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Carboxylic acids from methyl aryl ketones by means of a new composite aerobic oxidation process

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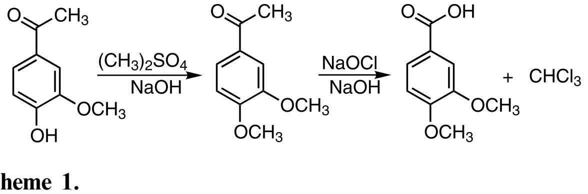
Abstract—A new aerobic oxidation method for conversion of methyl aryl ketones to the corresponding benzoic acids is presented. The method is cheap and environmentally friendly, which also makes it suitable for large scale industrial use. The method affords a yield of >75% with an almost 100% selectivity. Experiments have shown that the process operates following two mechanistic pathways, namely by base-catalysed autoxidation and by single electron transfer processes. © 2002 Elsevier Science Ltd. All rights reserved.

The lignosulfonate oxidation process for the production of vanillin[1] also produces several side-products such as 1-(4-hydroxy-3-methoxyphenyl)-ethanone (acetovanillone), vanillic acid, *para*-hydroxy benzaldehyde, and more. Acetovanillone serves as an industrial feedstock for 3,4-dimethoxybenzoic acid (veratric acid), which is an important intermediate for the synthesis of several pharmaceutical chemicals such as mebeverine,[2] vesnarinone,[3] and itopride.[4] A current industrial process to veratric acid that is based on acetovanillone is shown in Scheme 1.

The oxidation step of this process is based on the haloform reaction with NaOCl. However, this process suffers a serious drawback from an environmental point of view, since 1 equiv. of chloroform is produced for each molecule of target compound. Moreover, chlorinated aromatic side-products may also be formed during this process.[5]

Due to the continuing demand for more environmentally friendly industrial production processes we initiated a project with the goal to look for more green and environmentally benign selective processes for veratric acid. Recently, we reported a method based on the alkaline nitrobenzene lignin oxidation method for the oxidation of methyl aryl ketones.[6] Even though this method afforded both high yields and demonstrated good selectivity for the corresponding aromatic carboxylic acid, the method was encumbered with a drawback since the oxidant, 1,3-dinitrobenzene, was required in stoichiometric quantities.



Scheme 1.

In this context, we have, in an endeavour to develop the stoichiometric 1,3-dinitrobenzene oxidation method into a catalytic process, discovered a complex composite oxidation process, that is partly catalytic in 1,3-dinitrobenzene and partly proceeds as a base-catalysed autoxidation (Scheme 2).

We have discovered that one of the crucial points for the new oxidation method is the production of the enolate anion from the methyl aryl ketone. When the enolate anion is formed, the oxidation takes place by means of single electron transfer (SET) processes as we have reported earlier for the method using 1,3-dinitrobenzene as stoichiometric oxidant.[6] The SET processes and the oxygen atom transfer are illustrated in pathway (*a*) of Scheme 2. In our attempts to develop this process into a catalytic process using oxygen as the terminal oxidant, we discovered that by using only 5% (w/w) of 1,3-dinitrobenzene with concomitant bubbling of molecular oxygen through the reaction mixture, a high yield (>75%) of benzoic acid was obtained when acetophenone was used as a model compound.

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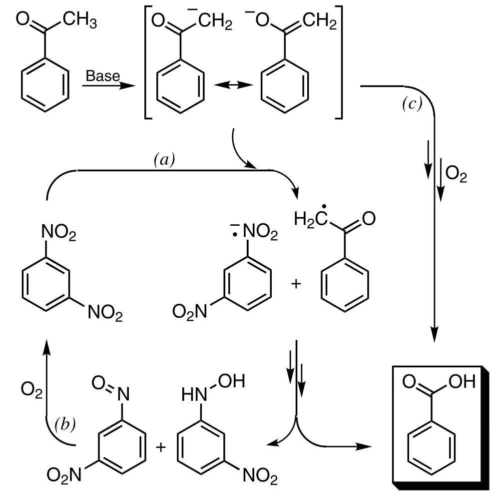


Scheme 2.

The outcome of the oxidation process was, however, very dependent on the reaction temperature as well as the quantity of base (experiments #1–4, Table 1). A maximum yield of 75.2% (entry #4) was obtained when acetophenone was oxidised.

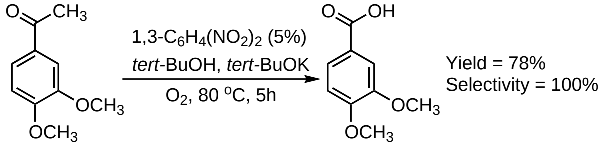
When attempts were made to carry through the oxidation by using water as solvent and sodium hydroxide as base (entry #5), the reaction failed. This is in contrast to the stoichiometric method which can be performed successfully under such conditions.[6]

Base-catalysed aerobic oxidation of acetophenone into benzoic acid is described in the old literature.[7] Later reports by Wallace et al.[8] and Petric et al.[9] describe such processes affording high yields. However, these processes also suffer from 'environmental drawbacks' because the two processes require the rather environmentally unfriendly solvents hexamethylphosphoramide (HMPA) and dimethylformamide (DMF), respectively. Moreover, the process using HMPA as reaction medium also needs a very long reaction time, which is a drawback from an industrial point of view.

When our new oxidation process was performed without the presence of the mediator, 1,3-dinitrobenzene (entry #6, Table 1), a surprisingly high yield of benzoic acid (58.2%) was produced. Hence, the base-catalysed autoxidation, pathway (*c*) of Scheme 1, is a substantial contributor to the overall picture. An experiment performed without bubbling oxygen (entry #7, Table 1), but with the catalytic quantity of 1,3-dinitrobenzene present, afforded, as expected, less than 8% of benzoic acid ascribed to the participation of 1,3-dinitrobenzene as stoichiometric oxidant.[6] The results of these experiments reveal a significant catalytic effect of 1,3-dinitrobenzene. The total outcome of the combined process, including pathways (*a*), (*b*), and (*c*) of Scheme 2, gives a high yield with an excellent selectivity (entry #4).

When the oxidation method was applied to the oxidation of acetoveratrone, the industrial feedstock for veratric acid (Scheme 3), an excellent yield and selectivity (78 and 100%, respectively) were achieved.

The reaction conditions and the solvent (*tert*-BuOH) may easily be implemented in a full scale industrial plant, however, the base *tert*-BuOK is expensive and preferably should be substituted with a cheaper one.



Scheme 3.

Table 1. Oxidation of acetophenone by means of 1,3-dinitrobenzene catalysed aerobic oxidation process

#	Reaction conditions[a]			Responses[b]		
	Base/(mmol)	*T* (°C)	$Ph(NO_3)_2$	Conv.	Yield	Selec.
1	*t*-BuOK/4.8	20	0.12	67.0	39.9	59.6
2	*t*-BuOK/4.8	50	0.12	74.6	53.5	71.5
3	*t*-BuOK/4.8	80	0.12	72.9	61.2	84.0
4	*t*-BuOK/8.0	90	0.12	75.8	75.2	98.9
5[c]	NaOH/15.0	80	0.12	–	–	–
6	*t*-BuOK/7.2	80	–	91.7	58.2	63.6
7[d]	*t*-BuOK/7.2	80	0.12	13.3	~8	60.0
8	KOH/4.8	80	0.12	73.8	12.1	16.4
9[e]	NaOH/38.5	80	–	52.4	22.5	43.4

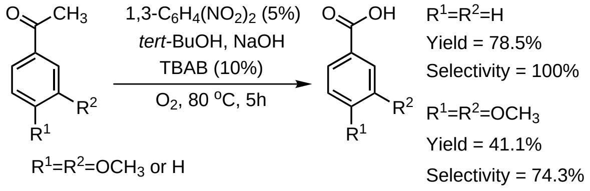
[a] Procedure: acetophenone (0.288 g, 2.4 mmol) was dissolved in *tert*-BuOH (12 mL) followed by adding *t*-BuOK and 1,3-dinitrobenzene (0.12 mmol) with oxygen bubbling through the reaction mixture. The reaction mixture was heated with stirring for a period of 5 h.

[b] Isolated product corrected for impurities using GC analyses.

[c] NaOH was added as a 30% (7.5 M) aqueous solution.

[d] Experiment performed without bubbling oxygen but under a nitrogen atmosphere. The isolated product was impure.

[e] Procedure: acetophenone (18.8 mmol) was dissolved in *tert*-BuOH (95 mL) and NaOH added as base. The reaction was conducted by using a mechanical stirrer to improve mixing.



Scheme 4.

Some experiments which were carried out using KOH and NaOH as base (entries #8 and #9 of Table 1) showed, however, disappointing results. We thought that this was due to solubility problems. Experiments conducted with a phase transfer catalyst (PTC) present, tetrabutylammonium bromide (TBAB), reveal our assumption to be correct. Scheme 4 shows results from an experiment when sodium hydroxide was used as base in the presence of TBAB (10%) as PTC. Other conditions were as described above. An excellent yield (78.5%) and selectivity (~100%) were achieved for the oxidation of acetophenone under these conditions. When acetoveratrone was submitted to the oxidative conditions using NaOH as base and TBAB as PTC, a somewhat lower yield and selectivity were obtained, but will, in future studies, be a subject for optimisation.

In summary, the oxidation method presented here requires basic conditions and molecular oxygen at a moderate temperature in order to operate.

The oxidation process proceeds by a composite mechanism constituting by two independent reaction paths. One of the paths is catalytic in 1,3-dinitrobenzene and the other one is a base-catalysed aerobic oxidation process.

The set-up of the new oxidation method makes it cheap and environmentally friendly as well as very suitable for large scale use.

Further studies are underway in order to improve the method as well as to explore the potential of the procedure as an oxidation method for other substrates.

Acknowledgements

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