An unprecedented radical ring closure on a pyridine nitrogen†

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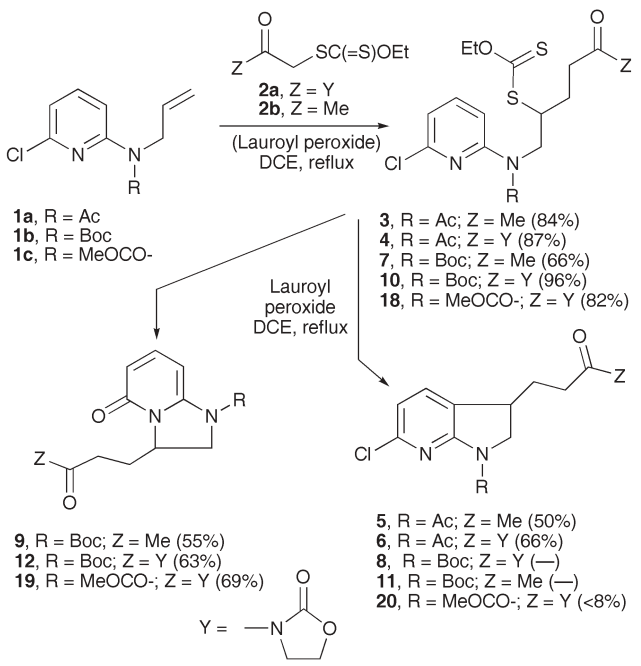
An unprecedented radical ring-closure onto the pyridine nitrogen was observed when certain types of substituents were present around the pyridine nucleus.

We recently described a convergent synthesis of azaindolines based on the intermolecular radical addition of a xanthate to a protected 2-*N*-allylaminopyridine followed by ring closure to the pyridine as illustrated by the conversion of **1a** into azaindolines **5** and **6** *via* adducts **3** and **4** (Scheme 1).[1] Both steps are mediated by a peroxide such as lauroyl peroxide. While the first step is a typical chain process, requiring only a small amount of initiator, the second step consumes stoichiometric amounts in order to re-aromatize the pyridine ring following the radical addition. This approach could be extended to the synthesis of structures containing 6- and 7-membered rings fused to the pyridine nucleus.

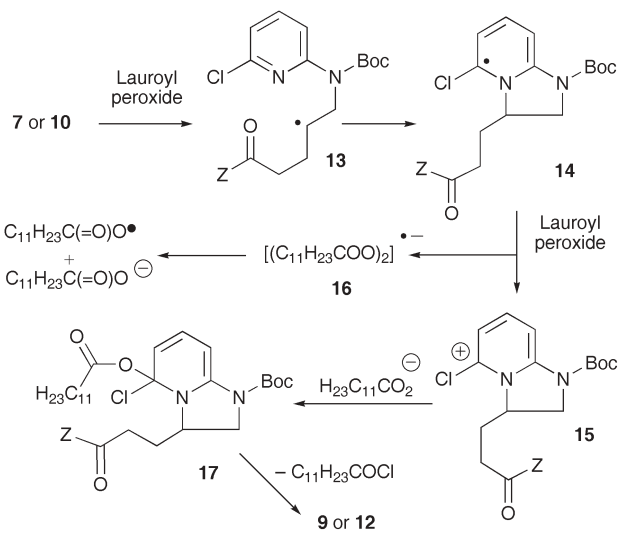
When we attempted to modify the protecting group on the nitrogen, by replacing the acetyl in **1a** by the more versatile *t*-butoxycarbonyl (Boc) group, we were surprised to find that the reaction of the corresponding acetonyl adduct **7** with lauroyl peroxide, under otherwise identical conditions, furnished a compound that was not the expected azaindoline **8**. The absence of chlorine in the mass spectrum, the pattern for the pyridine protons in the ^{1}H NMR spectrum, and the presence of an extra carbonyl group, as revealed by ^{13}C NMR spectroscopy, were compatible with structure **9**. In the same way, oxazolidone adduct **10** did not produce indoline **11** but gave a compound which had the spectral characteristics of **12**. Fortunately, the latter was crystalline allowing an unambiguous structural determination by X-ray diffraction on a single crystal.‡



Scheme 1 An unexpected ring-closure onto the pyridine nitrogen.

The formation of pyridones **9** and **12** can only arise through a ring closure of radical **13** on the pyridine nitrogen (Scheme 2).§ This is followed by an electron transfer from radical **14** to the peroxide to give stabilized cation **15** and radical anion **16**. The latter collapses into a laurate anion and the corresponding carboxylic radical. Quenching of **15** by its laurate counter-anion would lead to tetrahedral intermediate **17**, which can collapse into the observed pyridones **9** or **12**, depending on group Z, and lauroyl chloride. On a small scale, it is also quite possible that adventitious moisture could hydrolyze **15** directly into the corresponding pyridone.

As far as we are aware, such a radical closure on the pyridine nitrogen is unprecedented. Radical additions on the nitrogen atom of imines and related derivatives are rare and the yields tend to be very low.[2] Notable exceptions can be found in the recent work by Johnston *et al.*[3] and earlier model studies related to the mechanism of 2,3-lysine amino-mutase.[4] Additions to azides and to diazirines are also known,[5] and acyl radicals have been reported to add to the nitrogen atom of azomethines.[6]



Scheme 2 Mechanism for ring-closure onto the pyridine nitrogen.

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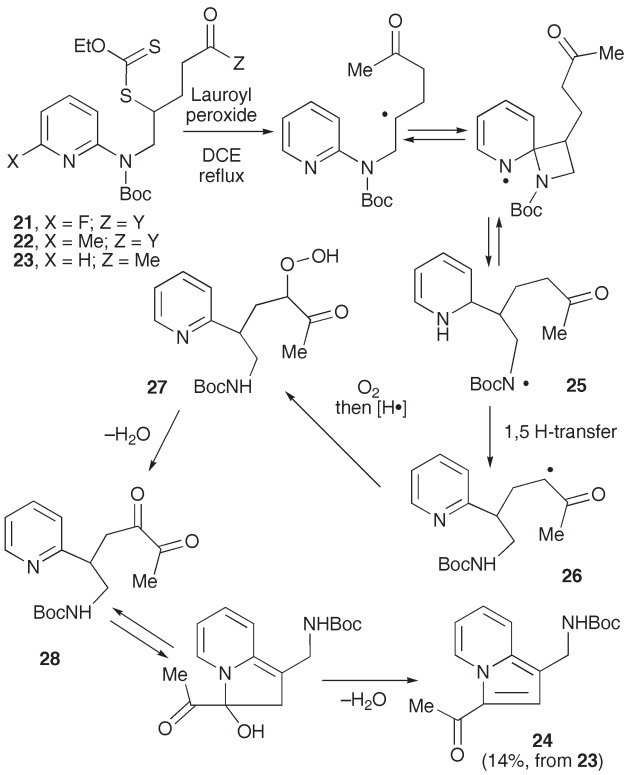
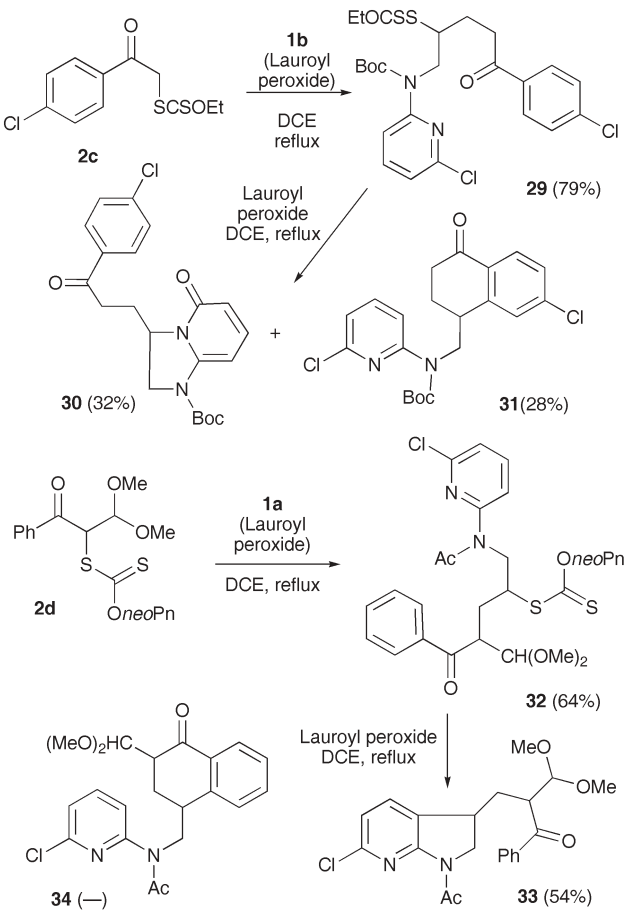


Scheme 3 Unexpected formation of an indolizine product.

The causes of the dramatic shift in the regiochemistry of the cyclisation, upon mere modification of the protecting group, are not clear and may be due to differences in rotamer population. When the Boc group in **10** was replaced by a methoxycarbonyl (*i.e.* **18**, in Scheme 1), the cyclisation still gave the corresponding pyridone, **19**, as the major product, in a similar yield of 69%, along with a small amount (<8%) of the "normal" indoline, **20**. The rotation barrier for carbamates is of the order of 16 kcal mole^{-1} and hence only slightly lower than that for amides.[7] Because of steric repulsion and very possibly unfavorable dipole–dipole interactions between the pyridine nitrogen and the carbamate oxygen lone pairs, the preferred rotamer is presumably the one where the alkoxy (*t*-butoxy or methoxy) portion of the carbamate is pushed away from the pyridine nitrogen. This brings the radical containing terminus into close proximity to the pyridine nitrogen and enhances the chances of C–N bond formation.

We also found that the chlorine atom exerts an important activating effect. Starting from the fluoro- analog **21**, the reaction was not very clean, but the same pyridone, **9**, was obtained, albeit in only 25% yield. Replacing the chlorine with a methyl group, as in **22**, resulted in a complex mixture with no discernible major product. A complex mixture was also observed with un-substituted parent derivative **23**, but in this case a compound could be isolated in low yield (14%) and identified as having indolizine structure **24**. A profound modification of the original structure has clearly occurred in this case (Scheme 3). The Boc group hinders closure to the "normal" azaindoline and the absence of the chlorine reduces the radicophilicity of the pyridine nitrogen. What remains is an unusual radical Smiles rearrangement through a 4-membered ring[8] to give **25**, followed by internal hydrogen abstraction. Radical **26** thus formed would evolve into diketone **28** by reaction with



Scheme 4 Competition experiments.

adventitious molecular oxygen *via* hydroperoxide **27**.[9] Ionic closure on the pyridine nitrogen followed by loss of water and prototropic shift finally gives the observed product. This mechanism remains a speculation at this stage and the low yield did not encourage a more detailed examination.

Evidently, the relative rates of the various modes of ring-closure dictate the ultimate outcome of the reaction. A feel for the rates could be obtained by carrying out the two sequences displayed in Scheme 4. The radical derived from adduct **29** can either cyclise on the pyridine nitrogen to give **30** or on the phenyl ring to give tetralone **31**. In the event, an almost equal yield of each was observed (32 and 28% respectively). In contrast, reaction of adduct **32**, derived from xanthate **2d** and olefin **1a**, and thus *bearing an N-acetyl protecting group*, furnished only the azaindoline **33** and none of the corresponding tetralone **34**. Closure on carbon leading to the azaindoline is clearly intrinsically faster than radical attack on the pyridine nitrogen, but the carbamate group somehow shuts down the former process, leaving the radical no option but to follow the latter course.

We have, in summary, uncovered a dramatic effect of a carbamate group on the regioselectivity of the radical ring-closure and, perhaps more importantly, documented a novel mode of cyclisation involving a radical attack on the pyridine nitrogen. From a synthetic standpoint, this new reaction provides access to a relatively rare class of compounds of potential importance in medicinal chemistry.[10] Broad diversity can be secured by merely

modifying the nature of the initial xanthate and the substitution pattern around the pyridine ring, with the exception of the key chlorine atom, which must be retained.

We thank Dr Eric Bacqué of Sanofi-Aventis for many friendly discussions.

Notes and references

‡ *Crystal data for* **12**: $C_{18}H_{23}N_3O_6$, M = 377.39 g mol^{-1}, monoclinic, space group $P2_1/c$, a = 17.4910 (10), b = 8.9170(10), c = 12.0560(10) Å, V = 1873.6(3) Å^3. Z = 4, ρ = 1.338 g cm^{-3}, μ = 0.101 cm^{-1}, F(000) = 800, crystal size = 0.22 × 0.20 × 0.10 mm, T = 150.0(1) K. Reflections measured 8739 (R(int) = 0.0143). The structure was refined to R = 0.0391 for all reflections. CCDC 601962. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b609021d

§ Although compounds **9** and **12** could also arise by an ionic substitution of the xanthate by the pyridine nitrogen, this is highly unlikely because of the poor leaving group ability of the xanthate with respect to S_N2 type displacements. Moreover, if this were indeed the case, significant amounts of **9** or **12** would have been observed during the preparation of their precursors **3** and **4** which, apart from the use of stoichiometric amounts of lauroyl peroxide, takes place under virtually identical conditions (refluxing DCE).

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