanes (10:90) as the eluent.

2-N-Acetyl-9-fluorenone (entry 7): m.p. 224–226°C (CH_2Cl_2/hexanes); UV (CH_2Cl_2): λ_{max} 273.14 nm (log ∈ = 4.63); IR (film) cm^{-1}: 3369, 2360, 1691, 1601, 1553, 1311, 1103, 855, 761, 734; ^{1}H NMR (300 MHz) $CDCl_3$ δ: 7.94–7.82 (1H, m, ArH), 7.64–7.52 (2H, m, ArH), 7.48–7.36 (4H, m, ArH), 2.22 (3H, s, CH_3); ^{13}C NMR δ: 193.581, 168.489, 144.460, 139.913, 138.945, 134.070, 134.255, 128.560, 125.464, 124.392, 121.021, 120.096, 115.801, 24.638. Anal.Calcd for $C_{15}H_{11}O_2N$: C, 75.94; H, 4.64; N, 5.90. Found: C, 75.74; H, 4.60; N, 5.85.

2-Methoxy 13-ketodibenzofluorene (entry 3): m.p. 180–182°C (acetone/hexanes); UV (CH_2Cl_2): λ_{max} 228.28 nm (log ∈ = 4.59), λ_{max} 249.83 nm (log ∈ = 4.36), λ_{max} 287.86 nm (log ∈ = 4.58); ^{1}H NMR (200 MHz) $CDCl_3$ δ: 8.51 (J = 7.93 Hz, d, 1H, Ar), 8.28–8.40 (m, 1H, Ar), 8.02 (J = 8.28 Hz, d, 1H, Ar), 7.92–7.76 (m, 2H), Ar), 7.74–7.42 (m, 5H, Ar), 7.12–6.94 (m, 1H, Ar), 3.99 (s, 3H, OMe); ^{13}C NMR δ: 196.344, 160.729, 147.156, 141.651, 137.957, 134.920, 132.217, 131.743, 130.039, 129.777, 129.686, 129.647, 128.692, 127.700, 127.573, 125.399, 124.558, 120.136, 119.438, 118.867, 101.357, 55.481; Anal. Calcd for $C_{22}H_{14}O_2$: C, 85.16; H, 4.51. Found: C, 85.00; H, 4.41.

General procedure under conventional method: To a solution of the alcohol (2.75 mmol) in anhydrous THF (10 ml) was added iodine crystals (0.55 mmol) and the mixture was stirred at room temperature. The progress of the reaction was followed by TLC (time 12–24 h). After evaporation of THF, water (2 ml) was added to the mixture and it was extracted with dichloromethane (50 ml), washed with saturated sodium thiosulfate solution, brine, dried and evaporated. The crude product on crystallization from CH_2Cl_2-hexanes gave the pure product[18] in comparable yield.

The above reaction was repeated under reflux (~6 h) and the product was obtained in comparable yield.

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13 The kinetics of the oxidation of benzhydrols to benzophenone by iodine in alkaline methanol was reported, see: Y. Ogata, Y. and K. Nagura, *J. Org. Chem*. 1974, **39**, 3680.

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15 We thank a reviewer for suggesting the consideration of the hypoiodite path.

16 It is convenient to irradiate the reaction mixtures under microwave periodically for 1- min intervals. The on–off cycle of the domestic microwave oven can be used to keep the temperature of the reaction mixture under 130°C. For better temperature control the use of a heat sink as described in the previous publications[11] is recommended. The open glass-system used in this study is very convenient, safe and it can prevent explosions due to rapid rise of pressure and temperature.

17 The compounds reported here gave satisfactory m.p., spectral data, and were compared with known authentic samples available from Aldrich chemical company. For the synthesis of 13-dibenzofluorenone (entry 2) see: R.G. Harvey, J. Pataki, C. Cortez, P. Di Raddo and C. Yang, *J. Org. Chem*. 1991, **56**, 1210.

18 Synthesis of these types of benzylic ketones was reported earlier by the oxidation of benzylic methylenes in alkali and acid media. For example see: (a) R. G. Harvey, E. Abu-shqara and C. Yang, *J. Org. Chem.* 1992, **57**, 6313; (b) B.K. Banik, M.S. Venkatraman, C. Mukhopadhyay, and F.F. Becker, *Tetrahedron Lett*. 1998, **39**, 7243 and references cited therein.