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A flexible radical approach to 5-substituted 4,5-dihydro-3*H*-pyrido[4,3-*b*]azepin-2-ones. Some mechanistic observations on the radical cyclisation-aromatisation process

Laurent Petit[a], Iuliana Botez[b], André Tizot[b], Samir Z. Zard[a,*]

[a] Laboratoire de Synthèse Organique, UMR 7652 CNRS, Ecole Polytechnique, 91128 Palaiseau, France
[b] Institut de Recherches Servier (IdRS), 125 chemin de Ronde, 78290 Croissy sur Seine, France

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ABSTRACT

Variously substituted novel dihydropyridoazepinones have been prepared by an intermolecular radical addition followed by a radical cyclisation on a pyridine ring. The latter process involved the use of a combination of two different peroxides, an experimental contrivance resulting from a careful product analysis and a better understanding of the cyclisation step.

Pyridine derivatives arguably represent a very important class of heterocyclic structures. They are used in a wide variety of applications such as pharmaceuticals, agrochemicals, vitamins, food flavourings, paints, dyes, rubber products, adhesives, etc. Thus, their preparation has garnered much interest in both academic and industrial settings.[1] The search for innovative and efficient access to this class of molecules is indeed one of the driving forces in this field. The degenerative transfer of xanthates and related groups discovered in our laboratory has proved efficient at accomplishing notoriously difficult radical transformations such as intermolecular additions to unactivated alkenes and ring-closure onto aromatic rings.[2] In this context, we have explored the synthesis of heterocyclic substructures using either a radical cyclisation onto the relevant aromatic ring or a combination of an intermolecular addition and a radical cyclisation. For example, azaindolines, diazaindolines, pyrimidinones, azaindoles, azaoxindoles, pyridones, tetrahydronaphthyridines and tetrahydroazaquinolones have all been assembled using this technology in a straightforward fashion.[3] Seven-membered rings fused to a pyridine core, such as pyridoazepines, are very scarce structures in the chemical literature, reflecting the difficulty of their access. Yet, they can be valuable targets, as demonstrated by the considerable effort invested by the process research department at Merck to develop a practical route to a non-peptidic $\alpha v\beta 3$ antagonist containing a tetrahydropyridoazepine ring (Scheme 1).[4] To date, the most useful method to construct this scaffold relies on the *ortho*-metalation of an *N*-acyl-aminopyridine followed by alkylation with a dihaloalkane and in situ cyclisation. However, this method, introduced by Spivey in 1998 for the synthesis of DMAP analogues,[5] is hampered by the limited access to suitable dihaloalkanes and by the low functional group tolerance inherent to the use of strong lithiated bases. We have reported a radical based approach to two examples of 6,7-dihydro-5*H*-pyrido[2,3-*b*]azepin-8(9*H*)-one (the extra-nuclear nitrogen atom is at the 2-position of the pyridine), but further investigation was required to generalise this strategy and to extend it to the synthesis of other isomers in this family.[2b]

We became interested in molecules bearing the nitrogen substituent at the 4-position of the pyridine ring because these isomers are virtually unknown in the literature.[6] Our synthetic analysis relies on a sequence consisting of an intermolecular radical addition of a xanthate to an unactivated olefin such as **1** to furnish xanthate **2**, followed by the radical cyclisation to give **3** (Scheme 2). The chlorines at the 2- and 6-positions were chosen to reduce the nucleophilicity and basicity of the pyridine nitrogen atom and to serve as further points of diversification.[2b] A nucleophilic pyridine slowly decomposes the xanthate group by an ionic process and the resulting sulphur-containing products can interfere with the radical sequence.

Initial studies revealed that the nitrogen atom at the 4-position needed to be substituted for the cyclisation to occur; otherwise, almost complete reduction of the xanthate function in **2** was

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[*] Corresponding author.
E-mail address: zard@poly.polytechnique.fr (S.Z. Zard).

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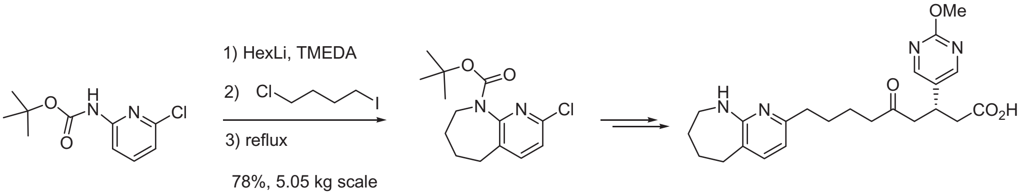
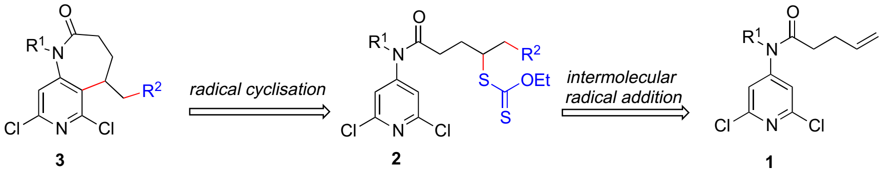


Scheme 1. Merck process route to a tetrahydroazepine.

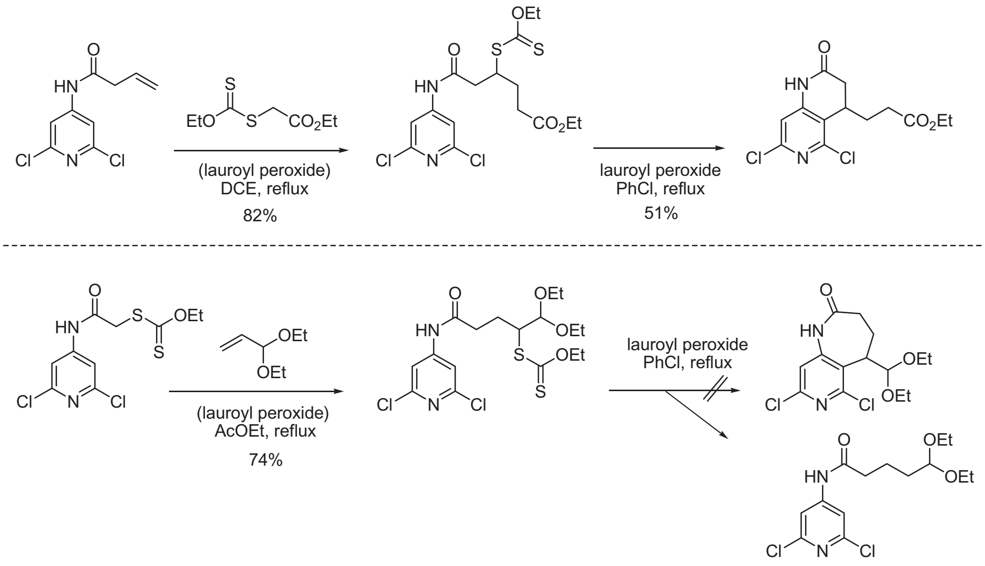


Scheme 2. Retrosynthetic analysis.

observed. While this failure may be attributed to the slow rotation around the amide bond and the predominance of the geometrically non-desired rotamer, this result must be contrasted with the surprisingly successful formation of a six-membered ring starting with an unsubstituted amide as in the first transformation shown in Scheme 3.[3a]

The methyl group was chosen as the substituent on the amide nitrogen. The preparation of olefin **1a** was executed in two steps. Reaction between 4-amino-2,6-dichloropyridine and 4-pentenoic acid chloride in the presence of di*iso*propylethylamine provided the corresponding secondary amide in 97% yield. Treatment of the latter with methyl iodide in acetone in the presence of potassium carbonate in a sealed vessel gave olefin **1a** in 93% yield. The intermolecular radical addition of the xanthate derived from chloroacetone proceeded smoothly under standard conditions [sub-stoichiometric quantities of dilauroyl peroxide (DLP) in refluxing ethyl acetate] furnishing xanthate **2a** in a good yield (61%). With this new xanthate in hand, the stage was set for the radical cyclisation. The first attempt using stoichiometric amounts of DLP in refluxing ethyl acetate resulted in a disappointingly poor yield (10%) of the desired heterocycle **3a**, along with the prematurely reduced compound **4** (15%) and a complex mixture of more polar by-products. These by-products were identified by HPLC/MS and crude NMR analysis as dimeric bicyclic compounds present as a mixture of regio and atropoisomers. For the sake of clarity only two of these, **5** and **6**, are shown (Scheme 4).

This was the first time such dimers were observed in the course of a radical cyclisation onto a pyridine ring. The radical cyclisation process usually entails four main steps. First, the radical is generated from the corresponding xanthate by the action of the peroxide under thermal conditions. Second, the key cyclisation event leads to a delocalised dihydropyridinyl radical. Third, the oxidation of this radical by the peroxide (used in stoichiometric amounts) by a one-electron transfer precedes the fourth and final rearomatisation steps through loss of a proton. In the present case, the oxidation of the dihydropyridinyl radical is clearly a relatively slow process. The lifetime of this radical intermediate is extended and its concentration therefore increases to the point where self-coupling becomes a very significant side reaction. Loss of two molecules of hydrochloric acid from the resulting dimer furnishes the observed dimeric products **5** and **6** and their various isomers. These mechanistic features are summarised in Scheme 5 (only one isomer is shown).



Scheme 3. Reactivity contrast between the six and the seven-membered ring formation with an unsubstituted amide.