Oxidation of organic substrates by molecular oxygen mediated by *N*-hydroxyphthalimide (NHPI) and acetaldehyde

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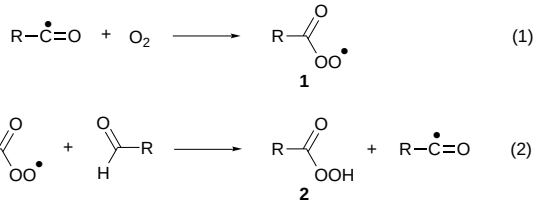
Various organic substrates, in particular hydrocarbons, are efficiently oxidized under mild conditions using molecular oxygen, *N*-hydroxyphthalimide and acetaldehyde, in the absence of metal catalysts.

The use of molecular oxygen for the selective oxidation of organic substrates, especially hydrocarbons under mild conditions, is still a major challenge for organic chemistry.[1] It constitutes an environmentally safe alternative to more conventional oxidants used in stoichiometric amounts and is therefore of high economic value in industrial chemistry.[2] Catalysis by transition metal complexes is the main way of controlling the partial oxidation of alkanes, alkenes and aromatic hydrocarbons.[3] Although they have been known for a long time, autoxidations *without transition metal catalysis* are often of low efficiency and selectivity. They proceed *via* a free radical chain mechanism promoted by catalytic amounts of radical initiators.[4] Aldehydes are exceptions among organic compounds as their autoxidation rates are very high with long propagation chains [reactions (1) and (2)] even at room temperature and atmospheric pressure. This property has been used in the so-called 'cooxidation' processes, in which a mixture of an aldehyde and another organic substrate is submitted to molecular oxygen. The autoxidation of the aldehyde then promotes the oxidation of the less reactive partner. Aldehyde-mediated cooxidations have been used for the epoxidation of alkenes,[5] Bayer–Villiger oxidation of ketones[6] and oxidation of alcohols and of some hydrocarbons.[7] We describe herein the oxidation of organic substrates, in particular hydrocarbons, under aldehyde-promoted cooxidation conditions, in the presence of *N*-hydroxyphthalimide (NHPI). NHPI has been used previously as an electron carrier for electrochemical oxidations.[8] More recently various oxidations have been conducted using molecular oxygen and NHPI, generally combined with transition metal salts, under nonelectrochemical conditions.[9] Our new combination of O_2–aldehyde–NHPI reveals several interesting features. When a 0.2 m solution of ethylbenzene, acetaldehyde (1 equiv.) and NHPI (0.1 mol%) in MeCN was vigorously stirred at room temperature under an oxygen atmosphere for 48 h, a 26% yield of acetophenone and a 6% yield of 1-phenylethanol were formed, with no further reaction after a longer reaction time. No further oxidation was observed after the addition of a second equivalent of acetaldehyde and an additional 48 h stirring time. No NHPI was recovered at the end of this experiment but an almost quantitative amount of phthalimide was isolated. Surprisingly, the same experiment carried out in the *absence of stirring* led to substantially different results; after keeping the reaction medium under oxygen without any stirring for 48 h the yields of ketone and alcohol were 50 and 6%, respectively, while TLC analysis of the solution indicated only a partial degradation of NHPI. The addition of a second equivalent of acetaldehyde and another 48 h standing period led to increased yields of 67 and 9%, respectively. Obviously the rate of aldehyde autoxidation, controlled by oxygen diffusion in the solution, plays a decisive role in the outcome of the reaction. High aldehyde autoxidation rates lead to fast NHPI degradation, no more ethylbenzene being oxidized after its complete disappearance.



Passive diffusion of oxygen in bulk solutions is very sensitive to geometric characteristics of the reactor and therefore difficulties in the reproducibility and scaling up of such experiments may be anticipated. We found that an efficient and reproducible way to perform such oxidations is to add *slowly* the aldehyde to the vigorously stirred reaction medium; when 1 equiv. of acetaldehyde was added over 5 h to a solution of ethylbenzene and NHPI under oxygen, and fast stirring maintained for an additional 5 h period, a 66% yield of acetophenone and a 4% yield 1-phenylethanol were obtained.† Table 1 shows further examples of oxidations performed under the same conditions: 4-nitro-1-ethylbenzene is oxidized with lower efficiency than ethylbenzene itself (run 3) whereas 4-methoxy-1-ethylbenzene is oxidized almost quantitatively (runs 4, 5). 1-Phenylethanol is oxidized only slowly to acetophenone (runs 6, 7) indicating that a direct pathway leading from ethylbenzene to acetophenone is likely. In the case of cumene, demethylation giving acetophenone competes with hydroxylation (run 8). Indane and isochromane are oxidized almost quantitatively (runs 9, 10). Surprisingly diphenylmethane is oxidized with a lower conversion (49%) than ethylbenzene (70%), with a relatively high alcohol : ketone ratio (run 11). A high conversion (94%) is obtained on the other hand with xanthene (run 12). Inactivated hydrocarbons are oxidized at a slow but nevertheless significant rate: 8% conversion of cyclohexane is observed after a 72 h reaction time, with a 1 : 7 alcohol : ketone ratio (run 13). Adamantane is oxidized almost exclusively to adamantan-1-ol with only trace amounts of adamantan-2-one (runs 14, 15).

In order to obtain information about the reaction mechanism of this oxidation, several parameters have been investigated. No oxidation occurs in the presence of either hydroquinone or TEMPO (1 mol%), confirming the free radical pathway of the reaction. No oxidation is observed at room temperature with NHPI alone.‡ Cooxidation of ethylbenzene and acetaldehyde (1 equiv.) in the absence of NHPI furnishes, after 48 h, only 7% ketone and 2% alcohol, indicating a strong cooperative effect of both NHPI and aldehyde under cooxidation conditions. Virtually no oxidation is observed when acetaldehyde is replaced by peracetic acid, clearly indicating that the species involved in these oxidations is not the peracetic acid **2** (R = Me) formed *in situ*, but is probably the acetylperoxy radical **1**. This radical **1** may in turn oxidize NHPI to phthalimide *N*-oxyl **3** [reaction (3)], a fairly stable but highly reactive free radical, which has been proposed as a key intermediate in NHPI-mediated oxidations.[8d,8h,9c]

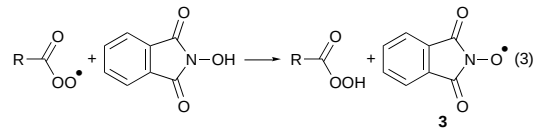
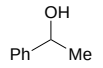
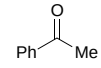
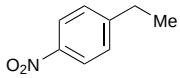
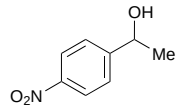
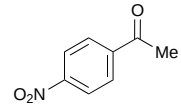
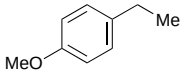
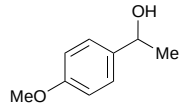
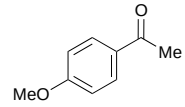
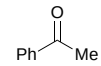
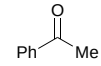
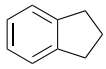
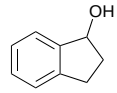
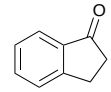
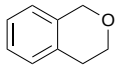
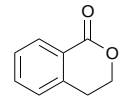
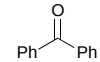
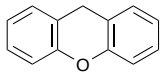
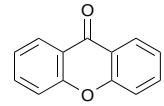
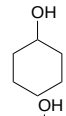
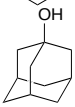
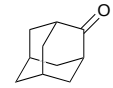


Table 1 Molecular oxygen oxidation of various substrates mediated by NHPI and acetaldehyde[a]

Run	Substrate	*t*/h[b]	Conversion (%)[c]	Products (yield, %)[d]			
1		5	48		(4)		(41)
2		10	70		(4)		(66)
3		10	24		(2)		(22)
4		5	75		(7)		(68)
5		21	97	—	(7)		(90)
6		5	3				(3)
7		72	37				(37)
8		19	75		(46)		(29)
9		10	99	—	(5)		(94)
10		15	100				(99)
11		10	49		(10)		(36)
12		19	94	—			(70)
13		72	8		(1)		(7)
14		9	5		(5)		(trace)
15		24	10		(10)		(trace)

[a] Performed on a 1 mmol scale, in the presence of 0.1 mmol NHPI, in 3 ml MeCN. A solution of 1 mmol acetaldehyde in 3 ml MeCN was added over 5 h *via* a syringe pump. [b] Including the aldehyde addition period. [c] Determined by calibrated quantitative GLC analysis using an internal standard. [d] Absolute yield determined by GLC.

The new oxidation system developed here allows aerobic oxidation of organic substrates under very mild conditions without any metal catalyst, and will therefore find many applications in synthesis. Further studies on the reaction mechanisms involved here are currently under way.

Footnotes

† Comparative experiments have been performed with benzaldehyde or isobutyraldehyde but with poorer results.

‡ Autoxidations of benzylic derivatives catalysed by NHPI alone have been described [see ref. 9(*a*)], but they occur at significant rates only at comparatively high temperature (100 °C) in benzonitrile as the solvent.

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