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PERSPECTIVE

A unified access to diverse heteroaromatic scaffolds using the radical chemistry of xanthates†‡

Myriem El Qacemi, Laurent Petit, Béatrice Quiclet-Sire and Samir Z. Zard*

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The degenerate transfer of xanthates allows generally difficult radical transformations, such as intermolecular additions to unactivated alkenes and cyclisations onto aromatic and heteroaromatic rings, to be accomplished under very practical experimental conditions. This translates into numerous approaches for the construction or modification of heteroaromatic structures. The present report aims to provide a brief overview of the various synthetic possibilities, with particular emphasis on medicinally interesting families of compounds.

1 Introduction

Heteroaromatics, and heterocycles in general, constitute the backbone of most medicinally interesting compounds. Accessing such structures has therefore been an ongoing endeavour since the dawn of synthetic organic chemistry, both in academia and in industry.[1] While ionic and organometallic reactions have found ample use in the preparation of heteroaromatics, the application of radical reactions has considerably lagged behind.[2] One of the reasons, especially as far as pharmaceutical applications are concerned, may be traced to the fact that synthetic radical chemistry has been dominated in recent times by organotin reagents,[3] and this has given rise to a common misconception that it is difficult to do useful radical chemistry without the use of heavy metals. Tin based radical chemistry is extremely powerful, but organotin derivatives are expensive, perceived to be toxic, and pose huge problems of purification and waste disposal upon scale up. This generally negative perception of radicals is compounded by the absence of full-fledged courses on radical reactions in most universities, including top tier ones, resulting in a dearth of synthetic chemists with a good grounding in radical chemistry. This unfortunate situation has all but discouraged industrial

Laboratoire de Synthèse Organique, UMR 7652, Ecole Polytechnique, 91128 Palaiseau, France. E-mail: zard@poly.polytechnique.fr; Fax: +01 6933 5972; Tel: +01 6933 5971

† This article is dedicated with respect and admiration to Professor Makhluf J. Haddadin (American University of Beirut) on the occasion of his 75th birthday.

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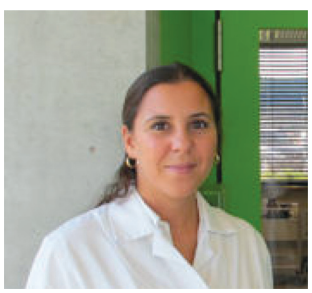


Myriem El Qacemi

Myriem El Qacemi obtained her MSc. degree in Chemistry in 2002 from the Ecole Supérieure de Physique et de Chimie Industrielles (ESPCI, Paris, France). She then studied for her Ph.D. degree (2005) under the guidance of Professor Samir Z. Zard. Her first postdoctoral appointment (2006–2007) was with Professor Marco Ciufolini at the University of British Columbia (UBC) in Vancouver. Myriem joined as a Post-Doc Syngenta Crop Protection (2007–2008) at the Jealott's Hill (UK) Research Centre of Syngenta. Subsequently, she started working in 2008 as a Team Leader in Chemistry at Syngenta Crop Protection at the Research Centre in Stein (Switzerland).

Laurent Petit

Laurent Petit was born in France in 1984. His chemistry training started at Cergy-Pontoise University and then at Ecole Polytechnique where he received his Ph.D. under the supervision of Samir Zard in 2010. His Ph.D. work was funded by Laboratoires Servier and concerned the application of the radical chemistry of xanthates to the preparation of (hetero)aromatic compounds. He then moved to the Australian National University in Canberra as a postdoctoral researcher under the supervision of Martin Banwell where he worked on the total synthesis of the crinine alkaloids hamayne and haemultine. He is currently a process chemist at Minakem in France.

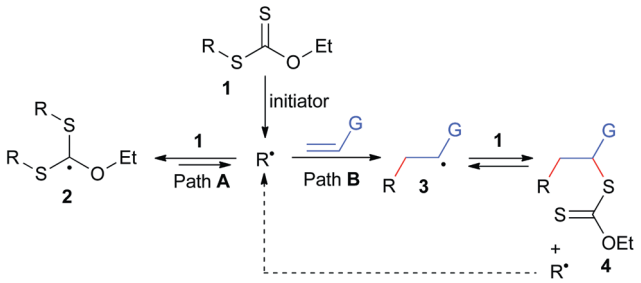
chemists from availing themselves of the enormous potential of radicals, both in the conception of drug candidates and in the development of industrial processes. In the light of a recent ongoing debate among medicinal chemists,[4] it is perhaps worth emphasising the broad tolerance of radical processes for common polar functional groups. Indeed, millions of tonnes of polymers are prepared every year by radical polymerisation in water emulsions. In the present brief report, we propose to highlight the practical utility of the degenerative radical exchange of xanthates for the construction of a large variety of heteroaromatic structures.

Over the past years, we have developed a new tin-free radical chemistry based on xanthates and related derivatives, and which has quite different characteristics as compared with conventional methods.[5] It provides, in particular, a practical and fairly general solution to a longstanding problem in organic synthesis, namely the *intermolecular* creation of new carbon–carbon bonds starting with simple non-activated alkenes. The mechanism for the addition of a xanthate to an alkene is outlined in a simplified form in Scheme 1. This mechanism embodies numerous subtle aspects, which will not be detailed here, but the interested reader is directed to the most recent review in ref. 5 for a more comprehensive discussion.

Apart from practical considerations related to the simplicity and safety of the experimental procedures, the cheapness and ready availability of the reagents, as well as the possibility of operating in a quite concentrated medium, three properties are especially important in the present context:

(a) The reaction of radical R˙ with its xanthate precursor **1** to give adduct **2** (path **A**) is very fast but degenerate and does not therefore consume the radical. This effective absence of competition gives the radical an *extended effective lifetime*, allowing it to be captured even by unactivated olefinic traps, either in an intra- or inter-molecular mode, to give finally addition product **4** (path **B**). In other words, and more generally, relatively slow radical transformations (additions, cyclisations, fragmentations *etc*.) can be performed without recourse to high dilution or syringe pump techniques.

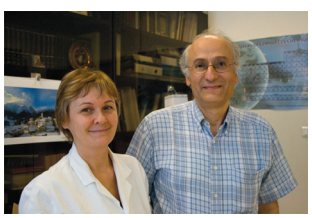
(b) The product, **4**, is itself a xanthate. This allows the implementation of another radical sequence (which can in turn lead to yet another xanthate), or the xanthate group can be used as an entry into the extremely rich "ionic" chemistry of sulfur.



Scheme 1 Simplified mechanism for the radical xanthate transfer.

Hence, a large array of transformations can now be marshalled to introduce further diversity and complexity into the structures. The fact that the addition leads to another xanthate has been exploited to make block polymers on an industrial scale. Thus, addition of xanthate **1** to an excess of an alkene monomer gives a functional (telechelic) polymer where the R-group is at one end and the xanthate at the other. This first polymer can then act as a substrate for another polymerisation involving a different monomer leading to a di-block polymer, and the process may be repeated to give tri-blocks and so on. The xanthate may be replaced by other dithiocarbonyl derivatives of general formula R–S(C═S)Z, such as dithioesters (Z = R′, usually Z = Ph), dithiocarbamates (Z = NR′R″), trithiocarbonates (Z = SR′). They all operate by exactly the same mechanism as for the xanthates (Z = OR′) and constitute what is now called the RAFT/MADIX technology. For an account of the discovery of the degenerate transfer of xanthates and related dithiocarbonyl derivatives and its applications in polymer science, see the last article in ref. 5.

(c) If the intermediate radicals are easily oxidised (*e.g.* **3**, with **G** = electron donating group), they may be converted into the corresponding cation by electron transfer to the peroxide. Peroxides, such as lauroyl peroxide (DLP) appear to be the most convenient initiators. This results in a crossover from the radical into the ionic manifold and increases further the synthetic possibilities. This aspect is particularly important when performing additions onto aromatic or heteroaromatic rings, since the oxidation step allows restoration of the aromaticity. In these transformations, the peroxide acts both as an initiator and as a stoichiometric oxidant.

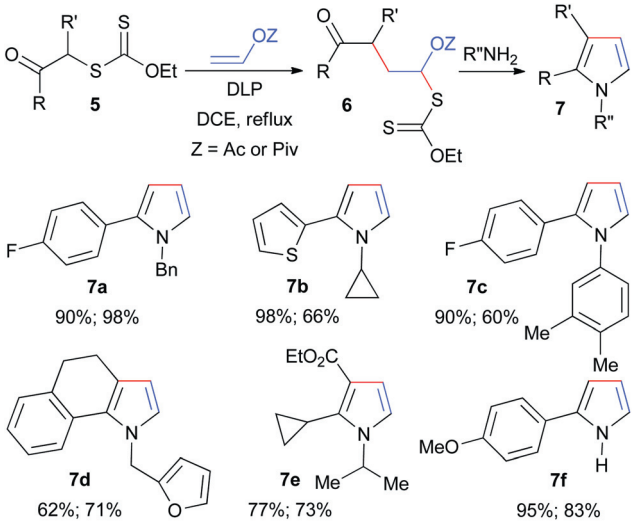


Béatrice Sire

Béatrice Sire (née Quiclet) obtained her MSc in biochemistry in 1976 from Université Paris-Sud, Orsay, France. She then completed her PhD thesis in 1980 at the same university under the supervision of Dr Stéphene Géro. She spent a post-doctoral year at the Microbiology Department of Sandoz, in Basel, Switzerland. In 1981, she obtained a position as a Chargée de Recherches in the CNRS in the group of Dr Stéphene Géro at the Institut de Chimie des Substances Naturelles (ICSN) in Gif-sur-Yvette. In 1993, she joined the group of Professor Samir Z. Zard, first at the ICSN, then at Ecole Polytechnique.

Samir Z. Zard (photographed with Béatrice Sire) was born in 1955 in Ife, Nigeria. His training as a chemist started at the American University of Beirut, then at Imperial College, London, and finally at the Université Paris-Sud, Orsay, France, where he received his doctorate under the supervision of Derek Barton in 1983. His main research concerns the study and development of new reactions and processes, with a special interest in radicals, organosulfur derivatives, alkynes, and nitro compounds. In addition to a number of academic awards, he received in 2007 the Croix de Chevalier de la Légion d'Honneur.

While the xanthate transfer technology has been extensively exploited for the synthesis of a large variety of heterocyclic structures, the present report will be limited, for the sake of space, to the assembly or modification of heteroaromatics. It will be divided into four sections dealing respectively with: (a) the construction of the heteroaromatic nucleus from open chain precursors; (b) the modification of heteroaromatic derivatives by intermolecular additions; (c) the construction of polycyclic heteroaromatics by radical cyclisations onto the heteroaromatic ring; and, (d), the description of some unusual transformations that are the consequence of the relatively long life of the intermediate radicals imparted by the degeneracy of the xanthate exchange process. A colour code is used throughout the schemes to make it easier for the reader to follow the various transformations: the xanthates are in black, the alkenes in blue, and the bonds made by the radical process in red.

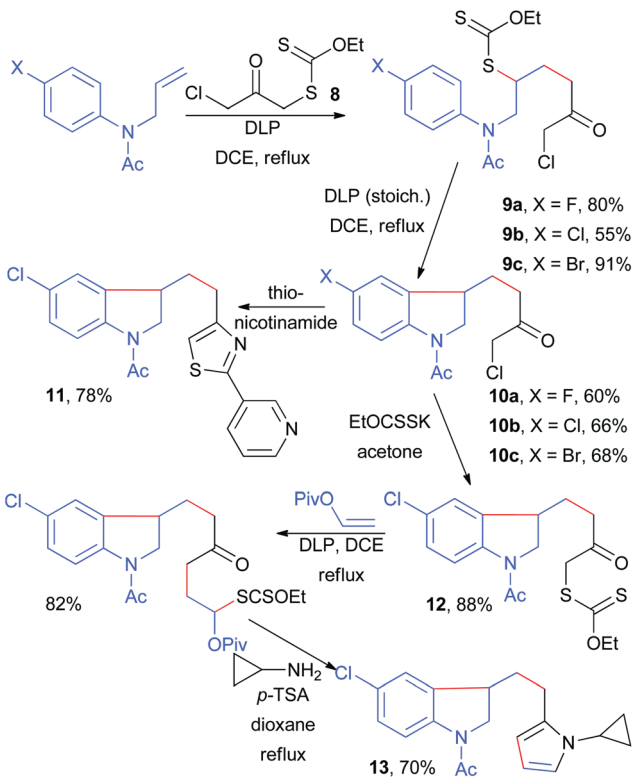


Scheme 2 Synthesis of pyrroles (DLP = lauroyl peroxide).

2 Synthesis of heteroaromatic derivatives starting from open chain precursors

The ability of xanthates to mediate intermolecular additions to unactivated alkenes allows a convergent and very flexible assembly of the elements necessary for building heteroaromatic structures. One simple illustration derives from the very efficient addition of α-xanthylketones **5** to commercially available and cheap vinyl acetate or pivalate. The reaction furnishes adducts **6**, which are synthetic equivalents of 1,4-ketoaldehydes (Scheme 2). Their reaction with ammonia, primary amines, or anilines thus gives rise to pyrroles **7**, by what may be viewed as a variant of the classical Paal–Knorr synthesis.[6] A selection of pyrroles obtained by this route is displayed in Scheme 2. The two yields given correspond to the radical addition and pyrrole formation respectively.

One particular xanthate of significant importance for the synthesis of heteroaromatics is α-chloroacetonyl xanthate **8**, since its addition to various alkenes leads directly to α-chloroketones.[7] α-Chloroketones, and more generally α-haloketones, constitute the key elements in numerous named and un-named classical syntheses of heteroaromatics, such as pyrroles (Hantzsch), furans (Feist-Bénary), thiophenes, imidazoles, thiazoles (Hantzsch), indolizines (Chichibabin), imidazopyridines, *etc.* The sequence pictured in Scheme 3 illustrates this approach and highlights at the same time the potential of radical closure onto aromatic rings.[7] Thus, addition of xanthate **8** to various *N*-acetyl-*N*-allyl anilines gives the corresponding chloroketones **9a–c**, which can be converted into indolines **10a–c** upon further exposure to stoichiometric amounts of lauroyl peroxide. It is remarkable, and a testimony to the mildness and neutrality of the experimental conditions, that two new carbon–carbon bonds could be created without the reactive chloroketone moiety being affected. Treatment of chloroketone **10b** with thionicotinamide produces thiazole **11** in good yield, while displacement of the chlorine with potassium *O*-ethyl xanthate gives a new α-xanthylketone **12**. The addition product of this xanthate to vinyl pivalate is readily transformed into pyrrole **13** by reaction with cyclopropylamine. The modularity and flexibility of this sequence are worth underlining.



Scheme 3 Synthesis of thiazoles and pyrroles.

Xanthates bearing latent 1,2-diketone or 1,2-ketoaldehyde motifs, as in compound **15**, can be applied in the synthesis of pyrazines and quinoxalines (Scheme 4).[8] The addition of this xanthate to *N*-allyl-*p*-methoxyaniline **14** leads to indoline **17** *via* open chain intermediate **16**, which was not isolated. An attempt to form directly a quinoxaline by heating indoline **17** with 1,2-diaminobenzene and *p*-toluenesulfonic acid (*p*-TSA) without prior hydrolysis of the acetal group furnished surprisingly a high yield of benzimidazole **18** containing one less carbon in the side-chain. This serendipitous synthesis of benzimidazoles

proceeds by an interesting mechanism and appears to be fairly general.[8] The conditions are sufficiently mild to preserve even a Boc protecting group, in contrast to more classical methods.

Hydrolysis of **17** with aqueous HCl liberated the highly reactive 1,2-ketoaldehyde **19**, which reacted rapidly with 1,2-diaminobenzene and 2,3-diaminopyridine to give quinoxalines **20a** and **20b**, and with 1,2-diaminomaleonitrile to afford pyrazine **21**. The radical addition of reagent **15** and related congeners to various alkenes provides thus a convenient, versatile route to functionalised 1,2-ketoaldehydes and 1,2-diketones, and these may be used in numerous heteroaromatic syntheses through condensation with appropriate bis-nucleophiles.

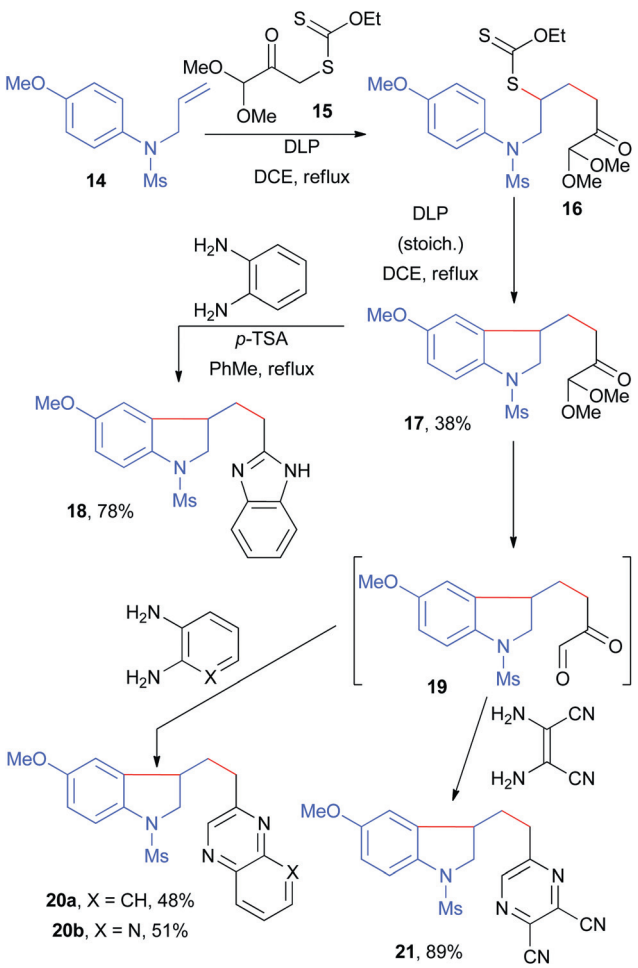
A variety of routes may be conceived for the synthesis of pyridines using xanthates. For example, radical addition of an α-xanthylketone **22** to Boc-protected allylamine produces a γ-aminoketone adduct **23**, which can be readily reduced by tributylstannane to give **24** in good overall yield.[9] Upon deprotection, the amine condenses spontaneously with the ketone. The resulting cyclic imine can be aromatised into pyridine **25** by a two-step sequence developed by De Kimpe (Scheme 5).[10] It must be noted that while tributylstannane was used to accomplish the reductive dexanthylation, this transformation may be effected by more ecologically acceptable reagents such as tris(trimethylsilyl) silane,[11] hypophosphorus acid salts,[12] or by a combination of isopropanol and lauroyl peroxide.[13] Furthermore, it is possible to extend this approach to the synthesis of azepines and azepinones by simply replacing the allylamine with a homoallylamine.[9] Even though azepines and azepinones are not heteroaromatics, they constitute a class of medicinally interesting compounds.

A more direct route to pyridines involves the addition of an α-xanthylketone **5** to a protected vinyl ketone to furnish a masked 1,5-diketone **26**.[14] Reductive dexanthylation, hydrolysis, and treatment with ammonium acetate under air gives pyridine **28** by way of 1,5-diketone **27**. Hydrolysis of adduct **26** without removal of the xanthate leads to 1,5-diketone **29**, which can be similarly converted into pyridine **30**. Hydrolysis of this compound would result in the formation of 3-mercaptopyridine **31**, a member of a relatively rare class of heteroaromatics. Since intermediate **29** is itself an α-xanthylketone, it can participate in a second intermolecular addition, allowing the incorporation of an additional substituent into the final pyridines **34** and **35**. Pyridines **28a**, **30a**, and **35a** are examples of pyridines prepared through this reaction manifold (Scheme 6).[14]

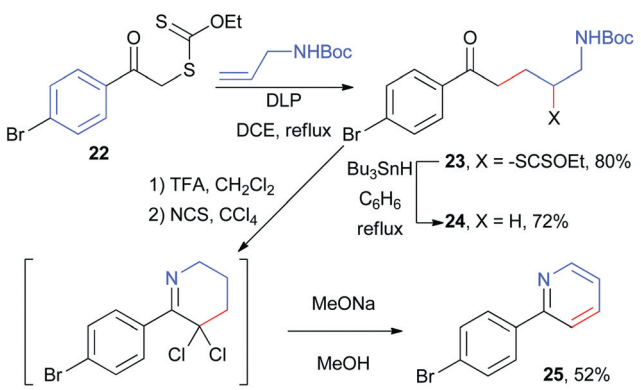
Yet another approach to pyridines is illustrated by the unusual synthesis of 3-arylpyridine **40** depicted in Scheme 7.[15] The strategy hinges on the 1,4-migration of an aryl ring that is initially part of a sulfonamide entity. Thus, exposure of adduct **37** to stoichiometric amounts of lauroyl peroxide in isopropanol regenerates intermediate radical **38** under conditions where it is sufficiently long-lived to undergo a radical Smiles rearrangement. This is followed by extrusion of sulfur dioxide and abstraction of a hydrogen atom from the solvent to give acetamide **39**. Finally, acid hydrolysis and dehydrogenation of the intermediate tetrahydropyridine furnishes pyridine **40** in good yield. Modifying the starting α-xanthylketone **36** and/or the *N*-allylsulfonamide would allow the introduction of a broad variety of substituents into the pyridine nucleus.

3 Modification of heteroaromatic rings

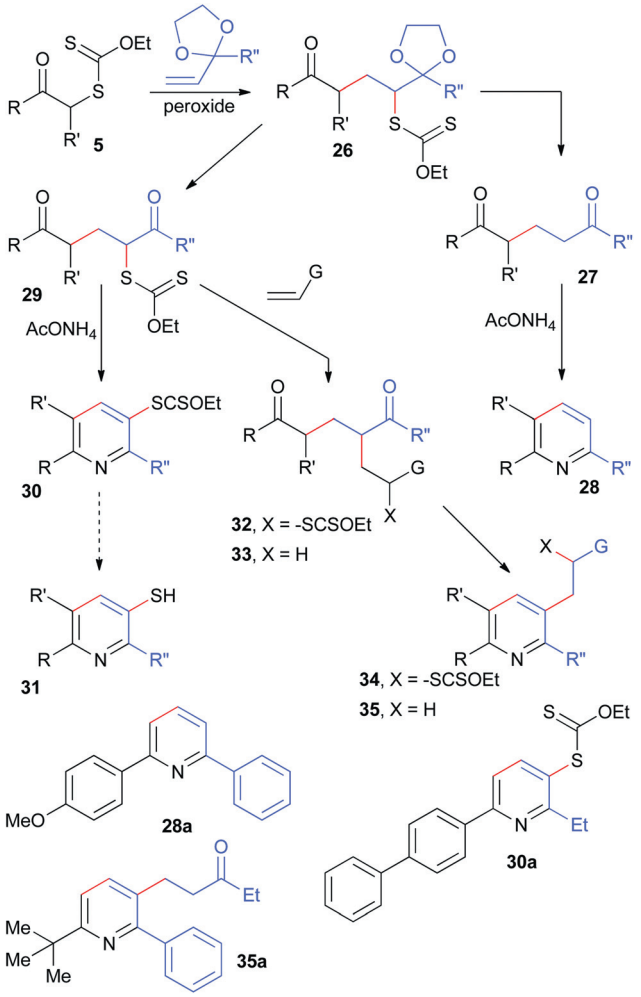
The modification of heteroaromatic rings may be accomplished in two ways. Either the xanthate group is attached to the heteroaromatic nucleus and used to mediate additions to alkenes or the xanthate is used to perform radical additions directly onto the heteroaromatic ring. The former variant may be illustrated by the side-chain extensions of imidazoles, tetrazoles, benzothiazoles,[16] and benzotriazoles[17] (Scheme 8). In the case of imidazoles, the



Scheme 4 Synthesis of benzimidazoles, quinaxolines, and pyrazines.



Scheme 5 Synthesis of a pyridine.

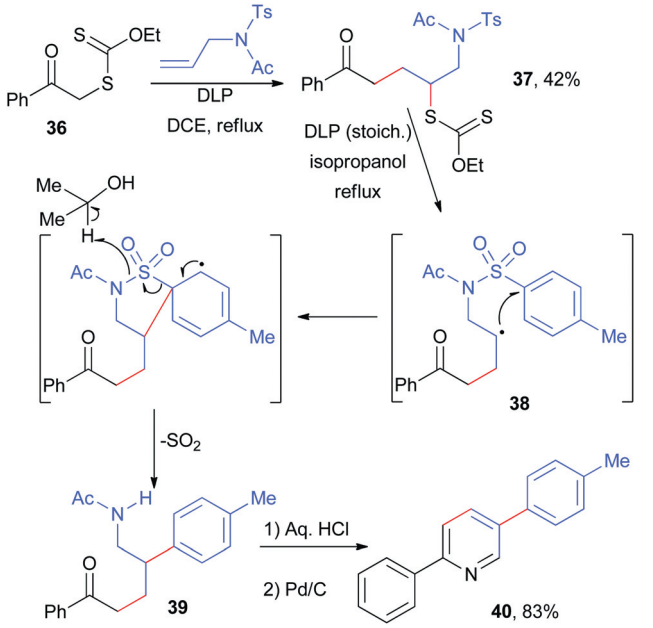


Scheme 6 A flexible route to pyridines.

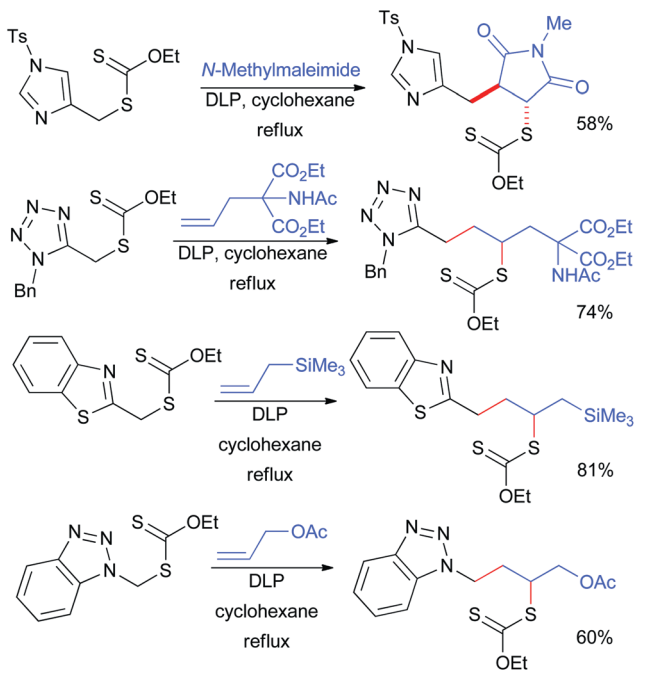
additions are so far limited to electron poor alkenes. Furthermore, the nucleophilicity of the imidazole must be subdued by placing a suitable bulky or electron-withdrawing substituent on the ring to avoid possible ionic side reactions with the xanthate group.

The nucleophilicity of the pyridine nitrogen must also be sterically blocked, by placing a substituent on the 2- and/or the 6-positions. Nevertheless, this is a minor constraint in view of the richness of the side chains that may be introduced through the radical additions, as indicated by the examples in Scheme 9.[18] All positions around the pyridine nucleus may thus be modified. The conversion of adduct **41** into the rare bicyclic derivative **42** illustrates one way of exploiting the simultaneous presence of a xanthate on the side chain and a chloride leaving group on position 2 of the pyridine ring.

The second approach for the modification of heteroaromatic structures is to use xanthates to promote an intermolecular addition directly to the ring. Radical addition to aromatic and heteroaromatic rings is a well-known process, albeit relatively seldom used. Yields are variable and often modest, and this is compounded by a general lack of regioselectivity, unless substituents are strategically placed to direct the addition to only one position.

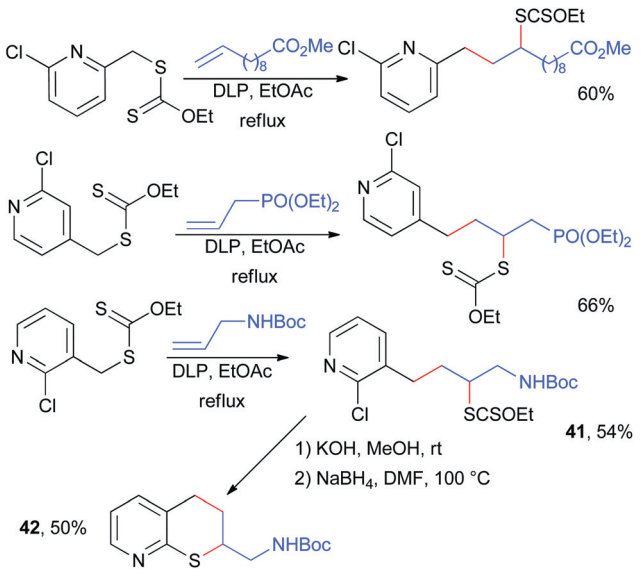


Scheme 7 3-Aryl-pyridine synthesis *via* a radical Smiles rearrangement.



Scheme 8 Radical modification of heteroaromatics.

The use of radicals derived from xanthates was first described by Minisci, who exploited cleavage of the C–O bond along the Barton–McCombie mode to accomplish intermolecular additions to pyridinium and quinolinium salts.[19] More recently, Miranda and co-workers reported the intermolecular additions of radicals derived from xanthates by scission of the C–S bond according to the mechanism in Scheme 1.[20] The reaction proved successful with indoles, pyrroles, furans, and thiophenes, but the scope of the process remains to be more completely delineated.

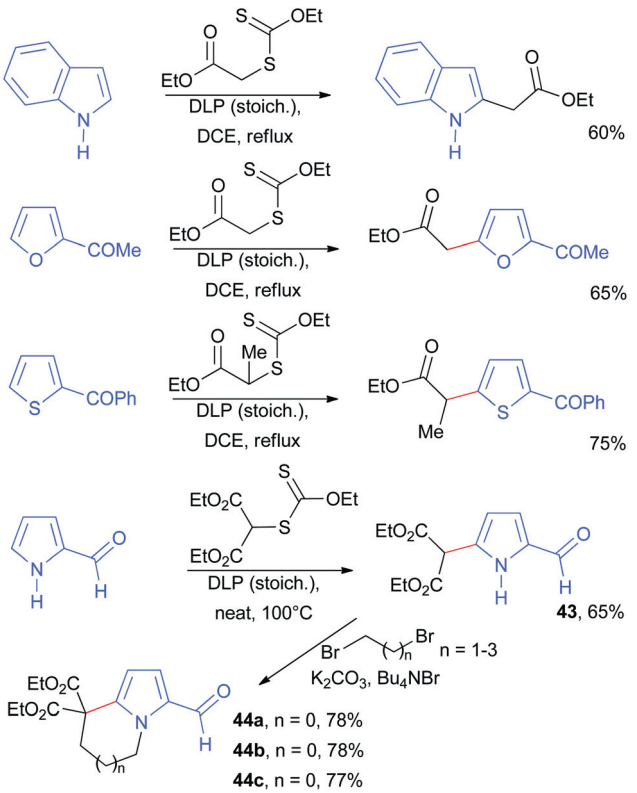


Scheme 9 Modification of pyridines.

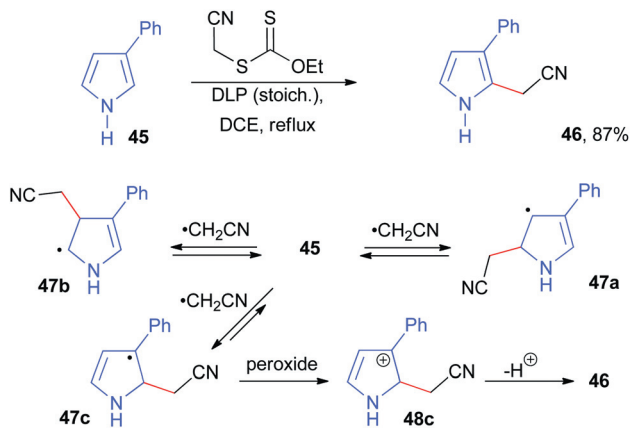
Nevertheless, the yields can be quite high, and very useful structures can be made in one step. Some examples are collected in Scheme 10. The synthesis of pyrrole **43** was accomplished without solvent (2 equivalents of the liquid xanthate were used) and the reaction was complete in 10 minutes.[21] The presence of the malonate group in pyrrole **43** was used to construct various bicyclic structures **44a–c** by a simple ionic annelation.

The regioselectivity in the additions that have been reported is often high and, in some cases, even surprising. For instance, additions to 3-substituted pyrroles such as **45** furnished the more congested 2,3-isomer **46** regioselectively (Scheme 11).[22] The most likely rationale for these observations hinges on the reversibility of the radical addition and the relative slowness of the oxidation step. By far the most stable of all three possible radical adducts **47a–c** is the 2,3-isomer **47c** as it is simultaneously allylic, benzylic, and tertiary. Not only does it dominate the other two in terms of concentration in the medium, but it is also the easiest to oxidise, as the ensuing cation **48c** is the most stabilised. Loss of a proton finally leads to the observed pyrrole. It is important to note that the initial radical in these examples is stabilised by an ester or by a nitrile group, which makes the reverse reaction particularly easy. This is in contrast to most of the earlier radical additions to aromatics and heteroaromatics, which have involved highly reactive and unstabilised species such as simple alkyl or aryl radicals, and which give rise to synthetically less interesting mixture of regioisomers. The stabilisation of the adduct radical, as suggested by theoretical calculations,[23] is therefore not sufficient by itself to explain the high and unusual regioselectivity. It is the combination of the reversibility of the intermolecular radical addition and the stabilisation of the radical adduct by the ring substituent that dictates the final outcome.

It is worth emphasizing the practicality of this approach for obtaining directly complex substituted heteroaromatic structures that would be very tedious to prepare by more conventional routes. This is illustrated by the three indole examples in Scheme 12,[24,25] and in particular by the last transformation



Scheme 10 Intermolecular radical additions to heteroaromatics.

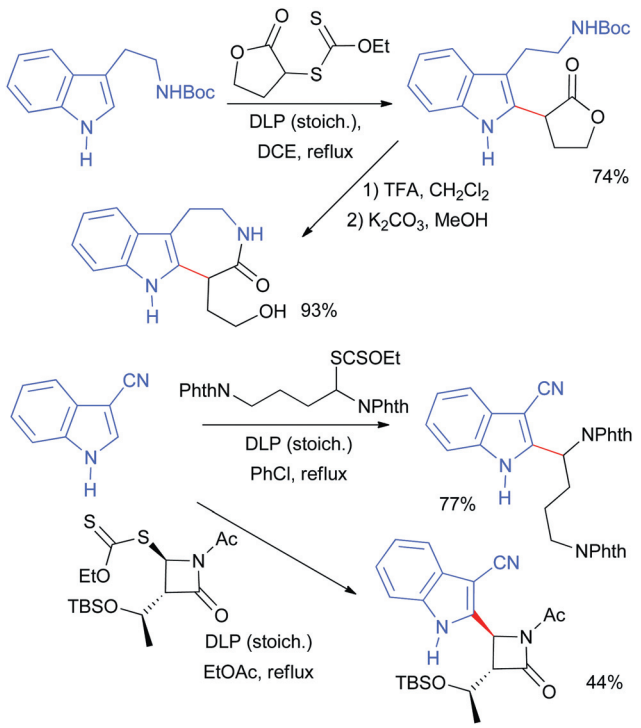


Scheme 11 Regioselectivity of the radical addition to pyrroles.

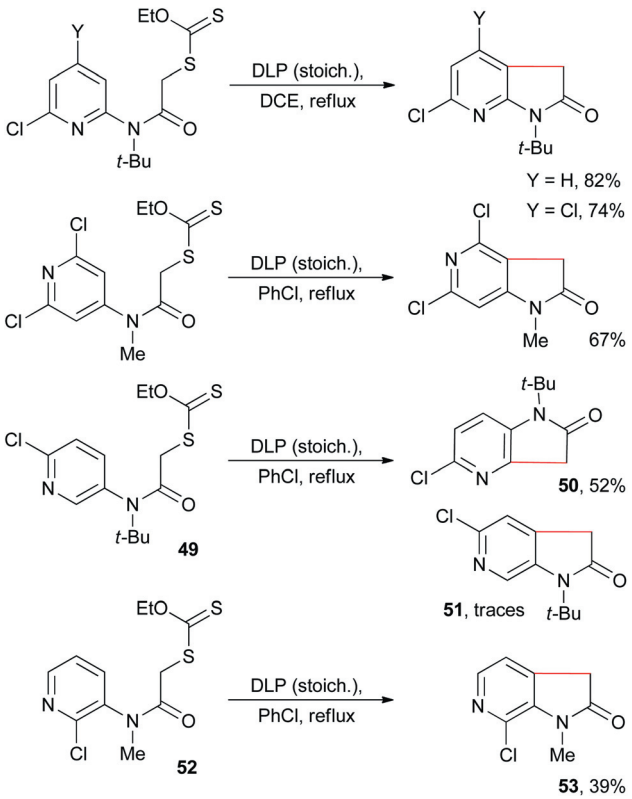
where a complex β-lactam could be attached to the indole nucleus.[25b]

4 Synthesis of polycyclic heteroaromatics

Intramolecular radical ring closure onto the heteroaromatic ring represents a very convenient route to polycyclic heteroaromatics. In the context of xanthate chemistry, the strength of this approach lies in the possibility of combining an intermolecular addition with the cyclisation step, thus allowing a convergent and swift assembly of very diverse structures.



Scheme 12 Intermolecular additions to indoles (PhthN = phthalimido).



Scheme 13 Syntheses of azaoxindoles.

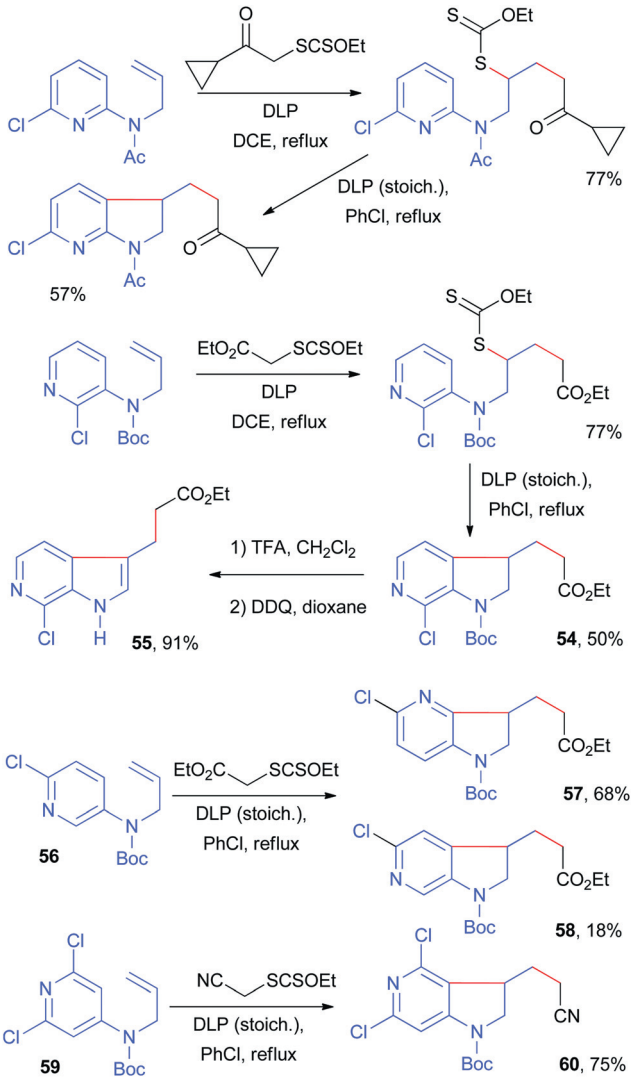
In Scheme 13, a simple cyclisation is used to prepare azaoxindoles starting from xanthates derived from *N*-chloracetylamino pyridines.[26] It is necessary to have a substituent on the extranuclear nitrogen, for otherwise no cyclisation takes place and only reduction of the radical is observed. The *t*-butyl group is particularly interesting as it can be removed by treatment with trifluoroacetic acid. By starting with the appropriate aminopyridine precursor, it is possible to prepare all azaoxindole isomers. In the case of 3-aminopyridine derivatives such as **49**, the radical has two possibilities for cyclisation but, for reasons still unclear, possibly related to the reversibility of the cyclisation step discussed above, it prefers to close onto the 2-position to give the 4-azaoxindole **50** and not the 6-azaoxindole isomer **51**, which is only formed in trace amounts. In order to obtain the 6-azaoxindole isomer, the 2-position must be blocked by a substituent such as a chlorine atom. This is illustrated by the conversion of xanthate **52** into 6-azaoxindole **53** in moderate yield.

Azaindolines are readily obtained by associating the intermolecular addition to an *N*-allylaminopyridine with the subsequent cyclisation of the adduct through further treatment with stoichiometric amounts of peroxide. All isomeric azaindolines may be obtained by starting with the appropriate *N*-allylaminopyridine (Scheme 14).[26] Modification of the starting xanthate allows considerable diversity to be introduced.

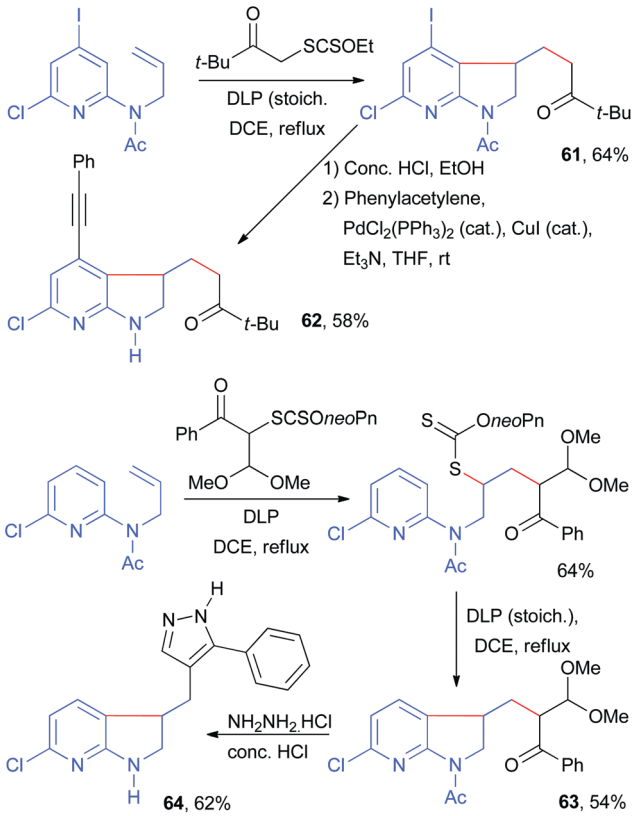
The azaindolines are readily converted into azaindoles, as shown by the efficient transformation of 6-azaindoline **54** into 6-azaindole **55**.[26b] In many cases, the intermediate xanthate adducts need not be isolated, since both the addition and cyclisation steps are mediated by the same peroxide. In this variant, moderate dilution of the reaction medium before addition of the stoichiometric amount of peroxide often proves beneficial. Thus, olefin **56** is directly converted into isomeric 4- and 6-azaindolines **57** and **58** in good combined yield. In contrast to the cyclisation of **49**, the regioselectivity in favour of the 4-azaindoline in this case is not complete.[26b] Not surprisingly, the addition and concomitant cyclisation to alkene **59** leads to only one product, **60**, in 75% yield.

The transformations pictured in Scheme 15 underscore the facile assembly of richly functionalised azaindoline scaffolds, which may be used to construct libraries of compounds. The radical process is compatible with the presence of iodine on the aromatic ring, opening access to compounds such as iodoazaindoline **61** which may be selectively modified by numerous palladium catalysed couplings. For instance, a Sonogashira reaction cleany gives alkyne **62**, but other transformations such as Suzuki, Heck, or Stille couplings could be applied if desired.[26b] The chlorine substituent and the amino nitrogen are other points for the introduction of diversity around the azaindoline ring. The second sequence in Scheme 15 showcases the variety that may be introduced through the xanthate component. Hydrolysis of the masked 1,3-ketoaldehyde supplied by the xanthate to azaindoline **63** in the presence of a hydrazine furnishes pyrazole **64**.[26b] The use of other hydrazines or other bis-nucleophiles would furnish diverse heterocyclic structures.

Perhaps more important is the observation that the radical chemistry of xanthates allows the fusing of six- and even seven-membered rings to aromatic and heteroaromatic structures leading to molecular architectures that would be particularly tedious to obtain by other routes. Examples of tetrahydronaphthyridines prepared by an addition–cyclisation sequence are displayed in Scheme 16.[26] A butenyl side chain on the extranuclear nitrogen results in the formation of tetrahydronaphthyridines



Scheme 14 Syntheses of azaindolines and azaindoles.



Scheme 15 Useful azaindoline scaffolds.

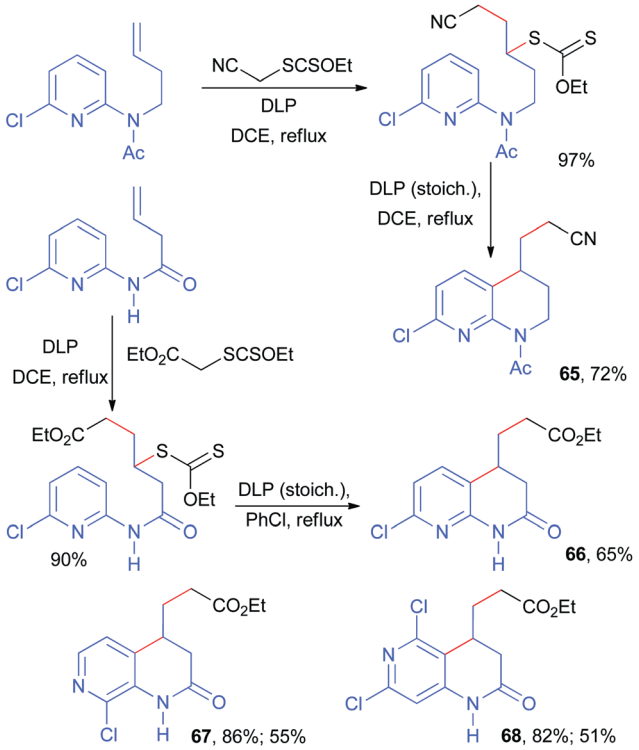
65, whereas a butenoyl side chain furnishes tetrahydronaphthyridinones **66**, **67**, and **68**.[26] In the case of **67** and **68**, the first yield corresponds to the intermolecular addition and the second to the cyclisation. Interestingly, it was found that a substituent on the amide nitrogen is not necessary for the cyclisation to occur, in contrast to the situation with azaoxindoles (Scheme 13) and pyridoazepinones (Scheme 17 below). The reason for this surprising difference is still not clear.

Examples of pyridoazepinones are collected in Scheme 17.[26a,27] Two complementary approaches may be employed: either the xanthate or the olefin can be attached to the pyridine moiety. The new carbon–carbon bond created in the intermolecular addition is not in the same position in both cases (*cf.* **70** and **72**),[26a] and this considerably augments the attainable diversity. Furthermore, the extranuclear nitrogen in the starting material can be moved around the ring, as shown by examples **73** and **74**.[27] As above, the first yield corresponds to the intermolecular addition and the second to the cyclisation.

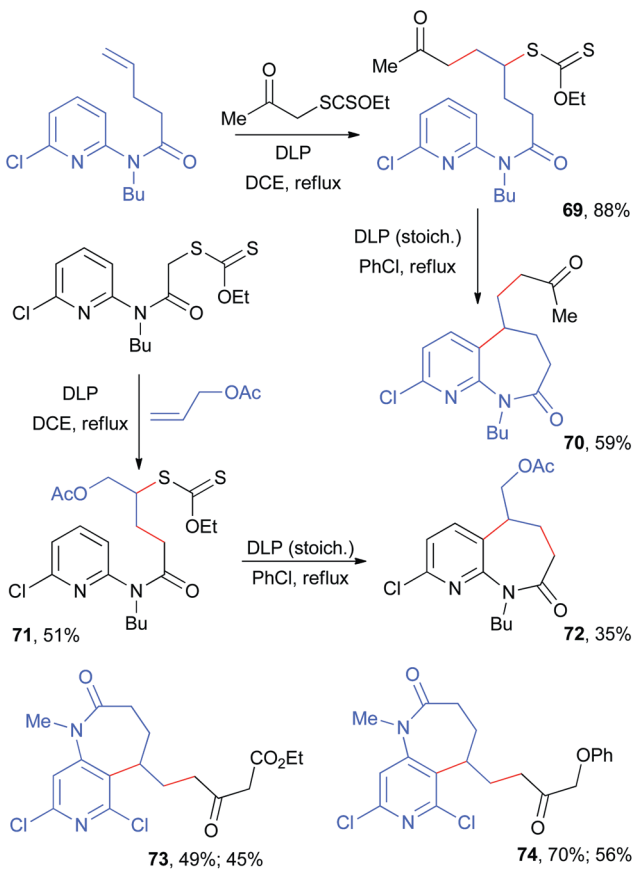
Not all variations have been examined, especially as concerns the formation of pyridoazepines, and additional studies are needed to delineate the complete scope of this synthetic strategy.

Furthermore, extensions to the pyrimidine and related series are still in an early stage but there is every reason to believe that a similar generality will obtain. Preliminary examples of a diazoxindole, **75**,[28] a diazaindoline, **76**,[29] and a tetrahydroazanaphthyridine, **77**,[30] are pictured in Scheme 18. The syntheses all start from readily available precursors and the presence of the chlorine atoms allow for numerous further modifications. For example, the chlorine in between the two nitrogens of the pyrimidine ring in **77** can be selectively replaced by various nucleophiles, as indicated by the nearly quantitative formation of cyclopropylamine derivative **78** upon treatment with cyclopropylamine in refluxing ethanol.[30]

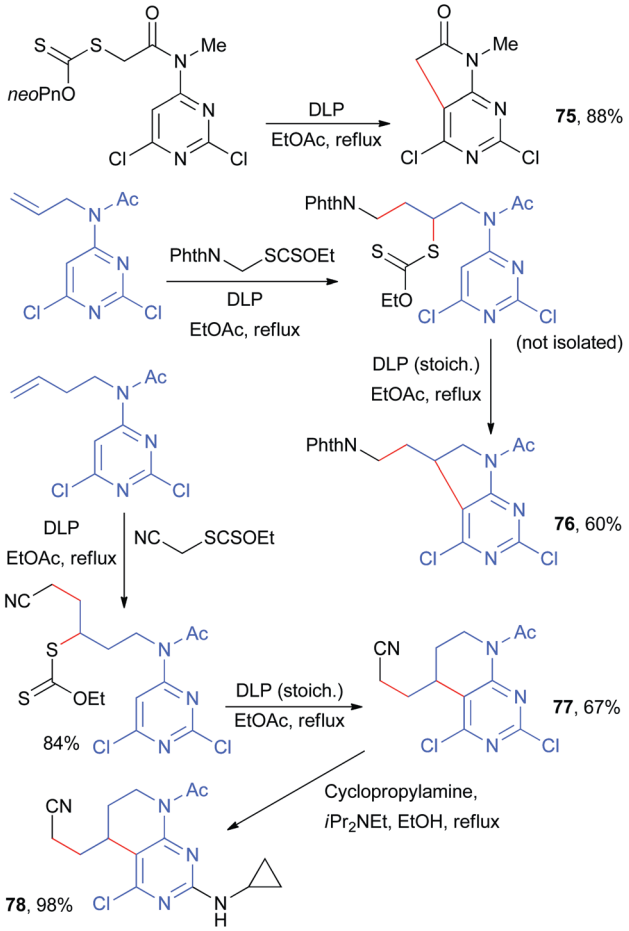
With pyrroles and indoles, the cyclisation process tends to be particularly easy, in part because of their lower aromatic character and because their electron rich nature facilitates the oxidation of the cyclised radical. There are several possible variations with both families, but only few have been implemented. An efficient addition–cyclisation on a pyrrole substrate leading to indolizidine intermediate **79** was used by Ozornio and Miranda in a short synthesis of (±)-desethylrhazinal **80** (Scheme 19).[31] A conceptually analogous sequence starting with xanthate **81** results in the formation of fused tricyclic derivatives such as spiro compound **82** or protected amine **83**, an advanced intermediate in a concise formal total synthesis of (±)-mersicarpine.[32] Numerous other alkenes may be employed. A substituent in the 3-position appears to be important for success. If this substituent is an electron-withdrawing group (*e.g.* ester in xanthate **81**), the aromatisation is not complete and further oxidation with manganese dioxide is sometimes necessary.



Scheme 16 Synthesis of tetrahydronaphthyridine derivatives.



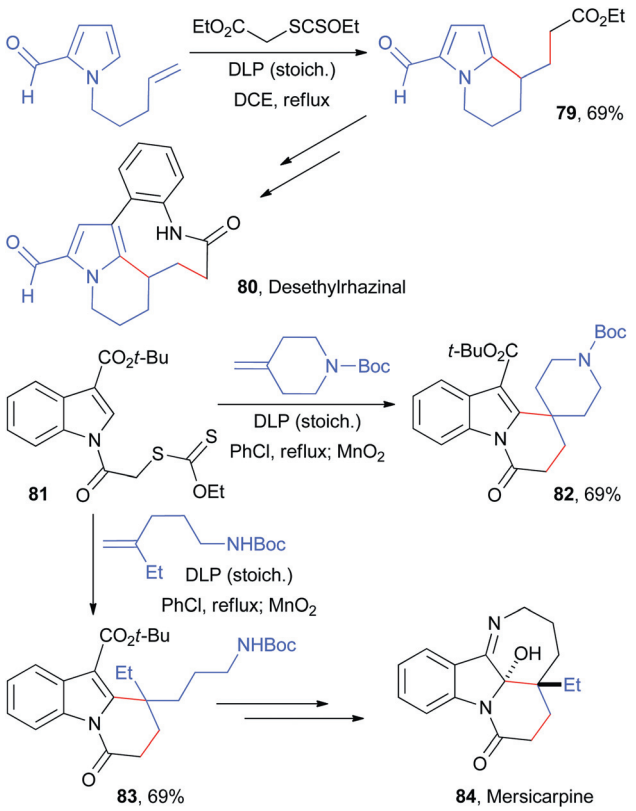
Scheme 17 Synthesis of pyridoazepinones.



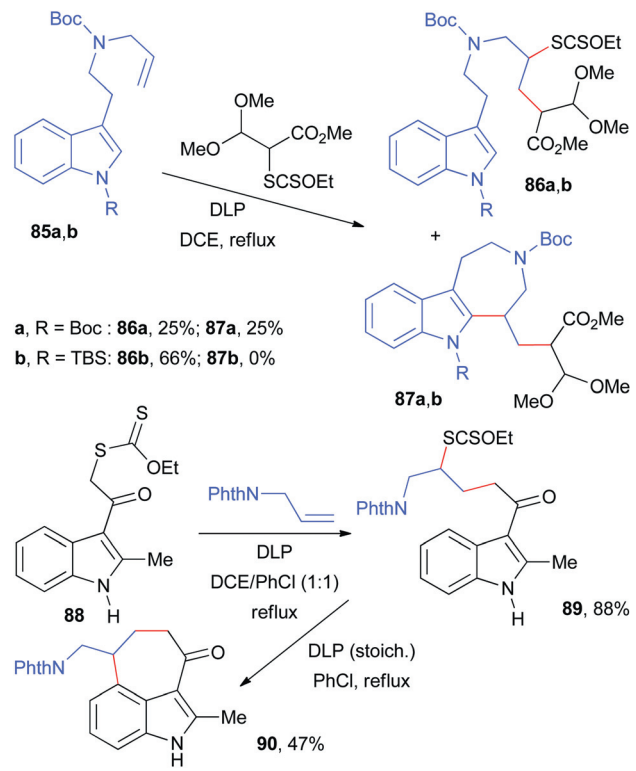
Scheme 18 Annelations on a pyrimidine ring.

The formation of seven-membered rings fused to indoles is illustrated by the two examples in Scheme 20. Compound **87a** is in fact an unwanted, major side-product observed in the synthesis of **86a**, a key intermediate in an approach to the eburna alkaloids.[33] By replacing the Boc-group by the much bulkier *tert*-butyldimethylsilyl (TBS) protection on the indole nitrogen of the starting material **85b**, it proved possible to sterically suppress the cyclisation and stop the radical sequence at the level of the desired open-chain adduct **86b**. If position-2 of the indole ring is blocked by a substituent, as in 2-methylindole derived xanthate **88**, the cyclisation of the intermediate adduct **89** takes place at the 4-position to give the interesting tricyclic product **90**.[34]

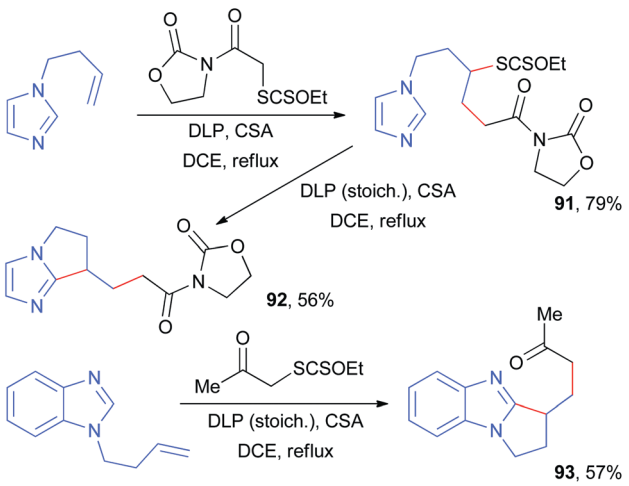
The use of azole-derived substrates in addition–cyclisation sequences is also possible. If needed, the nucleophilicity of the azole ring can be neutralised with a strong acid, such as camphorsulfonic acid. Anhydrous camphorsulfonic acid (CSA) is cheap and produces salts that are readily soluble in various organic solvents. Two azole structures, **92** and **93**, generated by this radical sequence from an imidazole and a benzimidazole precursor respectively, are shown in Scheme 21.[35] The intermediate adduct was not isolated in the case of the benzimidazole derivative **93**. This approach to novel azole structures is flexible and convenient, but its scope remains to be more completely explored.



Scheme 19 Annelation around pyrroles and indoles.



Scheme 20 Fusion of 7-membered rings around indoles.

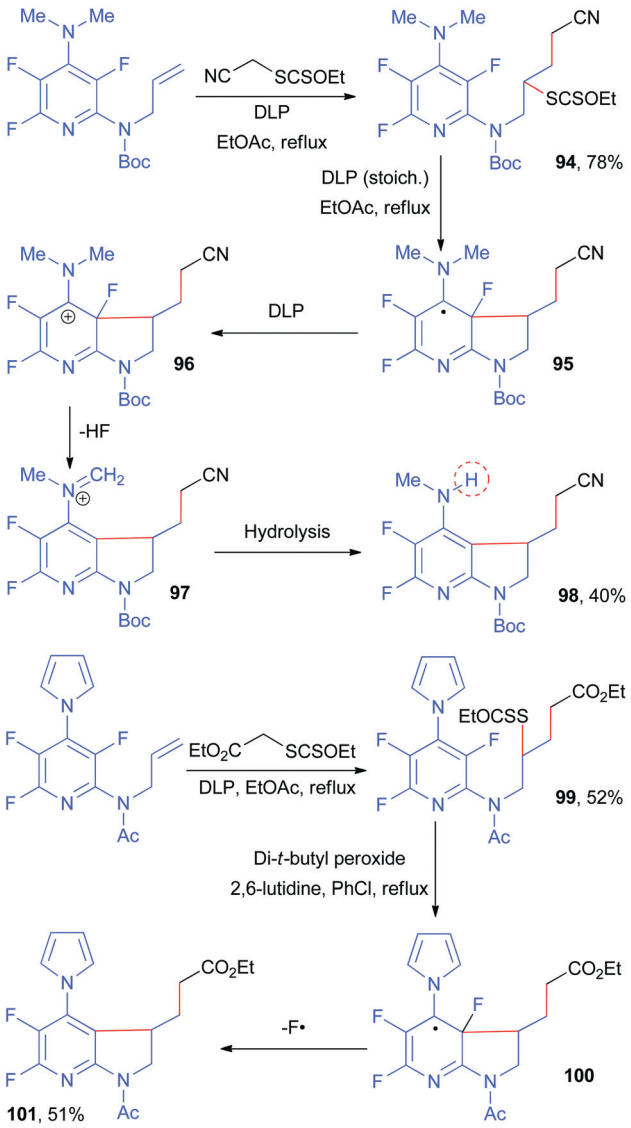


Scheme 21 Annelations on imidazole and benzimiadole rings.

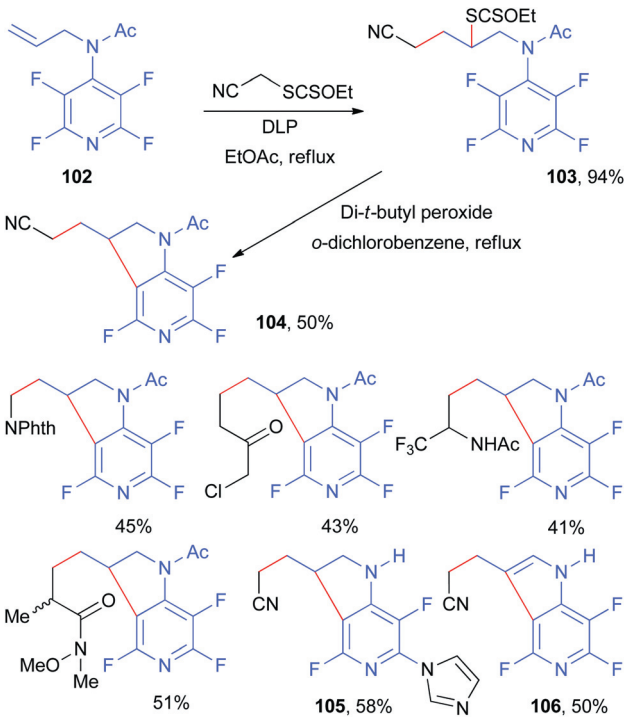
5 Unusual routes to nitrogen heterocycles

The transformations described in this section reveal interesting and unusual aspects of radical chemistry, observed when the intermediate radicals are given an extended lifetime under the xanthate transfer conditions. In an ongoing study involving fluoropyridines, we observed that treatment of xanthate **94** with stoichiometric amounts of lauroyl peroxide resulted in a modest yield of 7-azaindoline **98**, where a methyl group was lost from the dimethylamino substituent.[36] The proposed mechanism, shown in simplified form in Scheme 22, invokes loss of a fluoride ion from **96** following the oxidation of the cyclised radical **95** by the peroxide. Hydrolysis of **97** and loss of formaldehyde gives the demethylated indoline **98**. Replacing the dimethylamino group by a weaker electron releasing substituent such as the pyrrole in **99** slows down the oxidation of the intermediate radical **100** and aromatisation can now only be restored through *homolysis* of the carbon–fluorine bond.[30] Homolysis of such a strong bond with the elimination of a fluorine atom is almost without precedent; nevertheless, the recovered aromatisation energy and a favourable entropic term appear to constitute a sufficient driving force for the process. The expected fluoroazaindoline **101** is ultimately produced in a synthetically useful yield. The 2,6-lutidine is added to neutralise any hydrogen fluoride produced.

This approach can be extended to access a whole family of novel fluorinated heterocycles. By starting with the 4-*N*-allylamino isomer **10**, the sequence of intermolecular addition of cyanomethyl xanthate and intramolecular *ipso*-substitution of a fluorine atom gives rise to 5-fluoroazaindoline **104** (Scheme 23). The cyclisation of intermediate **103** requires rather harsh conditions (refluxing *o*-dichlorobenzene) and the replacement of the lauroyl peroxide by the more resistant di-*t*-butyl peroxide. A few other examples using various xanthates are also shown in Scheme 23. The yields given correspond to the cyclisation step. Preliminary studies have indicated that *o*-dichlorobenzene may be advantageously replaced by *n*-amyl acetate.[36b] Furthermore, the activated fluorine in the least hindered 6-position can be selectively substituted by various nucleophiles, such as amines, phenols, thiols, or imidazoles (*e.g.* **105**), allowing thus the facile



Scheme 22 Synthesis of difluoro-7-azaindolines.



Scheme 23 Synthesis of trifluoro-5-azaindolines and 5-azaindoles.

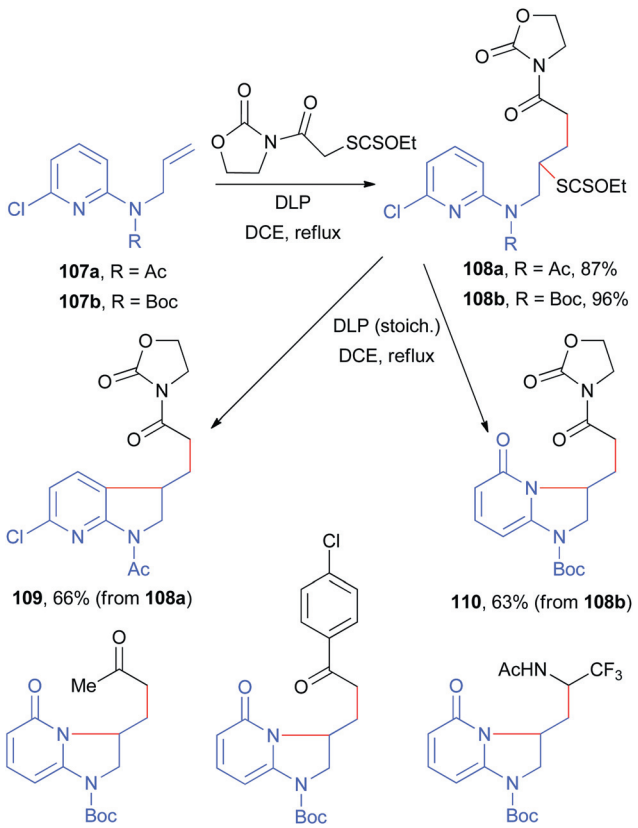
constitution of diverse libraries.[36b] Under the conditions of the substitution, the acetyl group is lost, freeing yet another site for further modification. Finally, it is possible to prepare the corresponding azaindoles (*e.g.* **106**) by first removing the acetyl group in **104** with K_2CO_3–MeOH then by oxidising with IBX.[36b] Weaker oxidising agents failed to perform the desired aromatisation, reflecting the strong electron-withdrawing effect of the three remaining fluorine atoms.

Another serendipitous finding occurred while studying the synthesis of azaindolines. We were indeed surprised to find that, whereas the cyclisation of *N*-acetyl adduct **108a** proceeded as expected to give azaindoline **109**, the *N*-Boc analogue **108b** furnished a completely different product, the structure of which was finally determined to be the novel pyridone **110** (Scheme 24).[37] The mere replacement of an acetyl by a Boc group completely altered the course of the reaction. Three other examples of this remarkable transformation are presented in the lower part of Scheme 24.

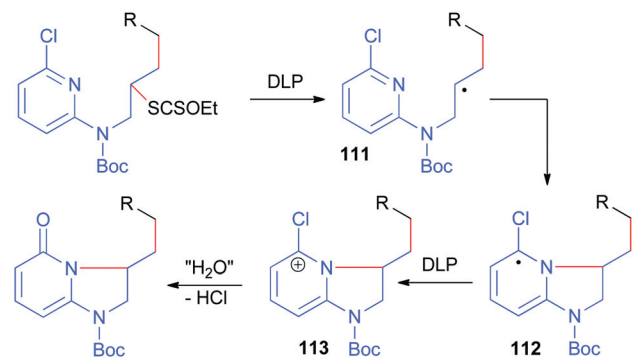
The reasons underlying this strange behaviour are unclear and still under study, but a mechanism can be proposed as outlined in Scheme 25. The presence of the Boc-group (or, more generally, a carbamyl), on the extranuclear nitrogen somehow encourages the intermediate radical **111** to attack the nitrogen atom of the pyridine motif instead of closing in the usual fashion on position-5 of the ring. The cyclised radical **112** is then oxidised by electron transfer to the peroxide and the resulting cationic species **113** ultimately converted with water into the observed pyridone. As far as we are aware, such a radical closure on the pyridine nitrogen is unprecedented. In this respect, we were fortunate to have a chlorine atom on position-2, which apparently activates electronically the nitrogen towards such an attack. A fluorine atom has a similar influence but, with other substituents or in the absence of a substituent, the reaction leads to complex mixtures.[37]

Extension of this chemistry to the pyrimidine series is particularly interesting. The radical addition products such as **114** derived from the symmetrical 2-*N*-allylamino substrates can only cyclise on either of the two pyrimidine nitrogens, whatever protecting group is present on the extranuclear nitrogen. Thus, exposure of *N*-acetyl adduct **114** to lauroyl peroxide in refluxing ethyl acetate furnishes a good yield of the expected pyrimidinone **116**.[29] Only one pyrimidinone isomer is obtained, resulting from the reaction of the delocalised cationic intermediate **115** at the least hindered C-6 position rather than at the more congested C-4. Three other examples starting from different xanthates are also included in the lower part of Scheme 26.

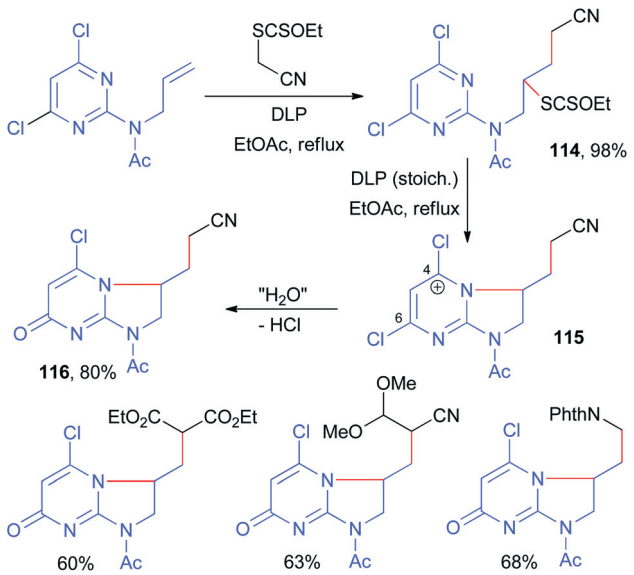
In contrast to the 2-amino precursors **114**, the adducts from the isomeric 4-amino derivatives **117a,b** are not symmetrical and can undergo cyclisation in two different manners. Placing a Boc-group on the extranuclear nitrogen causes the cyclisation to occur mostly on the nitrogen. This is illustrated by the reaction of xanthate **118a** which leads to a mixture of two isomeric



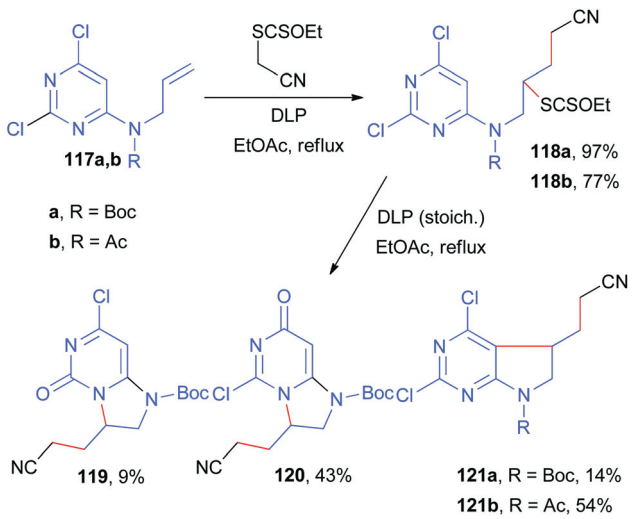
Scheme 24 An unprecedented ring-closure on a pyridine nitrogen.



Scheme 25 Mechanism for the formation of an unusual pyridone.



Scheme 26 Radical ring-closure onto a pyrimidine nitrogen.



Scheme 27 Synthesis of diazaindolines.

pyrimidinones **119** (9%) and **120** (43%) along with a small amount (14%) of diazaindoline **121a**. With an acetyl protecting group present in **118b**, only the "normal" closure on the carbon to give bicyclic aminopyrimidine **121b** is observed (Scheme 27; see also compound **76** in Scheme 18).

6 Summary and outlook

The ability of the degenerate xanthate transfer to mediate intermolecular radical additions on unactivated alkenes as well as cyclisations onto aromatic and heteroaromatic rings offers immense possibilities for the synthesis of new heteroaromatic structures or for shortening the routes to known derivatives. The convergence implied in the intermolecular addition step also represents a powerful means for introducing diversity, since a broad range of functional groups can be present on the xanthate and on the alkene partner. Indeed, the mildness and neutrality of the experimental conditions translate into a remarkable tolerance for numerous functional groups. The cheapness and ready availability of reagents and substrates are additional advantages. Once tethered by the radical addition, the various functional groups may be made to react together by applying appropriate reagents and reaction conditions. One further aspect that is worth underscoring is the ease with which fluorine substituents can be incorporated into the products by using one of a variety of fluorine substituted xanthate partners.

The cyclisation onto the heteroaromatic nucleus also warrants some comments. In this step, a carbon–hydrogen bond on the heteroaromatic ring is ultimately replaced with a carbon–carbon bond. While mechanistically one cannot invoke a C–H bond

activation, as is nowadays popular, the overall result is the same. The fact that naked heteroaromatics may be used is an enormous advantage of radical chemistry that is still under appreciated.

This brief overview gives a glimpse of the potential of xanthates and related derivatives for the synthesis or modification of heteroaromatics. Some interesting mechanistic questions have emerged from our studies, which need to be pursued in order to acquire a better understanding of the factors that govern the reactivity. In addition, numerous possibilities remain to be explored before a complete picture of the scope and limitations can emerge. It is hoped nevertheless that the preliminary results presented here will encourage discovery and process chemists to consider more frequently the use of radical reactions in their synthetic planning.

Acknowledgements

We thank warmly our current and former students and collaborators, whose names appear in the references and who have worked enthusiastically and tirelessly to develop the chemistry described herein. Fruitful discussions over the years with Dr Eric Bacqué (Sanofi-Aventis) and financial support from Ecole Polytechnique, the CNRS, CONACyT, Laboratoires Servier, and Sanofi-Aventis are gratefully acknowledged.

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