

HETEROCYCLES, Vol. 84, No. 1, 2012, pp. 291 - 299. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 17th May, 2011, Accepted, 17th June, 2011, Published online, 30th June, 2011
DOI: 10.3987/COM-11-S(P)24

A FLEXIBLE, CONVERGENT ROUTE TO AZAOXINDOLES, AZAINDOLINES, AZAINDOLES, AND TETRAHYDROAZAQUINOLONES

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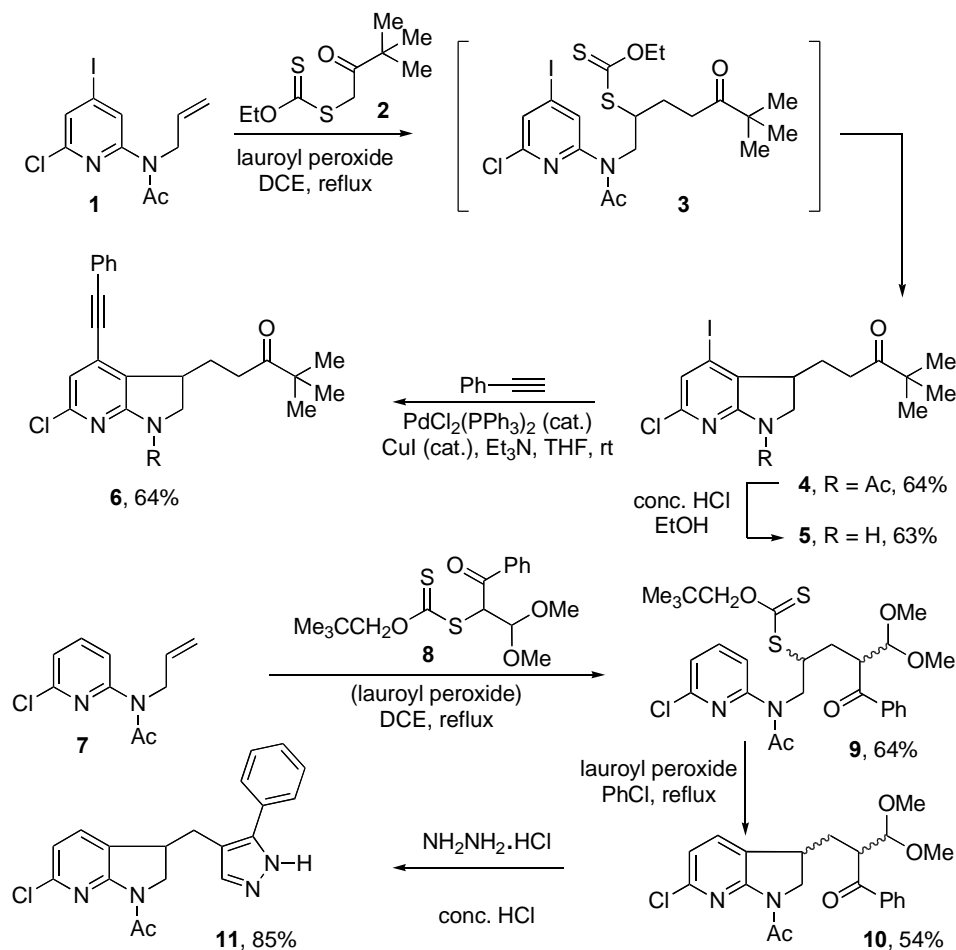
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This paper is dedicated with respect and admiration to Prof. Albert Padwa on the occasion of his 75th birthday.

Abstract – A variety of azaoxindoles, azaindolines, azaindoles, and tetrahydroazaquinolones can be readily prepared by cyclisation onto pyridine rings of radicals derived from xanthates. The xanthate precursors may themselves be produced by intermolecular radical addition-transfer to allylamino- or butenoylamide side-chains.

In recent years, much effort has been directed to the synthesis of azaindoles and related derivatives.¹ Such molecular scaffolds are related to the enormously important indoles and constitute therefore privileged structures in medicinal chemistry.² Indeed, aza-analogs of indole-based active compounds often exhibit improved solubility and bioavailability. Access to these derivatives is however much more difficult than for the indole series. Transposition of the classical indole syntheses to their aza analogs is hampered either by the limited availability of the requisite precursors or by reactivity problems. For instance, the immensely powerful and widely used Fischer indole synthesis often gives poor yields and sometimes completely fails when applied to the pyridine series.³ Furthermore, very few pyridinylhydrazines are commercially available. In order to address this important synthetic problem, we have examined the potential of the xanthate transfer process for constructing additional rings around the pyridine nucleus. The degenerative transfer of xanthates and related groups we discovered some years ago has proved quite efficient at accomplishing difficult radical transformations such as intermolecular additions to unactivated

alkenes and ring-closure onto aromatic rings.⁴ We have thus found that it was possible to prepare 7-azaoxindoles, 7-azaindolines, tetrahydro[1,8]naphthyridines, and tetrahydro-5*H*-pyrido[2,3-*b*]-azepin-8-ones by radical cyclisation onto the pyridine ring or by a combination of an intermolecular addition and a cyclisation.⁵



Scheme 1. Syntheses of 7-azaindolines

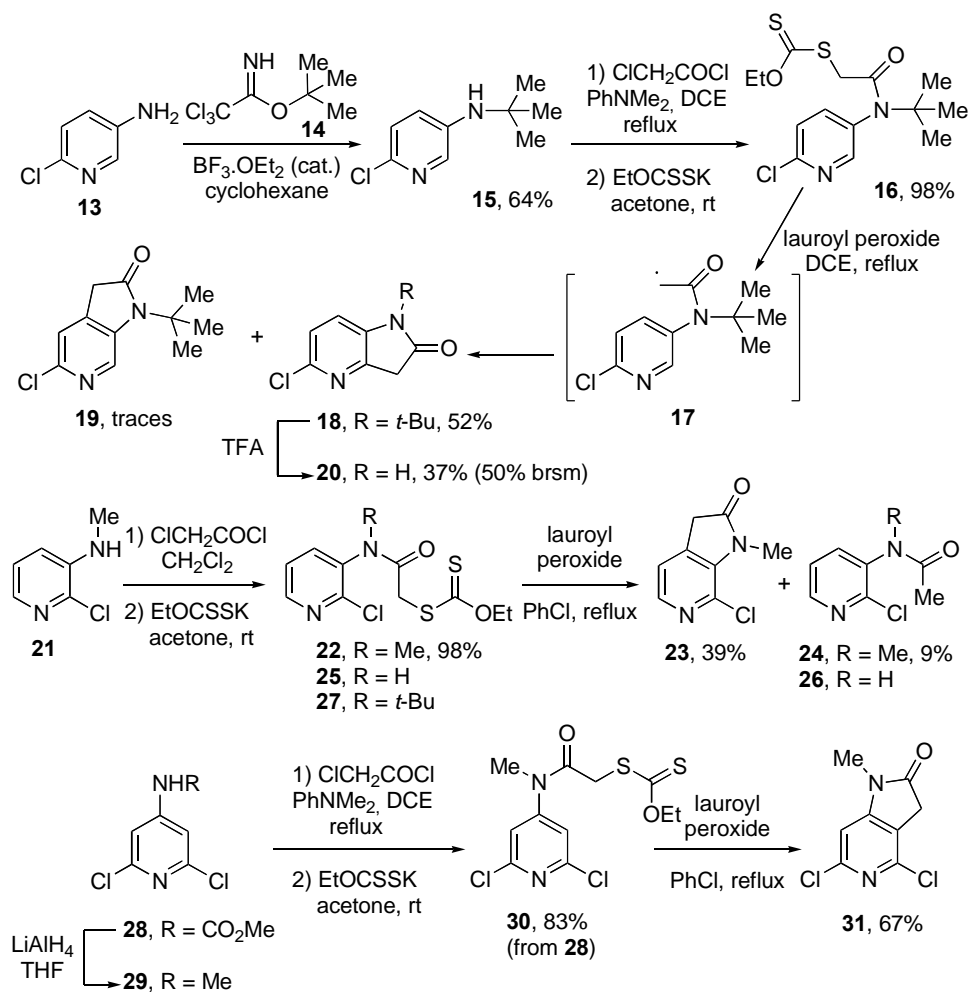
Additional examples of this approach to 7-azaindolines are displayed in Scheme 1. They illustrate the tolerance to functional groups, in particular to the presence of an iodide on the aromatic ring, as well as the rapidity with which a complex structure can be attained. In the first sequence, the intermediate adduct **3** arising from the addition of xanthate **2** to substrate **1** was not isolated but made to cyclise by treatment with a stoichiometric amount of lauroyl peroxide to give 7-azaindoline **4** in good overall yield. This derivative constitutes an ideal molecular scaffold for building large libraries of medicinally interesting compounds, since it contains several well-positioned functional groups with orthogonal chemical reactivity. For instance, the acetyl group can be easily cleaved to give **5** (and eventually replaced by other appendages), and a Sonogashira coupling selectively proceeds on the iodine to provide compound **6** in

high yield. Suzuki-Miyaura and other organometallic couplings could in principle be applied, and the use of different starting xanthates would allow an expedient modification of the side chain functionality.

This last possibility is illustrated by the sequence starting from pyridine **7** and xanthate **8** and proceeding by way of adduct **9**. The resulting 7-azaindoline **10** contains a masked 1,3-ketoaldehyde; its reaction with hydrazine under acidic conditions furnishes the corresponding pyrazole **11**. The nature of the side chain may in principle be easily modified by using substituted hydrazines or other 1,2- or 1,3-bis nucleophiles, such as hydroxylamines, amidines, or guanidines.⁶

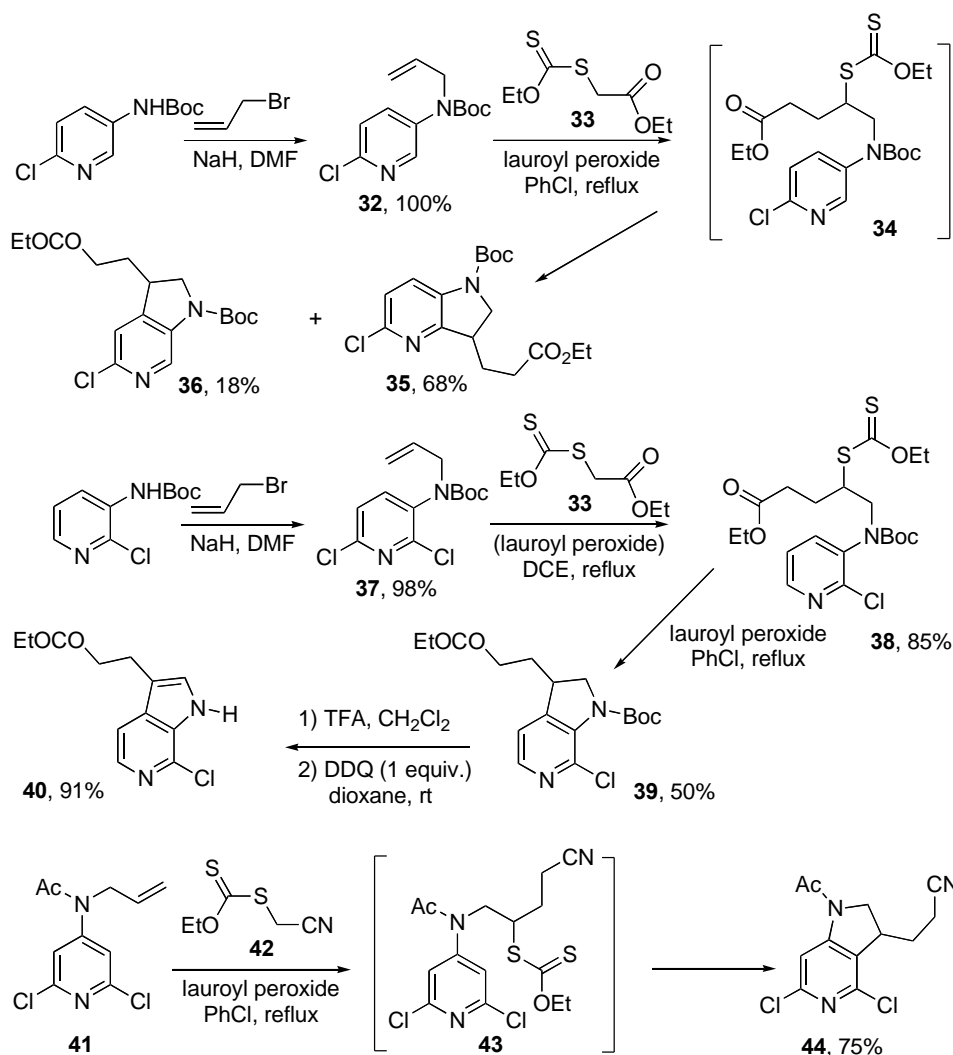
The two sequences in Scheme 1 highlight two procedures for constructing azaindoline structures: (a) a one-pot process where the intermolecular addition and ring closure are performed in the same flask by adding first a small amount of lauroyl peroxide to initiate the addition to the alkene, followed by portion-wise addition of a stoichiometric amount of peroxide to accomplish the ring-closure (prior two- to three-fold dilution with fresh solvent or replacement with a higher boiling solvent is often advantageous for the cyclisation step); (b) a two step process, where the first adduct, such as **9**, is separated and characterised (hence the placement of lauroyl peroxide inside parentheses to indicate that it is used in sub-stoichiometric amounts). We have tended to favour the latter as it allows a better monitoring of the reaction progress and provides useful intermediates for various other transformations.

Our next task was to extend this very promising strategy to the synthesis of the other members in the series, namely 4-, 5-, and 6- azaoxindoles, azaindolines, as well as to aza-tetrahydroquinolones. In the case of the 4- and 6- isomers, a problem of regioselectivity arises, that will also need to be examined. Addressing first the azaoxindoles, we prepared 5-(*N*-*t*-butyl)amino-2-chloropyridine **15** by reaction of the 5-amino-2-chloropyridine **13** with commercially available *O*-*t*-butyliminoether **14** in the presence of boron trifluoride etherate (Scheme 2). This reaction proved to be very convenient for attaching a tertiary butyl group on aminopyridines and anilines; it is based on an earlier example by Anderson and co-workers.⁷ Chloroacetylation followed by displacement of the chloride with potassium *O*-ethyl xanthate furnished the desired precursor **16** in good overall yield. Exposure of this substance to the action of lauroyl peroxide in refluxing chlorobenzene resulted in a highly regioselective ring-closure to give 4-azaoxindole **18** in 52% yield; only traces of the isomeric 6-azaoxindole **19** could be detected. This is an unexpected and interesting result since the intermediate radical **17** is electrophilic in character, yet it prefers to attack the most electrophilic of the two possible reaction sites.⁸ The underlying causes for this high regioselectivity are still not clear. A survey of the limited number of radical ring-closures onto pyridine rings reported in the literature shows mostly a lack of selectivity and the general obtention of regioisomers.⁹ In any case, the clean formation of the 4-azaoxindole without the need for blocking position-4 on the pyridine ring represents a very convenient synthetic asset. The tertiary butyl group may be removed by treatment with a strong acid such as trifluoroacetic acid, as shown by the formation of azaoxindole **20** unsubstituted on the lactam nitrogen.



Scheme 2. Syntheses of 4-, 5-, and 6-azaoxindoles

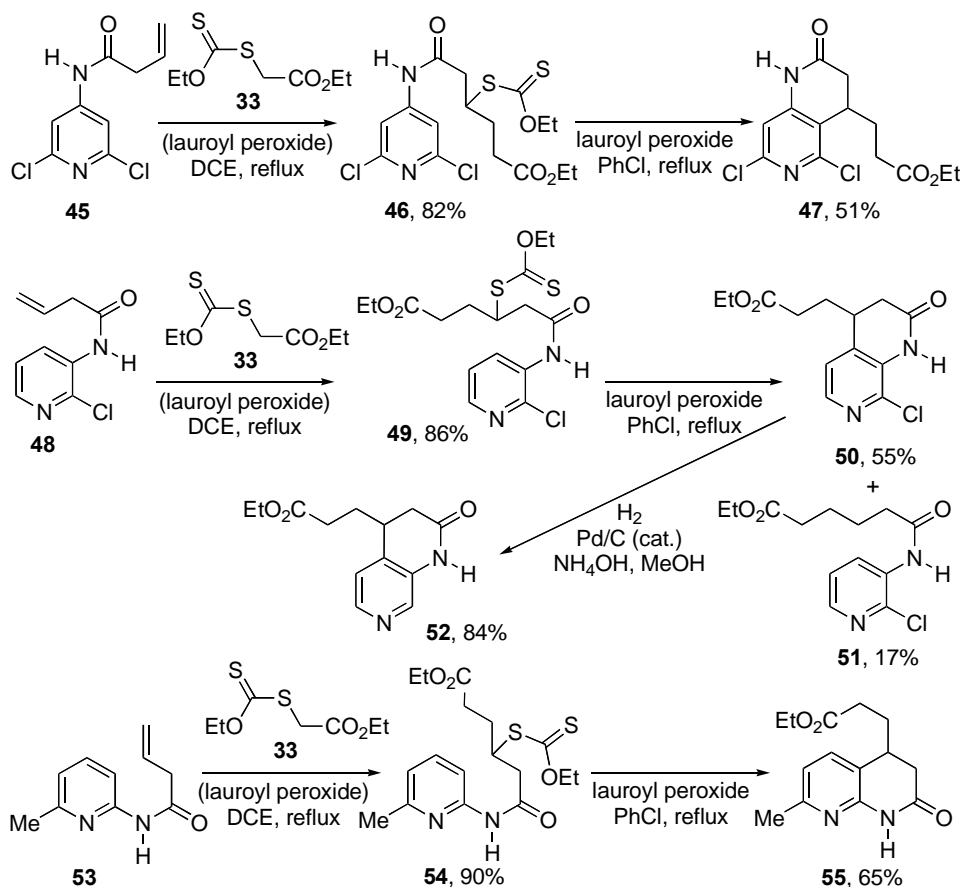
In order to obtain the 6-isomer, the position adjacent to the pyridine nitrogen had to be blocked. Thus, starting with 2-chloro-3-(*N*-methyl)aminopyridine **21**, xanthate **22** was prepared in high yield by a similar procedure to that used for compound **16**. Treatment with lauroyl peroxide in refluxing chlorobenzene afforded indeed the desired 6-azaoxindole **23** in 39% yield along with a small amount of reduced acetamide **24** (9%). The modest yield is due to restricted rotation caused by the presence of the adjacent chlorine. The unsubstituted amide **25** only gave reduced material **26** under all conditions tested, whereas *N*-*t*-butyl-substituted amide **27** underwent an unusual radical Smiles rearrangement proceeding through a spiro- β -lactam (Scheme 2).¹⁰ To complete the series, we prepared xanthate **30** from carbamate **28** and subjected it to the action of lauroyl peroxide in refluxing chlorobenzene. In this case, there are no regioselectivity issues, and the radical cyclisation provided 5-azaoxindole **31** in good yield.



Scheme 3. Syntheses of 4-, 5-, and 6-azaindoles and azaindoles

In contrast to the approach to azaoxindoles, the synthesis of azaindoles and azaindoles using xanthates is modular, and therefore offers many possibilities for introducing variety. This is illustrated by the transformations depicted in Scheme 3. Thus, intermolecular radical addition of xanthate **33** to *N*-allyl aminopyridine **32** furnished intermediate adduct **34**, which was not isolated but further exposed to a stoichiometric amount of lauroyl peroxide to give isomeric indolines **35** and **36** in 68% and 18% yield respectively. Thus, in contrast to the corresponding case of the azaoxindole above (cf. **18**), the regioselectivity is not complete, even if the cyclisation is also in favour of the 4-azaindoline isomer. As expected, placing a chlorine atom next to the pyridine nitrogen directs the cyclisation towards the 6-azaindoline regioisomer. This is shown by the clean conversion of *N*-allyl-3-amino-2-chloropyridine **37** into intermediate adduct **38**, and then into 6-azaindoline **39** in moderate yield. The corresponding 6-azaindole **40** may be readily obtained by first removal of the Boc group with trifluoroacetic acid in dichloromethane then by oxidation with DDQ.

The synthesis of 5-azaindoline **44** proved particularly effective. The intermolecular radical addition of xanthate **42** to alkene **41** and the subsequent ring-closure could be accomplished in 75% overall yield without isolation of intermediate adduct **43**.



Scheme 4. Syntheses of tetrahydroazaquinolones

The xanthate-based radical chemistry provides the intermediate radicals with sufficient lifetime to allow contemplating the extension of this strategy to the synthesis of tetrahydroazaquinolones (Scheme 4). Formation of 6-membered rings by radical cyclisation is usually more difficult and much less common than the corresponding 5-membered rings.¹¹ We first tested the feasibility of this approach starting with symmetrical butenylamide **45** to avoid complications due to regioselectivity. The intermolecular addition with xanthate **33** proceeded smoothly to give the corresponding adduct **46** in high yield. We were indeed relieved to find that exposure of xanthate **46** to stoichiometric amounts of lauroyl peroxide resulted in a reasonably efficient ring-closure to furnish tetrahydro-azaquinolone **47** in 51% yield. Of particular importance is the fact that the cyclisation is successful *in the absence of a substituent on the amide nitrogen*.¹² The origin of the success is not clear in the present instance, for radical cyclisations generally fail with secondary amides because of slow rotation around the amide bond and the domination of the “wrong” rotamer, which is unable to undergo closure owing to its *trans* conformation.¹³

A similar sequence was performed starting with butenoylamide **48**, which afforded tetrahydroazaquinolone **50** along with a small amount prematurely reduced amide **51**, both through the intermediacy of radical adduct **49**. The chlorine atom, which served to direct the regiochemistry of the cyclisation and to sterically block the nucleophilicity of the pyridine nitrogen and thus prevent any ionic degradation of the xanthate group, may be reductively removed by catalytic hydrogenation in the presence of ammonia. In this manner, compound **52** could be prepared in high yield.

A simple methyl group is sufficient to neutralise the untoward nucleophilicity of the pyridine nitrogen as illustrated by the conversion of butenoylamide **53** into adduct **54** and then into tetrahydroazaquinolone **55** in good overall yield, further demonstrating the synthetic potential of this novel chemistry.

In summary, we have developed a flexible approach to highly substituted and very diverse azaoxindoles, azaindolines, azaindoles, and tetrahydroazaquinolones, which complements the syntheses we described previously. Many of the compounds reported in the present work would be exceedingly tedious to make by more traditional routes. Indeed, the xanthate transfer technology represents a quite general solution to a longstanding problem in organic synthesis, namely the creation of a carbon-carbon bond in an *intermolecular* fashion starting with *non-activated* alkenes, as well as generalizing the ring closure onto aromatic and heteroaromatic structures.

ACKNOWLEDGEMENTS

We thank Sanofi-Aventis for generous financial support to one of us (M.E.)

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