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Tetrahedron Letters 44 (2003) 6919–6922

TETRAHEDRON
LETTERS

Selective functionalisation of hydrocarbons by nitric acid and aerobic oxidation catalysed by *N*-hydroxyphthalimide and iodine under mild conditions

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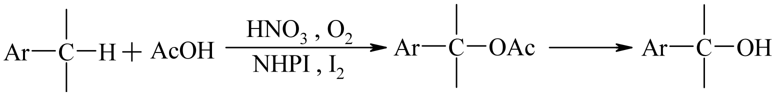
Received 8 June 2003; revised 4 July 2003; accepted 4 July 2003

Abstract—Alkylbenzenes are selectively functionalised to the corresponding acetates by nitric aerobic oxidation catalysed by *N*-hydroxyphthalimide and iodine. With cyclohexane the oxidation leads to a mixture of cyclohexyl acetate and *trans*-2-iodocyclohexyl acetate. The mechanism is discussed.

The selective functionalisation of hydrocarbons is a challenging process of the organic chemistry. It is a primary essential tool in organic synthesis and industrial chemistry.

Recently, we[1,2] have determinated the absolute rate constants in the hydrogen abstraction by the phthalimido-*N*-oxyl (PINO) radical from a variety of hydrocarbons (0.047, 0.38, 2.24, 3.25, 28.3 M^{-1} s^{-1} at 25°C for cyclohexane, toluene, ethylbenzene, cumene and benzyl alcohol, respectively). Since benzyl alcohols are much more reactive than toluene and ethylbenzene towards the hydrogen abstraction by the PINO radical, which is considered the rate-determining step in the aerobic oxidation of these substrates catalysed by *N*-hydroxyphthalimide (NHPI),[1,2] the oxidation of toluene and alkyl benzenes can not lead selectively to the benzyl alcohols, not even at low conversion. The higher reactivity of benzyl alcohol was mainly ascribed[2–4] to polar and enthalpic effects in the hydrogen abstraction by the PINO radical.

In this communication we report a new process, which allows us to obtain benzyl alcohols from alkylbenzenes through the corresponding acetates by nitric aerobic oxidation of alkylbenzenes, catalysed by NHPI an I_2 (Eq. (1)) in acetic acid solution.

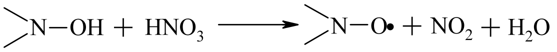


$$\mathrm{Ar{-}\overset{|}{\underset{|}{C}}{-}H} + \mathrm{AcOH} \xrightarrow[\mathrm{NHPI,\ I_2}]{\mathrm{HNO_3,\ O_2}} \mathrm{Ar{-}\overset{|}{\underset{|}{C}}{-}OAc} \longrightarrow \mathrm{Ar{-}\overset{|}{\underset{|}{C}}{-}OH} \qquad (1)$$

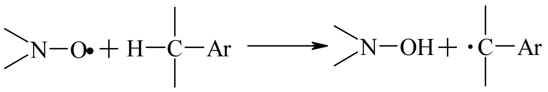
The results are reported in Table 1.

In a typical example, a solution of 4 mmol of Ph-CH_2-CH_3, 0.2 mmol of NHPI, 0.01 mmol of $Co(OAc)_2$, 2 mmol of I_2 and 0.4 mmol of HNO_3 68% w/w in 10 mL of AcOH was stirred for 6 h at 80°C under an atmosphere of air. The analysis by GC, by using benzyl acetate as internal standard, indicates a complete conversion of Ph-CH_2-CH_3 and a quantitative yield of Ph-CH(OAc)-CH_3. the AcOH solution was concentrated to 2 mL and a solution of $NaHCO_3$ was added to the residue. The extraction by CH_2Cl_2 provides 0.623 g of pure Ph-CH(OAc)-CH_3 (95%).

We explain the formation of benzyl acetates by a catalytic cycle initiated by the oxidation of NHPI by HNO_3 (Eq. (2)) with formation of the PINO radical, which abstract hydrogen from benzylic C–H bonds (Eq. (3)) with the rate constants above reported.



$$\mathrm{{>}N{-}OH} + \mathrm{HNO_3} \longrightarrow \mathrm{{>}N{-}O\bullet} + \mathrm{NO_2} + \mathrm{H_2O} \qquad (2)$$



$$\mathrm{{>}N{-}O\bullet} + \mathrm{H{-}\overset{|}{\underset{|}{C}}{-}Ar} \longrightarrow \mathrm{{>}N{-}OH} + \mathrm{\bullet\overset{|}{\underset{|}{C}}{-}Ar} \qquad (3)$$

Keywords: acetoxylation; *N*-hydroxyphthalimide; oxygen; functionalisation; alkylaromatics; iodine; cyclohexane.

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doi:10.1016/S0040-4039(03)01687-3

Table 1. Oxidation of hydrocarbons by O_2 and or HNO_3, catalysed by NHPI and I_2[a]

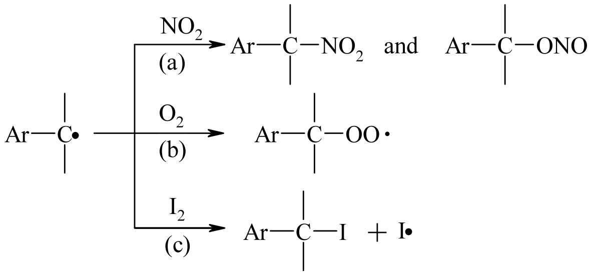
Entry	Hydrocarbon (4 mmol)	NHPI (mmol)	$Co(OAc)_2$ (mmol)	I_2 (mmol)	HNO_3 (mmol)	O_2, N_2 (1 atm)	T (°C)	Conversion (%)	Selectivity (%)
1	$PhCH_2Me$	0.2	0.01	2	0.4	Air	80	100	PhCH(OAc)Me (100)
2	$PhCH_2Me$	0.2	0.01	2	0.4	O_2	80	100	PhCH(OAc)Me (99.8)
3	$PhCH_2Me$	0.2	–	2	0.4	O_2	80	100	PhCH(OAc)Me (100)
4	$PhCH_2Me$	0.2	0.01	0.8	0.4	O_2	80	88	PhCH(OAc)Me (91) PhCOMe (8)
5	$PhCH_2Me$	0.2	0.01	0.4	0.4	O_2	80	78	PhCH(OAc)Me (78) PhCOMe (23)
6	$PhCH_2$ $CHMe_2$	0.2	0.01	2	0.4	Air	80	100	$PhCH(OAc)CHMe_2$ (95)
7	$PhCH_2$ $CHMe_2$	0.2	0.01	2	0.4	O_2	80	100	$PhCH(OAc)CHMe_2$ (97)
8	Ph-Me	0.4	–	2	4	N_2	100	30	$PhCH_2OAc$ (98)
9[b]	Ph-Me	0.2	0.02	0.8	0.4	Air	80	64	$PhCH_2OAc$ (89) PhCHO (11)
10[b]	Ph-Me	0.4	0.02	0.4	0.4	O_2	100	75	$PhCH_2OAc$ (84) PhCHO (16)
11	*p*-Cl-C_6H_4-Me	0.4	0.02	2	4	N_2	100	78	*p*-Cl-C_6H_4-CH_2OAc (72) *p*-Cl-C_6H_4-$CH(OAc)_2$ (10) *p*-Cl-C_6H_4-CHO (18)
12	*p*-NO_2-C_6H_4-Me	0.2	–	0.8	0.4	Air	100	20	*p*-NO_2-C_6H_4-CH_2I (94)
13	*p*-CN-C_6H_4-Me	0.4	–	4	4	O_2	100	58	*p*-CN-C_6H_4-CH_2I (86) *p*-CN-C_6H_4-CH_2OAc (14)
14	Tetralin	0.4	–	2	0.4	O_2	80	100	Naphthalene (100)
15[c]	Cyclohexane (10 mmol)	0.2	0.01	2	2	Air	80	100	*trans*-2-Iodocyclohexyl acetate (68) Cyclohexyl acetate (32)

[a] The reagents in the amounts reported in Table 1 in 10 ml of AcOH are stirred for 6 h at 80 or 100°C under an atmosphere of O_2, air or N_2. The reaction product were analysed by GC with internal standard (*m*-methylbenzyl acetate) utilising the response factors obtained from authentic samples.

[b] The reaction was carried out for 24 h.

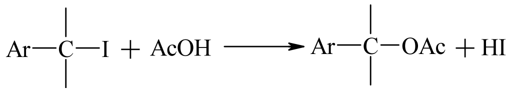
[c] An excess of cyclohexane (10 mmol) was utilised; conversion is based on HNO_3.

The benzyl radical can be trapped by three very fast reactions (Eq. (4)), all characterised by almost diffusion controlled rates (10^9–10^{10} M^{-1} s^{-1}).



$$\text{Ar—C}\bullet \xrightarrow[(a)]{NO_2} \text{Ar—C—NO}_2 \text{ and } \text{Ar—C—ONO}$$
$$\text{Ar—C}\bullet \xrightarrow[(b)]{O_2} \text{Ar—C—OO}\bullet \qquad (4)$$
$$\text{Ar—C}\bullet \xrightarrow[(c)]{I_2} \text{Ar—C—I} + I\bullet$$

Recently, the nitration of hydrocarbons by NO_2 and NHPI catalysis has been reported.[5,6] However benzyl iodides are selectively formed if the concentration of I_2 is much higher than that of NO_2 and O_2. Under the reaction conditions the solvolysis of benzyl iodides leads to benzyl acetates (Eq. (5)).

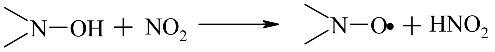


$$\text{Ar—C—I} + \text{AcOH} \longrightarrow \text{Ar—C—OAc} + \text{HI} \qquad (5)$$

Blank experiments have shown that under the reaction conditions benzyl iodides undergo solvolysis to acetoxy derivatives, with the exception for the presence of strongly electron-withdrawing groups (NO_2, CN) in the phenyl ring, plainly supporting the reaction mechanism.

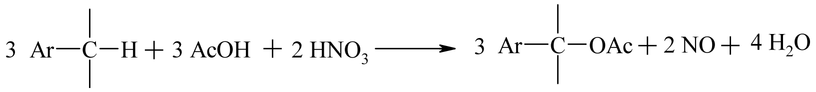
HI is quickly oxidised by HNO_3, NO_2 or O_2 to I_2, which is not consumed, acting as a catalyst. No benzyl acetate is formed under the same conditions in the absence of I_2.

When the oxidation is carried out with catalytic amount of HNO_3 in presence of O_2 the overall catalysis also involves the formation of the PINO radical by hydrogen abstraction from NHPI by NO_2 (Eq. (6)), generated in Eq. (2) and regenerated by the aerobic oxidation of NO, arising from the decomposition of HNO_2 and making catalytic the process in HNO_3.

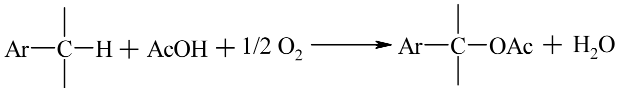


$$>\text{N—OH} + NO_2 \longrightarrow >\text{N—O}\bullet + HNO_2 \qquad (6)$$

Thus, the stoichiometry of the reaction with stoichiometric amount of HNO_3 under a nitrogen atmosphere is given by Eq. (7), while with catalytic amount of HNO_3 in the presence of O_2 the stoichiometry is given by Eq. (8).



$$3\ \mathrm{Ar{-}\overset{|}{\underset{|}{C}}{-}H} + 3\ \mathrm{AcOH} + 2\ \mathrm{HNO_3} \longrightarrow 3\ \mathrm{Ar{-}\overset{|}{\underset{|}{C}}{-}OAc} + 2\ \mathrm{NO} + 4\ \mathrm{H_2O} \qquad (7)$$



$$\mathrm{Ar{-}\overset{|}{\underset{|}{C}}{-}H} + \mathrm{AcOH} + 1/2\ \mathrm{O_2} \longrightarrow \mathrm{Ar{-}\overset{|}{\underset{|}{C}}{-}OAc} + \mathrm{H_2O} \qquad (8)$$

In both cases (Eqs. (7) and (8)) the reactions are catalytic in I_2, which is continuously regenerated, but they require a relatively high concentration of I_2 in order that Eq. (4c) can prevail over Eqs. (4a) and (4b). No oxidation occurs in the absence of NHPI, cleary showing the fundamental role of Eq. (3).

The reaction is particularly selective for the oxidation of the benzylic CH_2 group; the secondary benzyl acetate appears to be much less reactive than the starting alkylbenzenes and the further oxidation does not occur also with complete conversion of the alkylbenzenes (entries 1–3, 6–7). We ascribe this behaviour to the sensitivity to the polar effect[2–4] of acetoxy group in the hydrogen abstraction by the PINO radical.

Minor but significant amounts of acetophenone are formed when the concentration of I_2 is lower (entries 4 and 5), due to the competition of Eq. (4b).

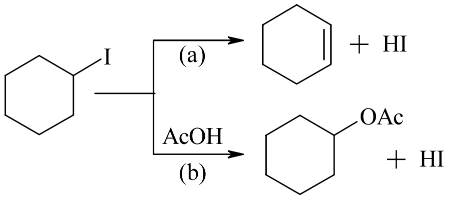
With toluene a high selectivity (entry 8) in benzyl acetate was observed by using stoichiometric amount of HNO_3 under a nitrogen atmosphere; however, in the presence of oxygen significant amounts of benzaldehyde are formed, due to the competition of Eq. (4b) (entries 9 and 10).

With isopropyl aromatics, as cumene, the reaction gives poor results, due to the formation of small amount of phenol by acid decomposition of hydroperoxide formed from the benzyl radical and O_2; phenol inhibits the free radical chain of Eqs. (2)–(4).

With tetralin the reaction initially leads to benzylic iodination and acetoxylation on the analogy of alkyl benzenes, but by increasing the conversions naphthalene is quantitatively formed by AcOH elimination.

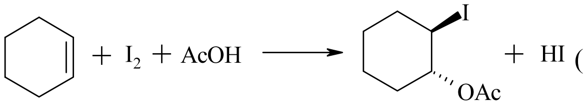
The Co(II) salt appears to have a two-fold function: it decomposes the hydroperoxides, formed from benzyl radicals and O_2 and it could catalyse the solvolysis of benzyl iodides.

With cyclohexane the main reaction product under the same conditions is the *trans*-2-iodocyclohexyl acetate, while cyclohexyl acetate is by-product. We explain its formation through cyclohexyl iodide, formed by reactions similar to Eqs. (2), (3) and (4c); under the reaction conditions the cyclohexyl iodide mainly undergoes elimination with formation of cyclohexene (Eq. (9a)) and to a minor extent nucleophilic substitution (Eq. (9b)).



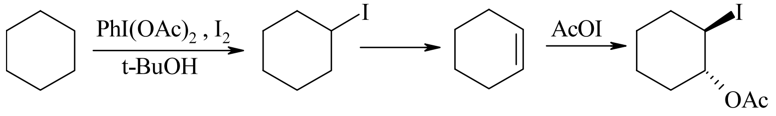
(9)

HI is fast oxidised to I_2 and the electrophilic addition to cyclohexene leads to the *trans*-2-iodocyclohexyl acetate (Eq. (10)).



(10)

Very recently[7] an analogous process has reported by oxidation of cycloalkanes by diacetoxyiodobenzene and *t*-BuOH (Eq. (11)), in which the hydrogen abstraction from the alkane occurs by the *t*-butoxyl radical,[8] but the suggested mechanism is somewhat different.



(11)

Moderate yields of benzylic acyloxylation of alkyl aromatic were previously obtained by a variety of much more complex and expensive processes, such as the use of $Pb(OAc)_4$,[9–12] $Pd(OAc)_2$,[13,14] peroxyesters,[15,16] hydroperoxydes,[17] peroxy acids;[18] most of these processes are characterised by free-radical mechanisms.

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