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A novel, selective free-radical carbamoylation of heteroaromatic bases by Ce(IV) oxidation of formamide, catalysed by *N*-hydroxyphthalimide

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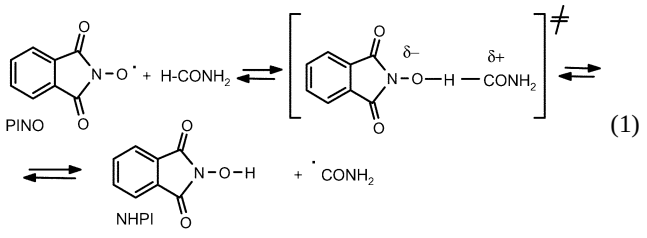
The Ce(IV)-NHPI system was used to generate a carbamoyl radical by oxidation of formamide; this nucleophilic radical has been successfully used in the carbamoylation of heteroaromatic bases.

The substitution of protonated heteroaromatic bases by nucleophilic carbon-centred radicals is one of the main general reactions of this class of aromatic compounds as a result of the large variety of successful radical sources, the high regio- and chemoselectivity and the simple experimental conditions. It reproduces most of the Friedel–Crafts aromatic substitutions, but with opposite reactivity and selectivity, due to the high sensitivity to polar effects. Absolute rate constants in the range 10^5–10^8 M^{-1} s^{-1} at rt make the most reactive bases effective traps for nucleophilic carbon-centred radicals. Practically all the σ-type carbonyl radicals (acyl, carbamoyl and alkoxycarbonyl) and the alkyl π-type radicals without electron-withdrawing groups directly attached to the radical centre are suitable for these substitutions.[1]

Recently, we have shown that hydrogen abstraction from C–H and Si–H bonds by the phthalimido-*N*-oxyl (PINO) radical is strongly affected by polar and enthalpic effects in the selective aerobic oxidation of alcohols,[2] amines,[3] amides[4] and silanes,[5] catalysed by *N*-hydroxyphthalimide (NHPI). The PINO radical was generated by hydrogen abstraction from NHPI by peroxyl and alkoxyl radical intermediates of the aerobic oxidations.

We have also evaluated the bond dissociation energy of the O–H bond in NHPI (88.1 kcal mol^{-1}) and the absolute rate constants for hydrogen abstraction from NHPI by the peroxyl radical (7.4×10^3 M^{-1} s^{-1} at rt, the rate being much higher with alkoxy radical for obvious enthalpic reasons) and from the benzylic C–H bond of cumene by the PINO radical (6.1 M^{-1} s^{-1} at rt).[4–6] The PINO radical is much more reactive than the TEMPO radical in hydrogen abstraction for both enthalpic and polar reasons. The effect is, in our opinion, similar to the one observed for acylperoxyl radicals, R–C(=O)OO·, compared to alkylperoxyl radicals, R–OO·.[4,7] The BDE value for the C–H bond in H–$CONH_2$ is about 94 kcal mol^{-1};[8] these thermochemical and kinetic data would suggest that hydrogen abstraction from formamide by PINO [eqn. (1)] could be a selective process.

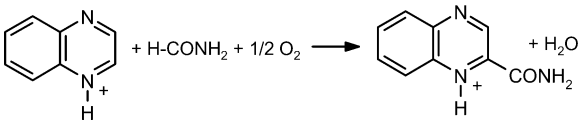


(1)

Thus we have considered the possibility of trapping the ·$CONH_2$ radical generated in eqn. (1) by protonated heteroaromatic bases.

On the basis of the enthalpic evaluation eqn. (1) can be considered an equilibrium process, which, however, could be shifted to the right by the fast reaction of the ·$CONH_2$ radical with either oxygen or a heteroaromatic base.

Actually, when the aerobic oxidation of formamide, catalysed by NHPI and Co(II) salt, was carried out in the presence of protonated quinoxaline the selective carbamoylation of the heteroaromatic base took place [eqn. (2)].



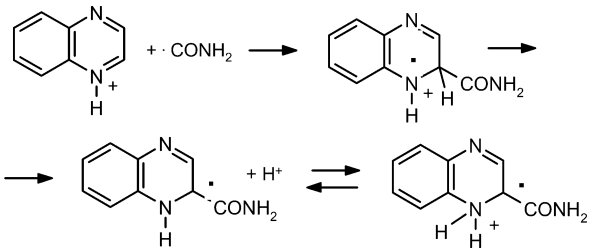
(2)

The selectivity was complete, but the conversion was moderate (18%) by using air at atmospheric pressure as the oxidant in order to keep the oxygen concentration low, meaning that the reaction of the carbamoyl radical was faster with oxygen than with quinoxaline. The conversions were even lower (< 10%) with less reactive heteroaromatic bases (pyridine and quinoline derivatives). The process shows a modest synthetic interest and, from a mechanistic standpoint, it proves the intermediate formation of the carbamoyl radical. We next considered the possibility of generating the PINO radical by a different oxidant, in the absence of O_2.

Cerium(IV) ammonium nitrate (CAN) proved to be particularly effective for this purpose [eqn. (3)].

$$>N–OH + Ce(IV) \rightarrow >N–O· + Ce(III) + H^+ \qquad (3)$$

When the oxidation of formamide by CAN, catalysed by NHPI, was carried out in the presence of protonated heteroaromatic bases in the absence of O_2, the selective carbamoylation of the heterocyclic compounds took place. In the absence of NHPI no reaction occurs, clearly showing that the ·$CONH_2$ radical is formed according to eqns. (3) and (1). CAN has a twofold function: it generates the PINO radical [eqns. (3)] and it determines the aromatisation of the radical adduct between the heteroaromatic base and ·$CONH_2$ [eqns. (4) and (5)], so that the overall stoichiometry requires 2 mol of CAN per mol of heterocyclic compound.



(4)

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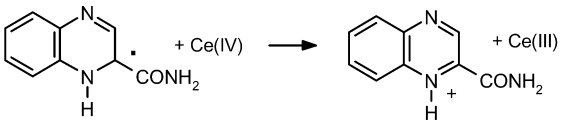

(5)

By using stoichiometric amounts of CAN the conversions, however, are not complete, as shown by the results reported in Table 1; this is due to a partial oxidation of the carbamoyl radical by the Ce(IV) salt [eqn. (6)].

$$\cdot CONH_2 + Ce(IV) + H_2O \rightarrow CO_2 + Ce(III) + NH_4^+ \quad (6)$$

Only the α- and γ-positions of the heterocyclic ring are involved, but the α-position appears considerably more reactive, as shown by the regioselectivity on quinoline and the low conversion with quinaldine compared to lepidine. The α : γ ratios for the attack of nucleophilic radicals to the heterocyclic ring are solvent-dependent for the most stabilised radicals (benzyl, *tert*-alkyl, α-tetrahydrofuranyl), due to the reversibility of the radical addition;[9] the high selectivity of carbamoylation in the α-position appears to be related to a low reversibility for the addition of the $\cdot CONH_2$ radical to the heterocyclic ring under the reaction conditions.

The protonation of the heteroaromatic base considerably increases the reactivity towards nucleophilic radicals (3–6 orders of magnitude) compared to the unprotonated base;[1] the introduction of a carbamoyl group, on the other hand, decreases the basicity of the heterocyclic ring thus reducing its protonation and preventing disubstitution.

Table 1 Carbamoylation of heteroaromatic bases by Ce(IV) oxidation of formamide, catalysed by NHPI[a]

Heterocyclic base	Conversion (%)	Selectivity (%)
Quinoxaline[b]	100	100 (2)
Quinoline	78	95 (2); 5 (4)
4-Methylquinoline	66	100 (2)
2-Methylquinoline	18	100 (4)
Isoquinoline	78	100 (1)
4-Cyanopyridine	57	100 (2)
Pyrazine	62	100 (2)
Quinazoline	52	100 (2)

[a] Procedure: A solution of 2.5 mmol of heteroaromatic base, 5 mmol of CAN, 2.5 mmol of NHPI, 5 mmol of CF_3COOH in 10 mL of formamide was warmed at 70 °C for 6 h. The solution was made basic with aqueous NaOH and extracted with CH_2Cl_2. The reaction products were identified by GC–MS and comparison with authentic samples. The quantitative analysis was carried out by GC, using nicotinamide as internal standard. [b] 5 mmol of H_2SO_4 were utilised instead of CF_3COOH.

Notes and references

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