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Tin-Free Radical Cyclizations for the Synthesis of 7-Azaoxindoles, 7-Azaindolines, Tetrahydro[1,8]naphthyridines, and Tetrahydro-5*H*-pyrido[2,3-*b*]azepin-8-ones

Eric Bacqué,[†] Myriem El Qacemi,[‡] and Samir Z. Zard*[,‡]

Laboratoire de Synthèse Organique associé au CNRS, Ecole Polytechnique, 91 128 Palaiseau Cedex, France, and AVENTIS Pharma, 94 400 Vitry sur Seine, France

zard@poly.polytechnique.fr

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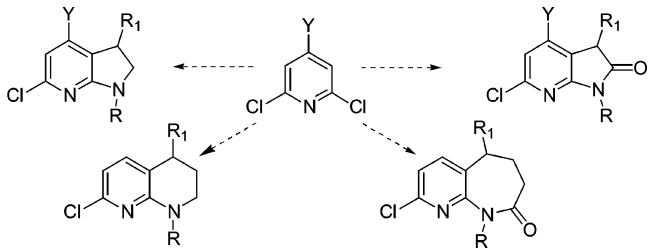
ABSTRACT



Compounds containing a pyridine nucleus fused to a saturated nitrogen-containing ring, including 7-azaoxindoles, 7-azaindolines, tetrahydro-[1,8]naphthyridines, and tetrahydro-5*H*-pyrido[2,3-*b*]azepin-8-ones, were prepared in good yield starting from various 2,6-dichloropyridines. The method hinges on a free-radical xanthate-mediated cyclization or intermolecular addition/cyclization sequence for the construction of the new fused rings.

For a convenient access to designed 7-azaoxindoles, which have potential biological activity,[1] it is essential that reliable, flexible, and general synthetic methods be readily available. However, the various synthetic routes toward these compounds are limited with respect to yield and scope.

There are three general approaches to 7-azaoxindoles. The first is the oxidative bromination of expensive 7-azaindole derivatives followed by a zinc-mediated reduction.[2] The second requires substituted pyridines such as 2-chloronicotinic acid[1b] or 3-pyridyl acetonitrile.[3] More recently, a third process based on the carbonylation of doubly lithiated 2-pivaloylaminopyridine to give the 7-azadihydroindol-2-one[4] was reported; this method was based on the previous lithiation studies of Turner starting from 3-methyl-2-aminopyridine.[5]

In a previous paper, we reported an efficient approach to indolines and indans and also described one example of a 7-azaindoline.[6] Herein, we wish to report a development of this method that leads to improved access to a wide range

[†] AVENTIS Pharma.
[‡] Ecole Polytechnique.

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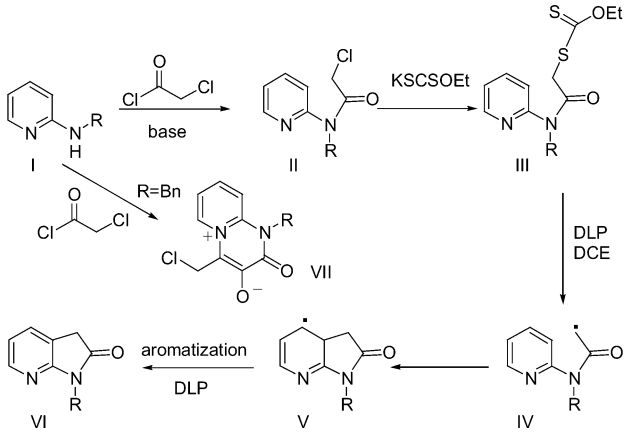
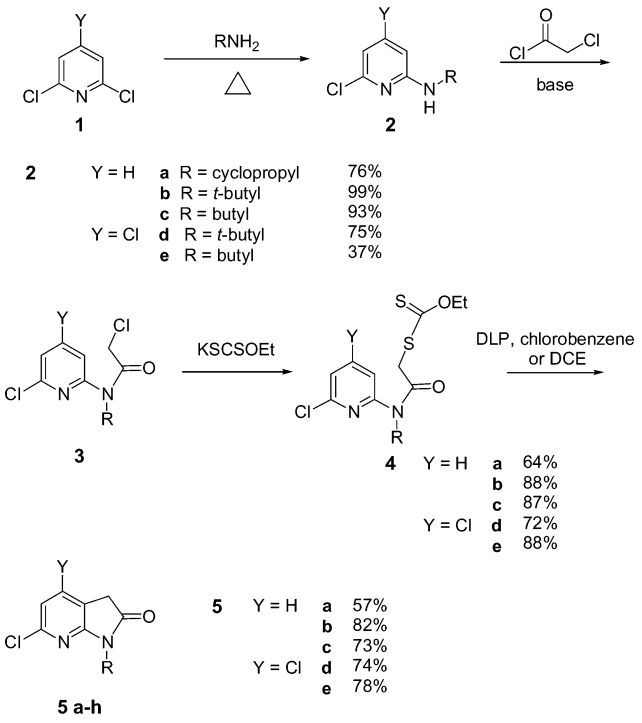
Scheme 1. Radical Sequence Plan



Scheme 2. Preparation of Radical Precursors and of 7-Azaoxindoles



of nitrogen containing rings fused to a pyridine nucleus, including 7-azaoxindoles. This new synthetic route involves a free-radical-mediated cyclization onto the pyridine ring as the key step.[7]

As part of our work on the free-radical xanthate-mediated chemistry, a radical cyclization onto the pyridine ring appeared to us as a potentially general approach toward compounds of such considerable pharmaceutical interest. Radical cyclizations using xanthates have numerous advantages such as experimental simplicity, the absence of heavy or toxic metals, and compatibility with a wide range of functionality since the conditions are mild and neutral.[7b]

In the present case, the xanthate precursor III would be produced from an aminopyridine I by reaction with chloroacetyl chloride to give an amide II followed by displacement of the chlorine with potassium *O*-ethyldithiocarbonate. Thus, upon exposure to lauroyl peroxide (DLP) in 1,2-dichloroethane (DCE) or chlorobenzene, radical IV is generated from the xanthate group and should cyclize onto the aromatic ring to give a new radical V which can be aromatized into azaoxindole VI by oxidation with the peroxide (Scheme 1).

Our initial studies in this area started with benzylaminopyridine. Unfortunately, under standard conditions to form the chloroacetamide derivative, the reaction afforded unexpectedly betaine VII, a compound described earlier in the literature.[8] The formation of this product is certainly a consequence of the high nucleophilicity of the pyridine nitrogen.

To circumvent this unwanted reaction, we decided to place a chlorine at the 6-position of the pyridine ring to sterically and electronically decrease the nucleophilicity of the nitrogen. 2-Amino-6-chloropyridines are accessible by substitution of commercially available 2, 6-dichloropyridine. Thus, heating the latter in refluxing cyclopropylamine afforded 2-(*N*-cyclopropylamino)-6-chloropyridine in 11% yield (Scheme 2). With the higher boiling *n*-butylamine, the yield was much better (74%). Unfortunately, with the bulkier *tert*-butylamine, the reaction was much slower and the yield disappointingly low (5%). Nevertheless, we secured enough material to carry out some preliminary experiments, which turned out to be successful (vide infra). Thus, the need for a precursor increased, and we decided to improve the synthesis of the 2-amino-6-chloropyridines. We eventually found that heating 2,6-dichloropyridine with *tert*-butylamine at 180 °C in a sealed tube for 4 days gave the desired aminopyridine **2b** in more than 99% yield (Scheme 2). The reaction was very clean despite the harsh conditions, which were applied to other amines and to more substituted dichloropyridines such as 2,4,6-trichloropyridine. All of these derivatives were readily converted into the corresponding xanthates **4**.

We were indeed pleased to find that addition of lauroyl peroxide to a refluxing solution of compounds **4** in DCE or chlorobenzene furnished 7-azaoxindoles in good yield. Our results are displayed in Scheme 2.

In addition to successfully blocking the deleterious nucleophilic activity of the pyridine nitrogen, the chlorine in position 6 provides a handle for further transformations. It can of course be reductively removed but may also be exploited for a new aromatic nucleophilic substitution or for various transition-metal-mediated couplings.

3-Substituted analogues may be accessed by Knoevenagel condensation of the azaoxindoles with aldehydes or ketones or by alkylation of the derived anion.

7-Azaindolines are pharmaceutically important compounds[9] and act often as precursors of 7-azaindoles, which have an even greater pharmaceutical potential, in particular

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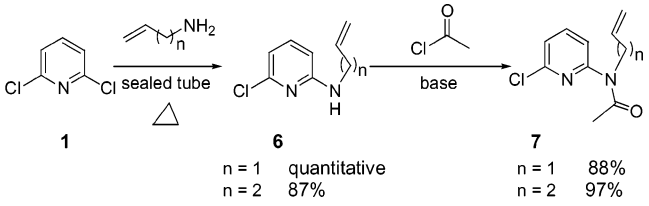
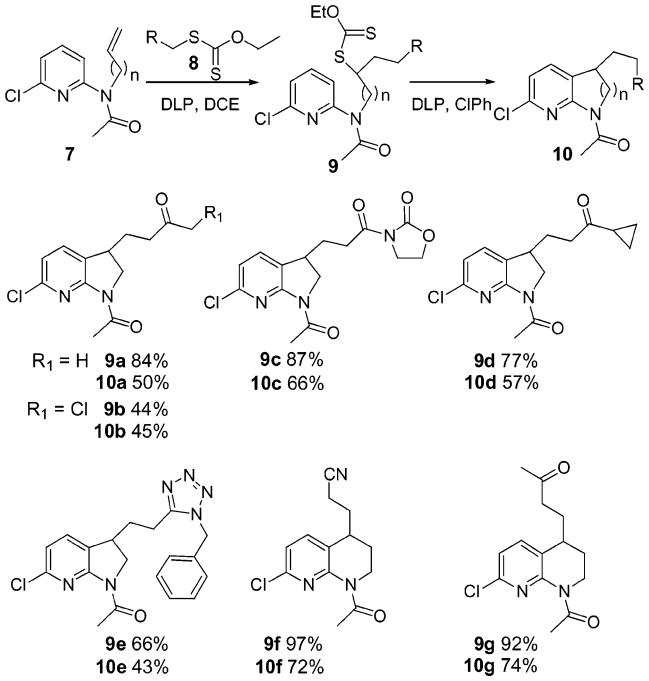
Scheme 3. Preparation of 2-Chloro-6-aminopyridines



Scheme 4. Synthesis of 7-Azaindolines and Tetrahydro[1,8]naphthyridines



as pertains their antiinflammatory properties.[10] However, it is a somewhat inaccessible class of derivatives. Recently, a free-radical-mediated aryl amination has been described whereby an aryl radical, generated by tributyltin hydride, adds to the nitrogen of an azomethine bond to give an azaindoline.[11] A second approach involving a directed ortho-metalation of aminopyridines has been described to access annulated pyridines derivatives.[12]

We have found that xanthate chemistry allows an expedient and especially versatile radical synthesis of azaindolines. The method employs cheap, nontoxic, and easy to handle compounds. Thus, treatment of 2,6-dichloropyridine with an excess of allylamine produced in a quantitative yield the 2-allylamino-6-chloropyridine, which was protected by an acetyl group before being subjected to the radical steps (Scheme 3). Indeed, an addition−cyclization sequence using xanthate derivatives provided the desired 7-azaindolines in good yield (Scheme 4).

The tremendous flexibility of this approach is demonstrated by the variety of the xanthates **8** that can be used (examples **10a**−**e** in Scheme 4). Furthermore, the oxazolidinone derivative **10c** can give rise to a wide library of amides when treated with various amines.[13] Compound **10b** is also of great interest since can be involved in a Hantzsch-type[14] reaction to form thiazole derivatives, which are known as bioisosteres of pyridine rings. Its chlorine atom can also be substituted by a xanthate group and engaged in a new radical addition onto another olefinic trap.[15]

The unique advantages of the xanthate technology can be appreciated in connection with the preparation of larger fused rings. 1,2,3,4-Tetrahydro[1,8]naphthyridine derivatives are of great pharmaceutical importance,[16] for instance, since several drugs possess this backbone. Yet, very few procedures have been reported for the synthesis of such compounds. The usual route involves a regioselective hydrogenation of naphthyridines which are prepared via a Skraup[17] or a Friedländer reaction.[18] An optimized intramolecular Chichibabin reaction was also applied to access these bicyclic heterocycles.[19]

In our case, all we had to do was to add one more carbon to the side chain. Thus, 2-homoallylamino-6-chloropyridine (**7**, $n = 2$) was prepared in good yield by reacting 2,6-dichloropyridine with excess 3-butenylamine in a sealed tube at 140 °C. The addition of *S*-cyanomethyl-*O*-ethyl xanthate gave an excellent yield of the corresponding adduct **9f** (97%), which underwent a smooth ring closure upon exposure to stoichiometric amounts of lauroyl peroxide providing the expected tetrahydronaphthyridine **10f** in 72% yield. The synthesis of **10g** represents another example.

Finally, we examined the possibility of constructing a pyridine fused to a seven-membered ring. Derivatives of tetrahydro-5*H*-pyrido[2,3-*b*]azepin-8-ones are very rare,[20] and a simple, efficient route to such structures would significantly

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contribute to the study of their chemistry and pharmacological profile. We explored two complementary routes. The first involved xanthate **4c** which, in the presence of allyl acetate, underwent preferentially an intermolecular addition to give adduct **11** in 51% yield instead of ring closing to the azaindoline **5c** as described above. This is a remarkable result since it indicates that ring closure to the pyridine ring is relatively slow (but nevertheless feasible through the xanthate approach) and can be overtaken by an intermolecular addition even to an unactivated olefin such as allyl acetate. This dichotomy in the reactivity translates in practice into a great flexibility for the introduction of variety into the structures. Ring closure starting from **11** occurred in a modest but still useful yield to give **12** (34%). The second approach involved addition of a xanthate to compound **13** followed by ring closure to the seven-membered ring, which occurred surprisingly efficiently. Compound **15** was thus obtained in 59% yield (Scheme 5).

In summary, we have presented some of our preliminary results relating to the synthesis of pyridine derivatives where the heteroaromatic ring is fused to five-, six-, or even seven-membered nitrogen-containing heterocycles. None of the yields have been optimized; nevertheless, this approach is far more general and flexible than traditional routes. It should now be possible to access simply and cheaply a vast number of hitherto unknown structures of high pharmaceutical interest.

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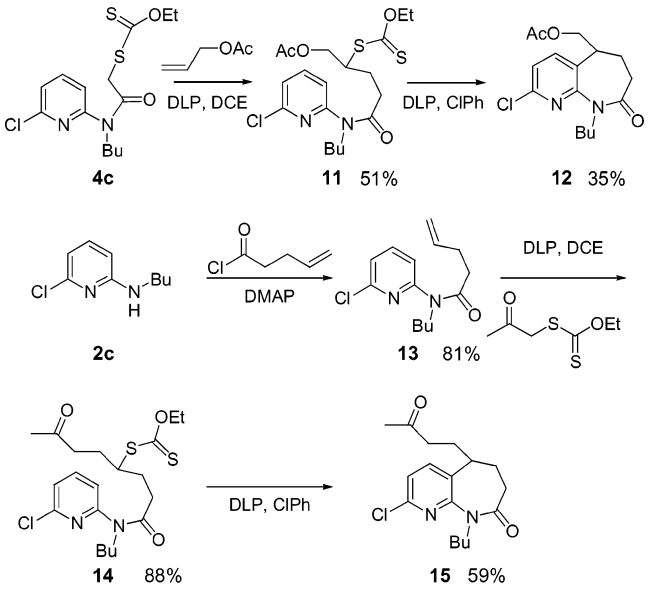
Scheme 5. Two Routes toward Tetrahydro-5*H*-pyrido[2,3-*b*]azepin-8-ones



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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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