

A new, highly selective synthesis of aromatic aldehydes by aerobic free-radical oxidation of benzylic alcohols, catalysed by *n*-hydroxyphthalimide under mild conditions. Polar and enthalpic effects

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A new selective synthesis of aromatic aldehydes is described, based on catalytic oxidation of benzylic alcohols with molecular oxygen at rt and atmospheric pressure.

Recently a variety of interesting aerobic oxidations of organic compounds, including alkanes, under mild conditions was achieved by using *N*-hydroxyphthalimide (NHPI) combined with Co salt catalysis, particularly by the Ishii group.¹ It was, in particular, reported² that primary alcohols are easily oxidised to carboxylic acids at rt and atmospheric pressure, but no example of benzylic alcohols was given; a few years ago the aerobic oxidation of benzyl alcohol catalysed by NHPI at 100 °C was reported, by the same research group, to give a mixture of benzoic acid and benzaldehyde.³ In all these oxidations the phthalimide-*N*-oxyl (PINO) radical, generated *in situ*, plays a key role in the catalytic process, acting as the hydrogen abstracting species.

Very recently we⁴ have reported a general, particularly convenient process for the aerobic oxidation of primary alcohols (both benzylic and non-benzylic) to aldehydes, catalysed by TEMPO (tetramethylpiperidine-*N*-oxyl) radical combined with transition metal salts. A main function of TEMPO, which makes the oxidation particularly selective, is to inhibit the further free radical oxidation of aldehydes by O₂.

We have supposed that the different catalytic behaviour of PINO and TEMPO (both *N*-oxyl radicals) is due to the different bond dissociation energy (BDE) of the O–H bond of the corresponding *N*-hydroxy derivatives. The BDE for the piperidine *N*-hydroxy derivative is known and it is relatively low (70 kcal mol⁻¹); thus we have tried to determine the BDE of the O–H bond for acyl *N*-hydroxy compounds by a method previously described,^{5–7} based on the size of the equilibrium constants for the hydrogen transfer between a reference phenol and the *N*-hydroxy derivative and the corresponding radicals (eqn. (1)) by means of EPR spectroscopy.

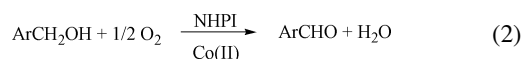


We succeeded in determining the BDE of the O–H bond for benzoylphenylhydroxylamine (PhCON(OH)Ph) (80 kcal mol⁻¹) but for NHPI, until now, only a lower limit (BDE for the O–H bond > 86 kcal mol⁻¹) was established. These results, even if not yet complete,⁸ clearly show that the substitution of an alkyl by an acyl group strongly increases the BDE of the O–H bond in *N*-hydroxy derivatives and explains well the opposite behaviour of PINO and TEMPO: the former plays a key role in determining free-radical chains, the latter inhibits free-radical processes.

On the other hand, recently, we⁹ have reported the oxidation of alcohols, ethers and amides by H₂O₂, catalysed by bromine; in particular primary benzylic alcohols give selectively the aromatic aldehydes, while non-benzylic alcohols give the carboxylic acids, even at low conversions. Since the selectivity

in the H₂O₂ oxidation is determined by hydrogen abstraction by the electrophilic bromine atom,⁹ these results suggest that hydrogen abstraction by the electrophilic PINO radical could also show a similar selectivity.

Actually the aerobic oxidation of primary benzylic alcohol, catalysed by NHPI and Co salts under mild conditions in MeCN solution leads to aromatic aldehydes with high selectivities, without appreciable formation of carboxylic acids (Table 1) (eqn. (2))



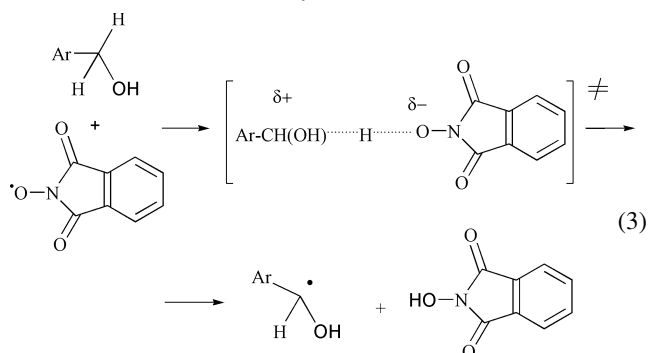
Under the same conditions non-benzylic alcohols lead to carboxylic acids, even at low conversions. A variety of metal salt complexes (Ru,¹⁰ Cu,¹¹ Mn,⁴ Co,⁴ Pd¹²) in combination^{4,10,11} or not^{12,13} with TEMPO, was utilised for the aerobic oxidation of primary alcohols to aldehydes. To the best of our knowledge, the catalysts Mn(II) and Co(II) or Cu(II) nitrates in combination with TEMPO⁴ or Co(OAc)₂ in combination with NHPI, described in this Communication, appear to be the cheapest and the most effective (the oxidation takes place in both cases with air at atmospheric pressure and rt with high selectivity), and suitable for industrial applications. The advantage in using TEMPO is related to the general character of the oxidation of benzylic and non-benzylic alcohols, while the use of NHPI is limited to benzylic alcohols for the below discussed mechanistic aspects, but NHPI (obtained from phthalic anhydride and NH₂OH) is cheaper than TEMPO and moreover it can be more easily recovered and recycled, due to its low solubility in several solvents.

Table 1 Oxidation of benzylic alcohols, X-C₆H₄-CH₂OH, to aromatic aldehydes by oxygen^a

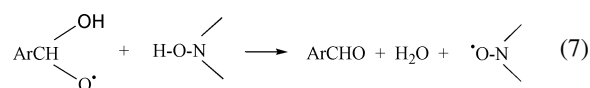
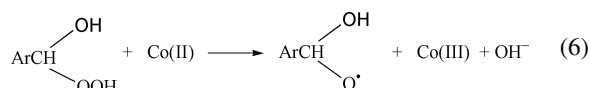
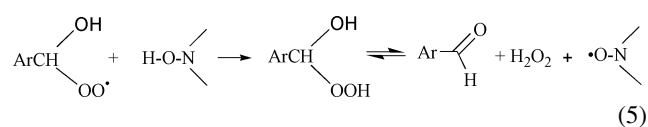
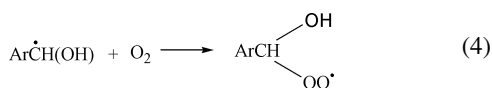
X	Time/h	Conversion (%)	Selectivity (%)
H	2	100	92
H ^b	4	85	94
H ^c	3	86	91
<i>p</i> -OMe	1	75	94
<i>p</i> -OMe ^d	2	100	—
<i>m</i> -OMe	3	85	99
<i>p</i> -NO ₂	3	100	98
<i>p</i> -NO ₂ ^b	4	Traces	—
<i>m</i> -NO ₂	4	88	91
<i>p</i> -Cl	3	100	95
<i>m</i> -Cl	3	92	97
<i>p</i> -Me	2	100	95
<i>m</i> -CN	4	100	98

^a Standard procedure: 3 mmol of benzylic alcohol, 0.3 mmol of NHPI, 0.015 mmol of Co(OAc)₂, 0.15 mmol of *m*-chlorobenzoic acid in 15 mL of acetonitrile with O₂ at atmospheric pressure and rt. ^b As in (a) without *m*-chlorobenzoic acid. ^c As in (a) with air instead of O₂. ^d 98% of *p*-methoxybenzoic acid was obtained.

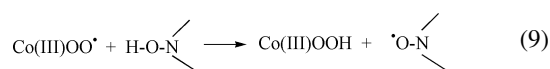
The enthalpic effect is similar for the hydrogen abstraction from both benzylic alcohols and aromatic aldehydes by PINO (BDE is about 87 kcal mol⁻¹ for both ArCHOH-H and ArCO-H bonds) and the polar effect (eqn. (3)) plays a key role in determining the selectivity of eqn. (2), making the alcohol much more reactive than the aldehyde.



The aldehyde is formed in catalytic cycles according to eqn. (3)–(7).



Co(III) can be reduced to Co(II) by NHPI (with formation of PINO) or by hydroperoxide generating a redox chain. The initiation of the chain process of eqn. (3)–(7) can be ascribed to eqn. (8),(9).



With non-benzylic primary alcohols the enthalpic effect is dominant for eqn. (3) (the BDE of the RCHOH-H bond is 8–10 kcal mol⁻¹ stronger than that of the RCO-H bond), which makes the aldehyde much more reactive than the alcohol, leading selectively to the carboxylic acid. Thus *n*-hexanol, oxidised according to procedure (a) of Table 1 in the presence of 1% of *m*-chloroperbenzoic acid, gives after 10 h a 49% conversion with 96% selectivity in hexanoic acid; hexan-1-ol is less reactive than benzyl alcohol for obvious enthalpic reasons.

The polar effect is supported by the result of the competitive oxidation of benzyl and *m*-nitrobenzyl alcohol (a 1:1 molar ratio of benzyl and *m*-nitrobenzyl alcohol gives after 1 h 45% of benzaldehyde and 25% of *m*-nitrobenzaldehyde), and by the oxidation of *p*-methoxybenzyl alcohol, which gives a good selectivity in aldehyde only for short reaction times. For longer reaction times (2 h), it is oxidised to the carboxylic acid, while this does not occur with the other benzyl alcohols for the times reported in the Table. The nitro group deactivates and the *p*-methoxy group activates the oxidation in agreement with the polar transition state of eqn. (3).

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