Pergamon

Tetrahedron Letters 43 (2002) 3605–3607

TETRAHEDRON
LETTERS

A new selective free radical synthesis of aromatic aldehydes by aerobic oxidation of tertiary benzylamines catalysed by *N*-hydroxyimides and Co(II) under mild conditions. Polar and enthalpic effects

Andrea Cecchetto,[a] Francesco Minisci,[a,*] Francesco Recupero,[a] Francesca Fontana[b] and Gian Franco Pedulli[c]

[a]*Dipartimento di Chimica, Materiali e Ingegneria Chimica 'G.Natta', Politecnico di Milano, via Mancinelli 7, 20131 Milano, Italy*
[b]*Dipartimento di Ingegneria, Università di Bergamo, viale Marconi 5, 24044 Milano, Italy*
[c]*Dipartimento di Chimica Organica 'A.Mangini', Università di Bologna, via S.Donato, 15, I-40127 Bologna BO, Italy*

Received 25 January 2002; accepted 8 March 2002

Abstract—Tertiary benzylamides are easily and selectively converted into aldehydes by molecular oxygen; the reaction is catalysed by *N*-hydroxyamides and Co(II). © 2002 Published by Elsevier Science Ltd.

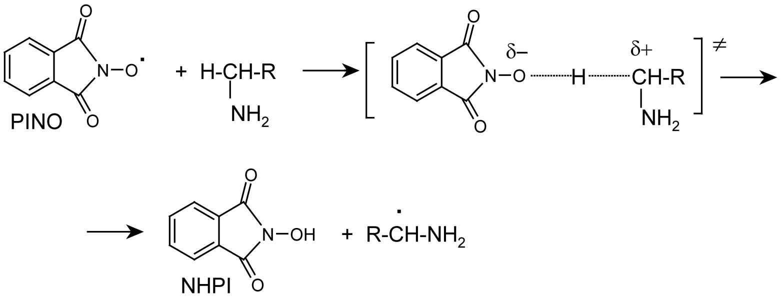
Recently we have developed simple, selective and convenient syntheses of aromatic aldehydes by aerobic oxidation of primary benzyl alcohols under *N*-oxyl radical catalysis. We have utilised tetramethylpiperidine-*N*-oxyl (TEMPO, a persistent radical)[1] and phthalimide-*N*-oxyl (PINO), generated in situ from *N*-hydroxyphthalimide (NHPI).[2] Both these *N*-oxyl radicals catalyse the selective aerobic oxidation of primary benzyl alcohols to the corresponding aromatic aldehydes in combination with transition metal salt catalysis (Co(II), Mn(II), Cu(II)) under mild conditions (room temperature and atmospheric pressure) (Eq. (1)), but with quite different mechanisms.

$$\text{Ar-CH}_2\text{OH}+1/2\text{O}_2\rightarrow\text{Ar-CHO}+\text{H}_2\text{O} \qquad (1)$$

TEMPO, in the presence of the Mn(II)–Co(II) or Mn(II)–Cu(II) couples as cocatalysts, has a twofold function: it determines the formation of an oxoammonium salt, which is the actual oxidant of the alcohol, and it inhibits the further free-radical oxidation of the aldehyde by O_2, which occurs in the absence of TEMPO under the same conditions.[1]

PINO acts as a hydrogen abstracting species from C–H bonds in free-radical chains.[2,3]

We ascribed the different behaviour of the two *N*-oxyl radicals to the values of the bond dissociation energies (BDE) of the O–H bonds, which we[2] have evaluated as at least 16 kcal mol^{-1} higher for NHPI (>86 kcal mol^{-1}) than for *N*-hydroxypiperidine (70 kcal mol^{-1}).[4] Thus, hydrogen abstraction from C–H bonds by PINO is justified on enthalpic grounds, while it is too endothermic to occur by TEMPO, which is a well-known inhibitor of free-radical chains.[4] This inhibition makes oxidation to aldehydes quite selective and general for benzylic and non-benzylic primary alcohols,[1] while the free-radical oxidation, catalysed by PINO, is strongly affected by polar and enthalpic effects.[2] In this latter case, the oxidation of benzylic alcohols is governed by the polar

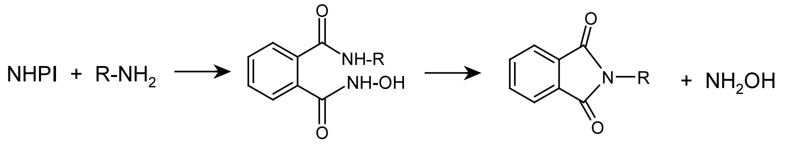


(2)

---

* Corresponding author. Fax: +39 02 2399 3080; e-mail: francesco.minisci@polimi.it

0040-4039/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4039(02)00474-4



(3)

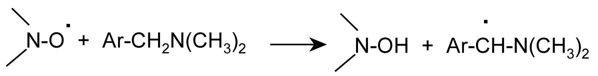
effect, which makes the alcohols much more reactive than the corresponding aldehydes, which are therefore obtained with very high selectivity. With non-benzylic alcohols, the enthalpic effect is dominant in hydrogen abstraction by PINO (BDE values for RCHOH-H are 6–8 kcal mol^{-1} higher than RCO-H) and it makes the aldehydes much more reactive than the starting alcohols, leading selectively to carboxylic acids, even at very low conversions of the alcohols.

The amino group is a more effective electron-releasing substituent than the hydroxy group and therefore we would expect a higher reactivity and a stronger polar effect (Eq. (2)) for the oxidation of alkylamines by O_2 and NHPI catalysis compared to the corresponding alcohols.

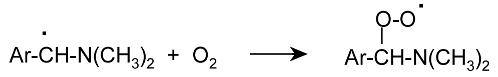
However, primary and secondary benzylamines are completely inert towards the oxidation by O_2 and NHPI catalysis under the same conditions in which primary and secondary alcohols are easily oxidised. We soon realised that this behaviour was related to the reaction of amines with NHPI according to Eq. (3), which deactivates the catalyst.

Tertiary benzylamines cannot react with NHPI according to Eq. (3) and we report in this letter a new, simple and selective oxidation by O_2 to the corresponding aldehydes under mild conditions.

The mechanism of the oxidation involves a superimposition of a redox chain to a free-radical chain (Eqs. (4–8))

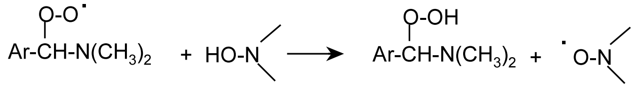


(4)

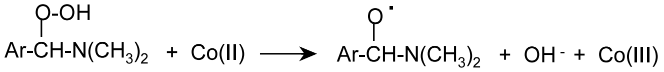


$$Ar\text{-}\dot{C}H\text{-}N(CH_3)_2 + O_2 \longrightarrow Ar\text{-}\overset{O\text{-}O^\bullet}{CH}\text{-}N(CH_3)_2$$

(5)

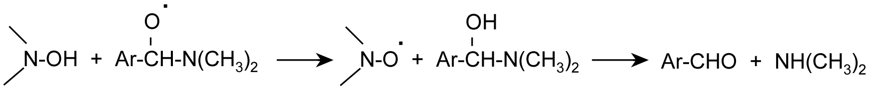


(6)



$$Ar\text{-}\overset{O\text{-}OH}{CH}\text{-}N(CH_3)_2 + Co(II) \longrightarrow Ar\text{-}\overset{O^\bullet}{CH}\text{-}N(CH_3)_2 + OH^- + Co(III)$$

(7)



(8)

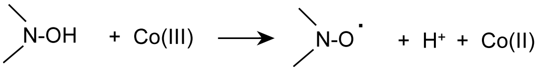
Table 1. Oxidation of benzyldimethylamines X-C_6H_4-CH_2-$N(CH_3)_2$ to the aldehydes X-C_6H_4-CHO by O_2 catalysed by NHSI and NHPI[a]

Entry	X	Catalyst (%)	T (°C)	t (h)	Conv. (%)	Select. (%)
1	H	NHSI (7)	35	2	42	91
2	H	NHSI (7)	35	8	100	78
3	H	NHSI (10)	50	2.5	100	88
4	H	NHPI (7)	35	2	75	81
5	H	NHSI (7)	35	8	80	78
6	H	NHPI (10)	50	9	90	70
7	*m*-Cl	NHSI (7)	35	7	100	78
8	*m*-Cl	NHPI (7)	35	7	90	68
9	*p*-Cl	NHSI (10)	50	7	100	86
10	*p*-Cl	NHPI (10)	50	7	90	86
11	*p*-OMe	NHPI (7)	40	3	96	84
12	*p*-CN	NHSI (10)	50	4	100	86
13	*p*-NO_2	NHSI (10)	50	2	37	92
14	*p*-NO_2	NHSI (10)	50	9	90	80
15	*p*-NO_2	NHPI (7)	35	2	64	88
16	*p*-NO_2	NHSI (7)	35	7	72	82
17	*p*-NO_2	NHSI (7)	35	10	75	76
18	*p*-NO_2	NHPI (10)	50	9	83	60

[a] Standard experimental procedure: a solution of 7 mmol of benzylamine, NHSI or NHPI in the amounts reported in Table 1, 0.07 mmol of $Co(OAc)_2$ in 15 mL of acetonitrile was stirred at the temperatures and for the times reported in Table 1 in the presence of O_2 at atmospheric pressure. The catalysts were separated by flash chromatography on silica gel and the reaction products were analysed by GLC and GC–MS and comparison with authentic samples.

Co(III), formed in Eq. (7), can be reduced to Co(II) either by the hydroperoxide (Eq. (9)) or by NHPI (Eq. (10)), generating a redox chain.

$$\text{R-OOH}+\text{Co(III)}\rightarrow\text{R-OO}^{\bullet}+\text{H}^{+}+\text{Co(II)} \qquad (9)$$



(10)

The overall stoichiometry is given by Eq. (11):

$$\text{ArCH}_2\text{N(CH}_3)_2+1/2\text{O}_2\rightarrow\text{Ar-CHO}+\text{HN(CH}_3)_2 \qquad (11)$$

The results are reported in Table 1. *N*-Hydroxysuccinimide (NHSI, entries 1–3, 7, 9, 12–14 in Table 1) appears to give even better results than NHPI. The latter is a more effective catalyst (entries 4–6, 8, 10, 11, 15–18 in Table 1), but it has two main drawbacks compared to NHSI: it catalyses faster the initial oxidation of the benzylamines, but it is deactivated before the completion of the oxidation, particularly with the less reactive benzylamines, such as the nitro-substituted ones (entries 13–18 in Table 1). With NHSI the reaction is slower, but it goes to completion without deactivation of the catalyst, which is due to the formation of Me_2NH (Eq. (11)), according to Eq. (3); competitive experiments with NHPI and NHSI with Me_2NH have shown that the former reacts faster than the latter. Moreover, the faster oxidation by NHPI catalysis makes the reaction somewhat less selective compared to the slower NHSI catalysis, the main by-product being the benzamide, ArCONMe_2, which is formed by the further oxidation of the hydroxyamine (Eq. (12)) before the hydrolysis according to Eq. (8).

$$\text{Ar-CHOH-NMe}_2+1/2\text{O}_2\rightarrow\text{Ar-CO-NMe}_2+\text{H}_2\text{O} \qquad (12)$$

The hydroxyamine is more reactive than the starting benzylamine in hydrogen abstraction by the *N*-oxyl radicals for both polar and enthalpic effects.

Since the selectivity of the oxidation is determined by hydrogen abstraction, the high selectivity in aldehydes and the absence of carboxylic acids reflect a much higher rate of hydrogen abstraction from benzylamines than from the corresponding aromatic aldehydes. This appears as the result of a high sensitivity to the polar effect for hydrogen abstraction by the *N*-oxyl radicals (Eq. (2)), since the enthalpic effect is substantially similar for the benzylamines and the corresponding aldehydes (BDE values for the C–H bond in benzylamines and the corresponding aldehydes are similar, about 87 kcal mol^{-1}). In this sense we have verified our hypothesis that benzylamines should be more reactive than the benzyl alcohols; a competitive experiment between benzyldimethylamine and *m*-methylbenzyl alcohol leads to the formation of 75% of benzaldehyde and only traces of *m*-methylbenzaldehyde when 80% of the amine has reacted (no substantial oxidation of the alcohol occurs). In the absence of the benzylamine the benzyl alcohol is substantially oxidised to aldehyde under the same conditions.

References

1. Cecchetto, A.; Fontana, F.; Minisci, F.; Recupero, F. *Tetrahedron Lett.* **2001**, *42*, 6651.
2. Minisci, F.; Punta, C.; Recupero, F.; Fontana, F.; Pedulli, G. F. *Chem. Commun.*, in press.
3. Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393.
4. Mahoney, L. R.; Mendenhall, G. D.; Ingold, K. U. *J. Am. Chem. Soc.* **1973**, *95*, 8610.