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THE XANTHATE ROUTE TO BENZAZEPINONES AND THEIR AZA CONGENERS

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Abstract – The present brief overview highlights and discusses the synthetic potential of the degenerative radical addition of xanthates for the synthesis of benzazepinones and their aza congeners. Various routes are presented, including direct cyclisations onto the aromatic or heteroaromatic ring, intermolecular radical additions followed by ring closure, and Beckmann ring expansion of tetralones produced by radical addition-cyclisation. Many of the compounds described are medicinally relevant and not readily available by more conventional methods.

CONTENTS

1. INTRODUCTION

The conformational flexibility of seven-membered rings often allows a better adaptation to receptor sites and improves the biological activity and pharmacological profile.[1] The benzazepine motif and its aza congeners, in particular, have emerged over the years as highly privileged pharmacophores in medicinal chemistry.[2] This structural entity is thus present in numerous medicinally important alkaloids,[3] such as

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This paper is dedicated with respect, admiration, and friendship to Prof. Somsak Ruchirawat on the occasion of his 80th birthday.

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morphine **1**, galanthamine **2**, cephalotaxine **3**, and cytisine **4**, and in clinically useful synthetic drugs, a few of which are also displayed in Figure 1.

Rucaparib **5** is an anticancer PARP inhibitor,[4] while Tolvaptan **6** is a vasopressin V_2 receptor antagonist currently in clinical use to treat, among other ailments, low blood sodium levels (hyponatremia).[5] It is noteworthy that this substance is sold as the racemic modification. Benazepril **7** (Lotensin) is an ACE inhibitor that combats high blood pressure and heart failure.[6] 1-Azakenpaullone **8** is a selective inhibitor of glycogen synthase kinase-3 beta (GSK-3beta) and a promising anticancer substance.[7] Finally, Nevirapine **9** (Viramune) is a non-nucleoside inhibitor of HIV-1 reverse transcriptase used as a medication for AIDS.[8]

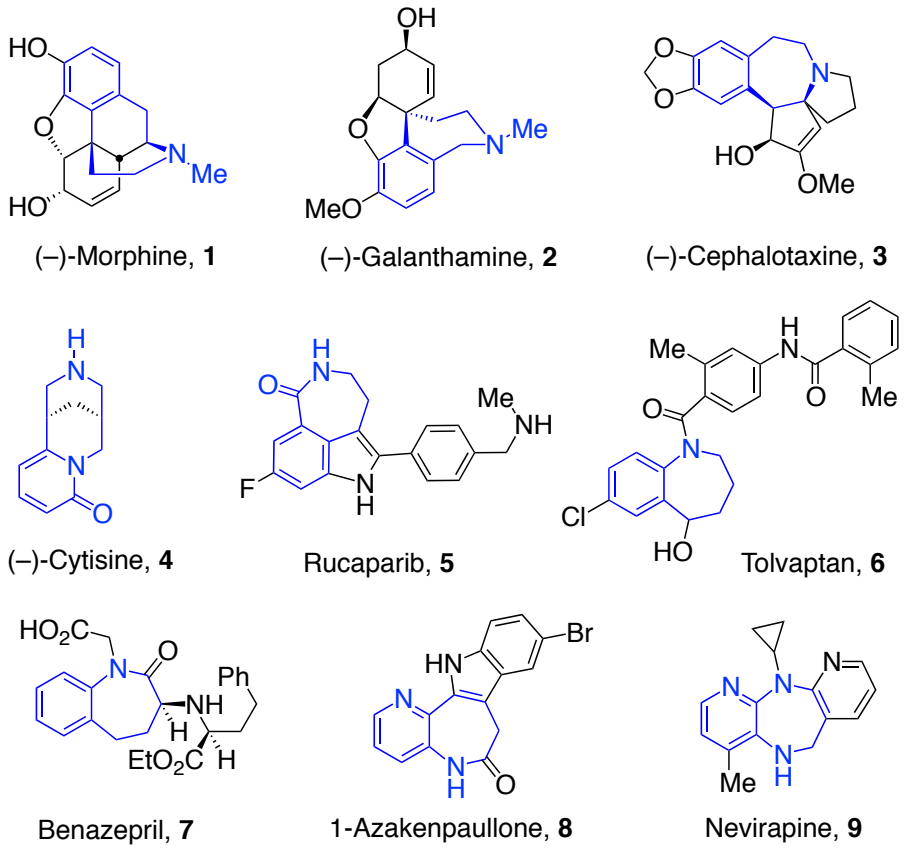
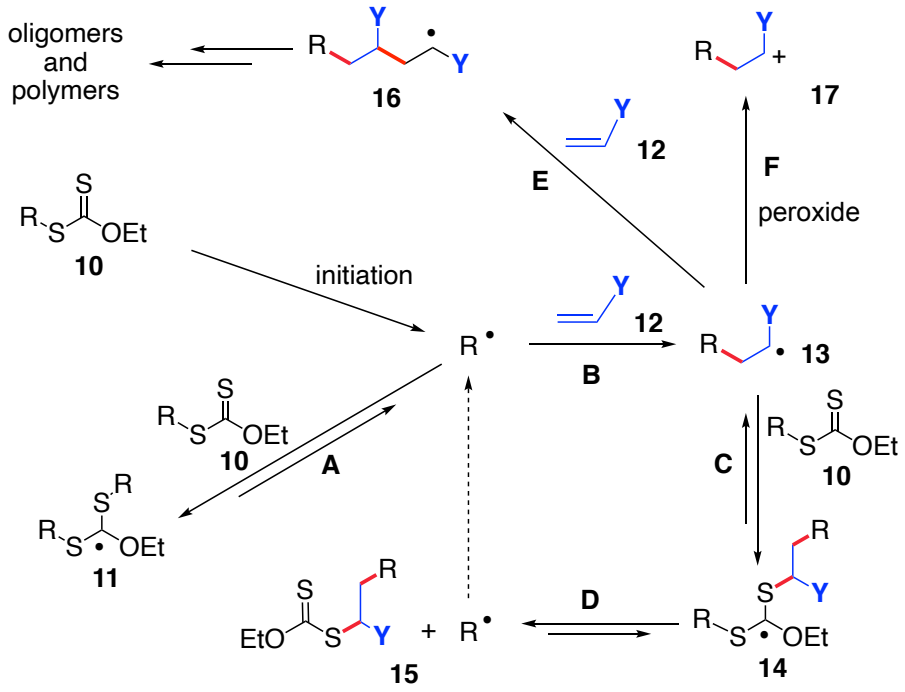


Figure 1. Examples of Alkaloids and Synthetic Drugs Containing a (Aza)benzazepine Core

Not surprisingly, a vast amount of work has been invested in developing efficient routes to such molecular architectures. These synthetic approaches can be classed into two broad categories, namely the construction of the seven-membered ring starting with adequately substituted aromatic or heteroaromatic templates and ring-expansion of smaller rings fused to the aromatic or heteroaromatic nucleus.[9] The former strategy relies on classical processes, such as the Friedel-Crafts reaction,[10] organometallic couplings,[11] cycloadditions,[12] the metathesis reaction,[13] and photochemistry (the so-called Witkop

cyclization).[14] The latter revolves mostly on the Beckmann and related rearrangements to effect ring enlargement of tetralones and their aza congeners.[15] Radical reactions have seldom been applied hitherto because of the inherent difficulty in forming seven-membered rings by direct radical cyclization.[16] This gap in methodology is however being gradually filled by novel radical processes based on the degenerative exchange of xanthates we have developed over the years.[17] This unique chemistry allows access to a broad array of benzazepine structures only tediously obtained by more conventional approaches and expands considerably the basis set of building blocks available to medicinal chemists, as will be discussed in the present overview.

First, it is important to briefly discuss the basic mechanistic underpinnings of this rather remarkable chemistry, as outlined in the simplified manifold displayed in Scheme 1.[18] Following initiation, most simply by thermolysis of a peroxide, radical R• is produced from xanthate **10** and swiftly intercepted by its xanthate precursor to give radical **11** (path **A**). However, this step is reversible and degenerate, so radical R• is not irreversibly consumed but constantly regenerated. Its effective lifetime is therefore considerably increased, allowing it to add to even unactivated alkene **12** to furnish ultimately adduct **15**, via paths **B** → **C** → **D** and intermediates **13** and **14**. Radicals **11** and **14** are hindered and stabilized by three heteroatoms; they also lack β-hydrogens and are thus unable to disproportionate. They behave like semi-persistent species that reversibly store radicals R• and **13** in a relatively non-reactive form. The consequence is a lowering of the *absolute* concentration of radicals R• and **13** (and in fact any other active radical in the medium) and a significant diminution of unwanted radical-radical interactions.



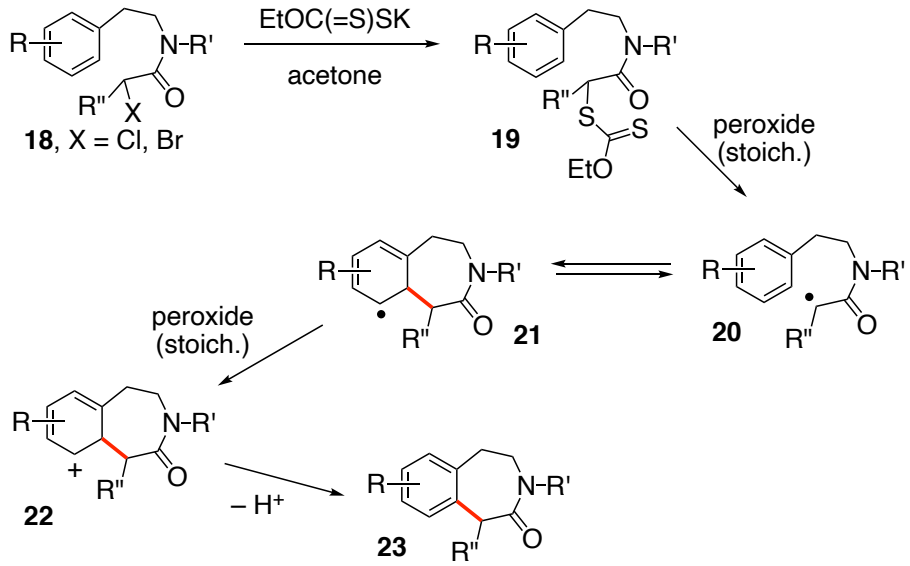
Scheme 1. Simplified Mechanism for the Radical Addition of a Xanthate to Alkenes

The *relative* concentrations of radicals R• and **13** are also regulated by the reversibility of steps **A**, **C**, and **D**. This reversibility also implies *that initial radical R• has to be more stable than adduct radical **13*** to ensure that the steady-state concentration of the former remains sufficiently greater than that of the latter and thus limits the formation of oligomeric side-products by further additions of adduct radicals **13** to alkene **12** (path **E**). Polar effects have been neglected in this discussion but can be important in certain situations. Interestingly, the formation of polymers according to path **E** can be encouraged and, indeed, finely controlled. This novel radical chemistry of xanthates and related thiocarbonylthio derivatives (dithioesters, trithiocarbonates, and dithiocarbamates) constitutes the foundation of the exceedingly powerful RAFT/MADIX technology for the manufacture of block copolymers. Essentially all commercial monomers can be employed and at least 10 000 publications and 1000 patents have appeared reporting studies and applications in this field.[19] One last important pathway is the oxidation of adduct radical **13** to the corresponding cation **17** by a one-electron transfer to the peroxide (path **F**). This happens when substituent **Y** on the alkene is electron-donating and stabilizes the incipient cation. The ability to crossover from the radical to the ionic manifold adds another dimension in terms of synthetic possibilities. In the present context, this oxidation step allows rearomatization following intramolecular radical addition to an aromatic or heteroaromatic ring.

2. SYNTHESIS OF BENZAZEPINONES BY DIRECT CYCLIZATION

The addition of carbon radicals to aromatic systems is usually more difficult (i.e., slower) than the corresponding addition to alkenes, hence the traditional use of benzene as the reaction medium, even if the tendency is to shun this solvent because of toxicity concerns. This addition is furthermore reversible in most cases. The relatively long life of radicals generated form xanthates as discussed above allows nevertheless the formation of 5-, 6-, and 7-membered rings fused to aromatics and heteroaromatics. For the synthesis of benzazepinones, one simply starts from 2-arylethylamines, which are chloro- or bromo-acetylated to give precursors **18** (Scheme 2). Substitution of the halide with a xanthate salt furnishes the required substrate **19**. Heating with a suitable peroxide causes the formation of the corresponding radical **20**, which undergoes reversible cyclisation onto the aromatic ring to give cyclohexadienyl radical **21**. As stated in the introductory section above, in order to efficiently propagate the chain process, the initial radical (here **20**) has to be more stable than the adduct radical (here **21**). This is not usually the case, as cyclohexadienyl radical **21** is highly stabilized. This species can however be oxidized into corresponding cation **22** by single electron transfer (SET) to the peroxide. Final loss of a proton regenerates the aromaticity and completes the sequence leading to benzazepinone **23**. The peroxide is thus acting as both an initiator and a stoichiometric oxidant. Notice that cation **22** is the same species that would be formed in a Friedel-Crafts cyclisation, the so-called Wheland intermediate.[20] In

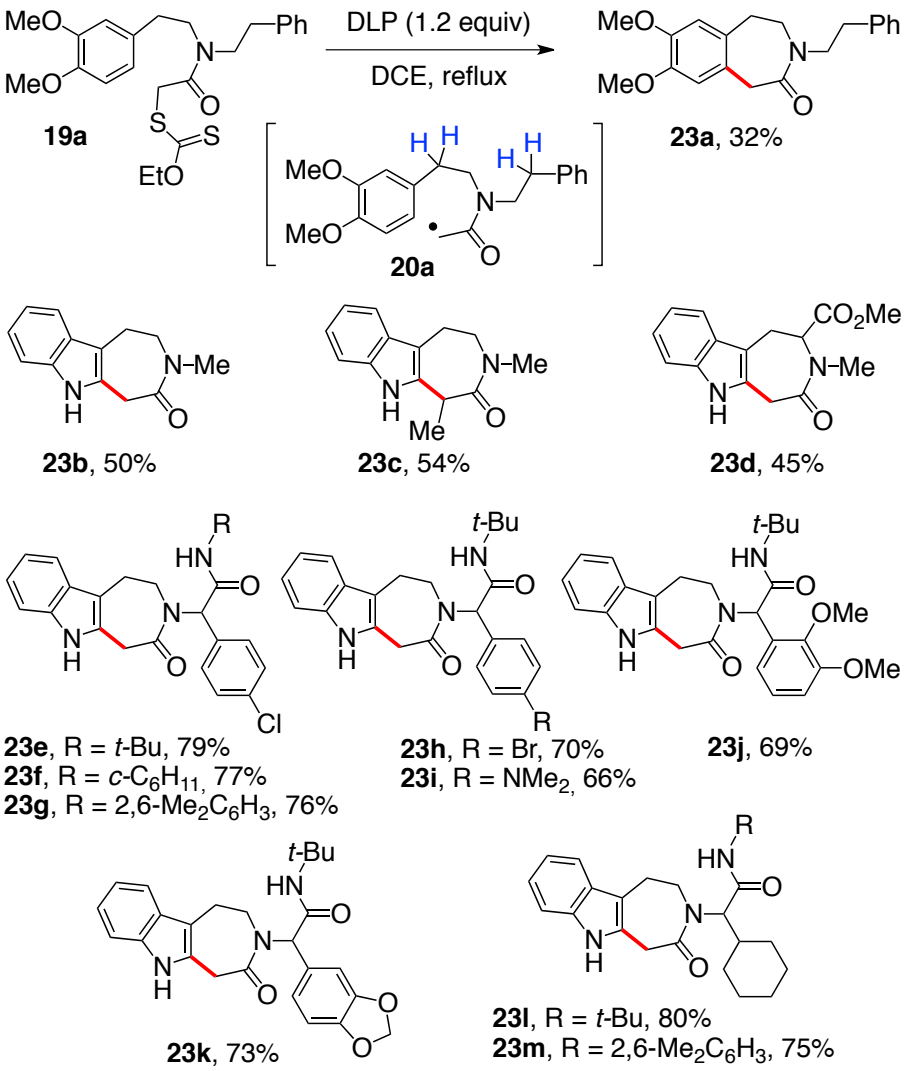
contrast to the electrophilic aromatic substitution which requires strongly acidic conditions, the radical cyclisation proceeds under much milder neutral conditions. This allows for a much broader functional group tolerance, as will be demonstrated by the examples in the present review.



Scheme 2. Synthesis of Benzazepinones by Direct Radical Cyclization

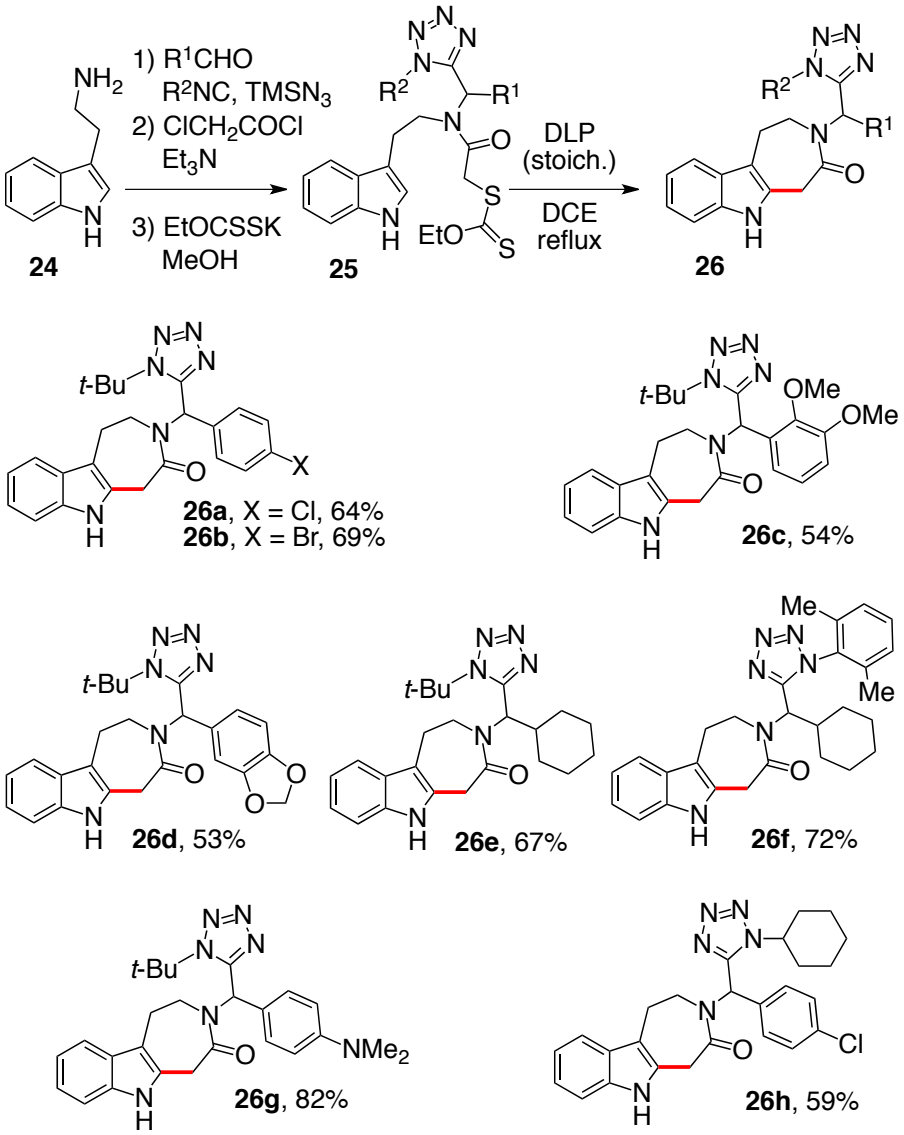
The first example in Scheme 3 starting with xanthate **19a** leads to benzazepinone **23a** in modest yield.[21] The reaction involves simply portion-wise addition of dilauroyl peroxide (or DLP; also sold as lauroyl peroxide, Laurox® or Luperox LP®) to a solution of the xanthate in refluxing 1,2-dichloroethane (DCE). The modest yield reflects on one hand the intrinsic difficulty of this cyclisation and, on the other, side reactions arising most likely from intramolecular abstraction of one of the four benzylic hydrogens highlighted on blue in intermediate radical **20a**. These easily abstracted benzylic hydrogens are well located for a 1,5-hydrogen atom shift.

The cyclisation is more effective when the closure occurs on the more reactive (and less aromatic) pyrrole subunit of the indole nucleus, as illustrated by examples **23b-m**.[21,22] Not only is the cyclisation step faster but these compounds also contain only two benzylic-type hydrogens and unwanted radical translocations are less of a complication. The precursors for products **23e-m**, examples taken from the work of Gámez-Montaño and co-workers,[22] were prepared through the powerful Ugi 4-component reaction.[23]



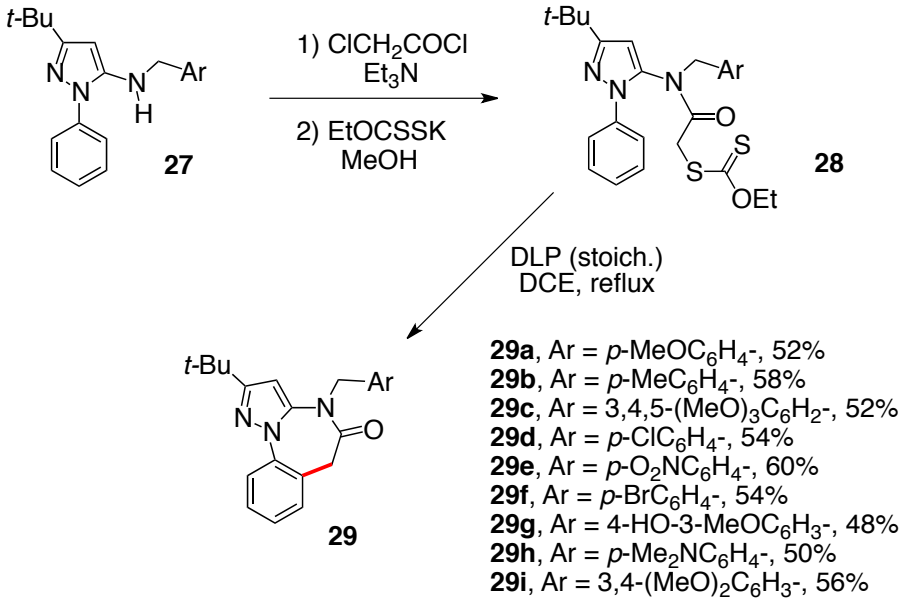
Scheme 3. Examples of Benzazepinones and Indolazepinones by Direct Radical Cyclization

Gámez-Montaño further replaced the carboxylic acid component in the Ugi reaction with trimethylsilyl azide to generate xanthates **25** starting from tryptamine (Scheme 4).[24] Exposure to peroxide induces ring closure to give indoloazepinones possessing a tetrazole side-chain. In all the examples in Schemes 3 and 4, only the parent indole nucleus was used, but the reaction tolerates in principle the presence of many substituents on the indole ring. A broad diversity of medicinally interesting structures should thus be easily accessible.



Scheme 4. An Alliance with an Unusual Variant of the Ugi Reaction

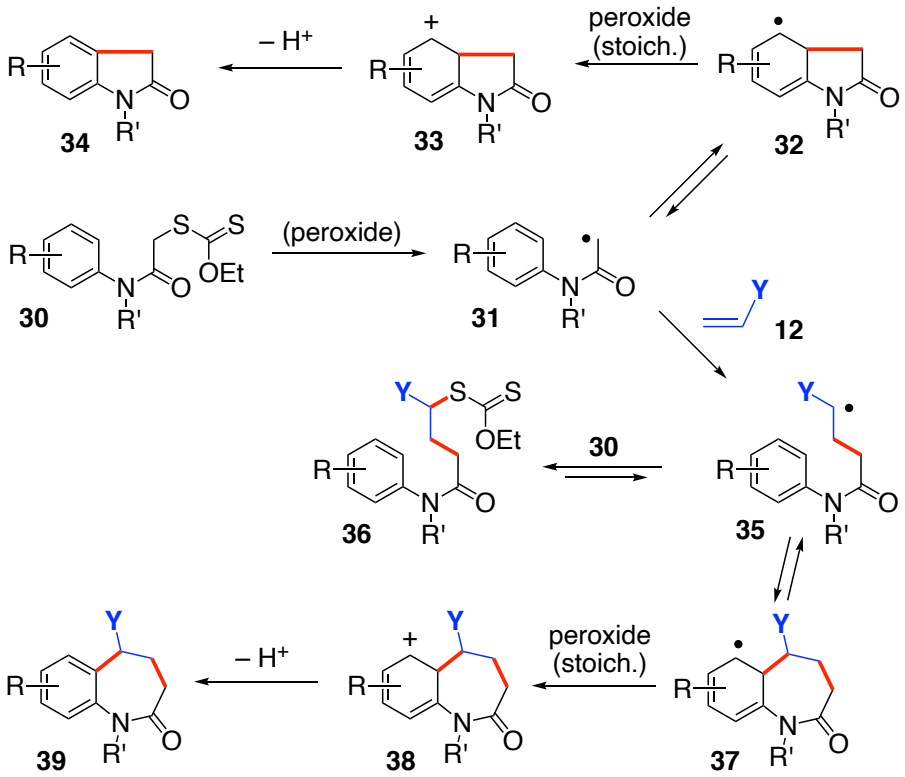
Abonia and co-workers described the synthesis of benzopyrazolodiazepinones **29a-i** by direct radical closure onto a benzene ring (Scheme 5).[25] These are novel, medicinally relevant structures that are not readily available by other approaches. It is nevertheless unfortunate that here, too, no effort was apparently made to decorate the benzene ring or replace it with heteroaromatic motifs and thus demonstrate the variety of accessible members of this family.



Scheme 5. Synthesis of Benzopyrazolodiazepinones by Direct Radical Cyclization

3. SYNTHESIS OF BENZAZEPINONES BY INTERMOLECULAR ADDITION AND CYCLIZATION

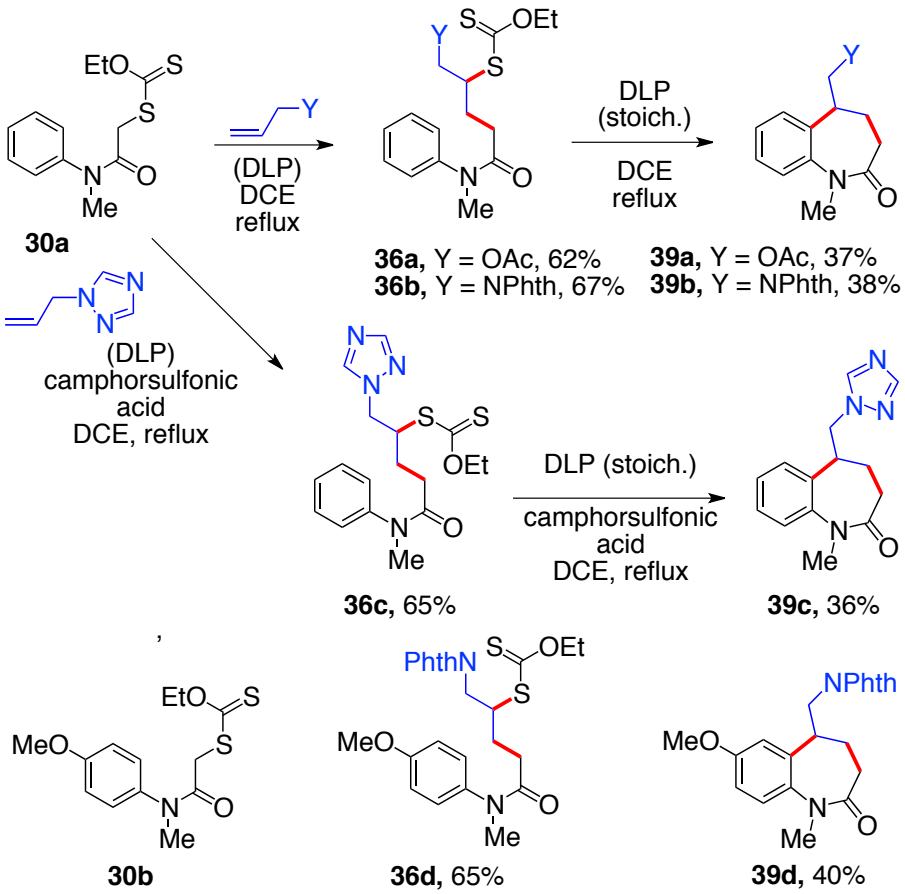
A more generally powerful route to benzazepinones is outlined in Scheme 6. It associates an intermolecular radical addition with the cyclisation step. Xanthates **30** derived from anilines give rise to radicals **31**, which cyclize to give intermediate cyclohexadienyl radicals **32**. Oxidation to cation **33** and loss of a proton furnishes oxindoles **34**. This constitutes a straightforward, practical synthesis of these important compounds. The radical cyclisation step is however relatively slow and reversible.[26] Indeed, it proved possible to capture radicals **31** with an external alkene to give radical **35** and thence adduct **36** by a reversible favorable xanthate exchange with starting xanthate **30**. Exposure of adduct **36** to stoichiometric peroxide regenerates reversibly intermediate radical **35** under conditions where the cyclisation into cyclohexadienyl radical **37** becomes the main pathway. Again, oxidation into cation **38** and proton loss gives the desired benzazepinone **39**. The disposition of the nitrogen atom in the azepinone subunit is different from the benzazepinones described in the previous section. Furthermore, the complications due to the presence of internally abstractable benzylic hydrogens (cf. **20a** in Scheme 3) are not of concern in this case, assuming R' ≠ H. The importance of the substituent on the nitrogen is discussed in the next section.



Scheme 6. A Modular Route to Benzazepinones

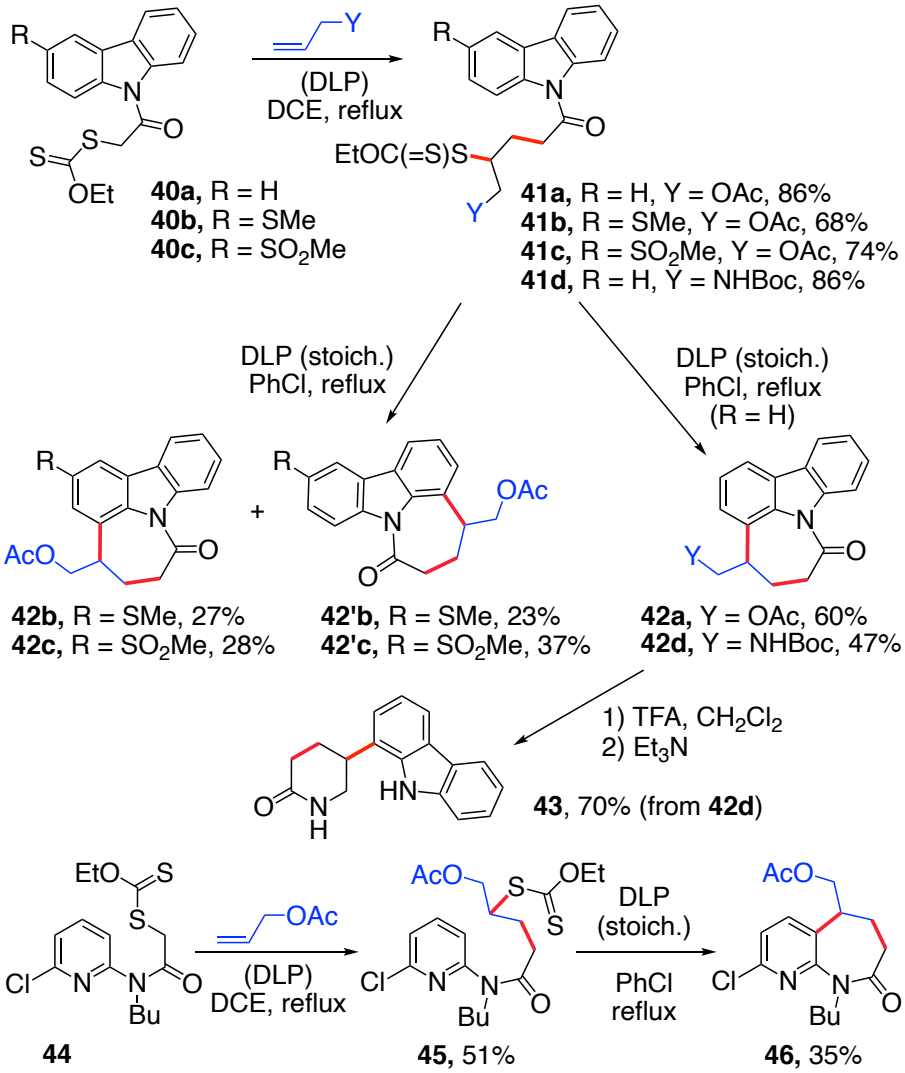
The pathways leading respectively to oxindole **34** and to adduct **36** are always in competition. By operating at high concentration and at moderate temperatures, the sluggish intermolecular addition is usually favored over the equally slow unimolecular cyclisation. Once adduct **36** is in hand, then further treatment with peroxide induces ring closure into benzazepinone **39**. In most cases, the two steps were accomplished separately by first isolating adduct **36** before subjecting it to the action of stoichiometric amounts of peroxide. However, if desired, both the addition and the cyclisation could be conducted in the same pot. The excess alkene **12** is simply removed, by distillation when possible, and fresh solvent is added so that the medium is 3- to 5-fold more dilute before portion-wise addition of the peroxide.

A few examples are presented in Scheme 7. Thus, *N*-methylaniline derived xanthate **30a** adds smoothly to allyl acetate and *N*-allylphthalimide to give adducts **36a** and **36b** respectively.[21] Treatment with stoichiometric DLP furnishes the corresponding benzazepinones **39a** and **39b** in modest yield. Triazole substituted benzazepinone **39c** was prepared via adduct **36c** in the same manner, except that camphorsulfonic acid (CSA) was added to neutralize any nucleophilic activity by the slightly basic triazole nucleus.[27] Under identical conditions to those used to obtain benzazepinone **39b**, methoxy-substituted analog **39d** was prepared from xanthate **30b** and its corresponding adduct **36d** to *N*-allylphthalimide.[21] Notice that the intermolecular addition to the alkene in all these examples is higher yielding than intramolecular cyclisation step. This is a fairly general observation and a clear reflection of the sluggishness of the 7-membered ring formation.



Scheme 7. Examples of Benzazepinones by Addition-Cyclization

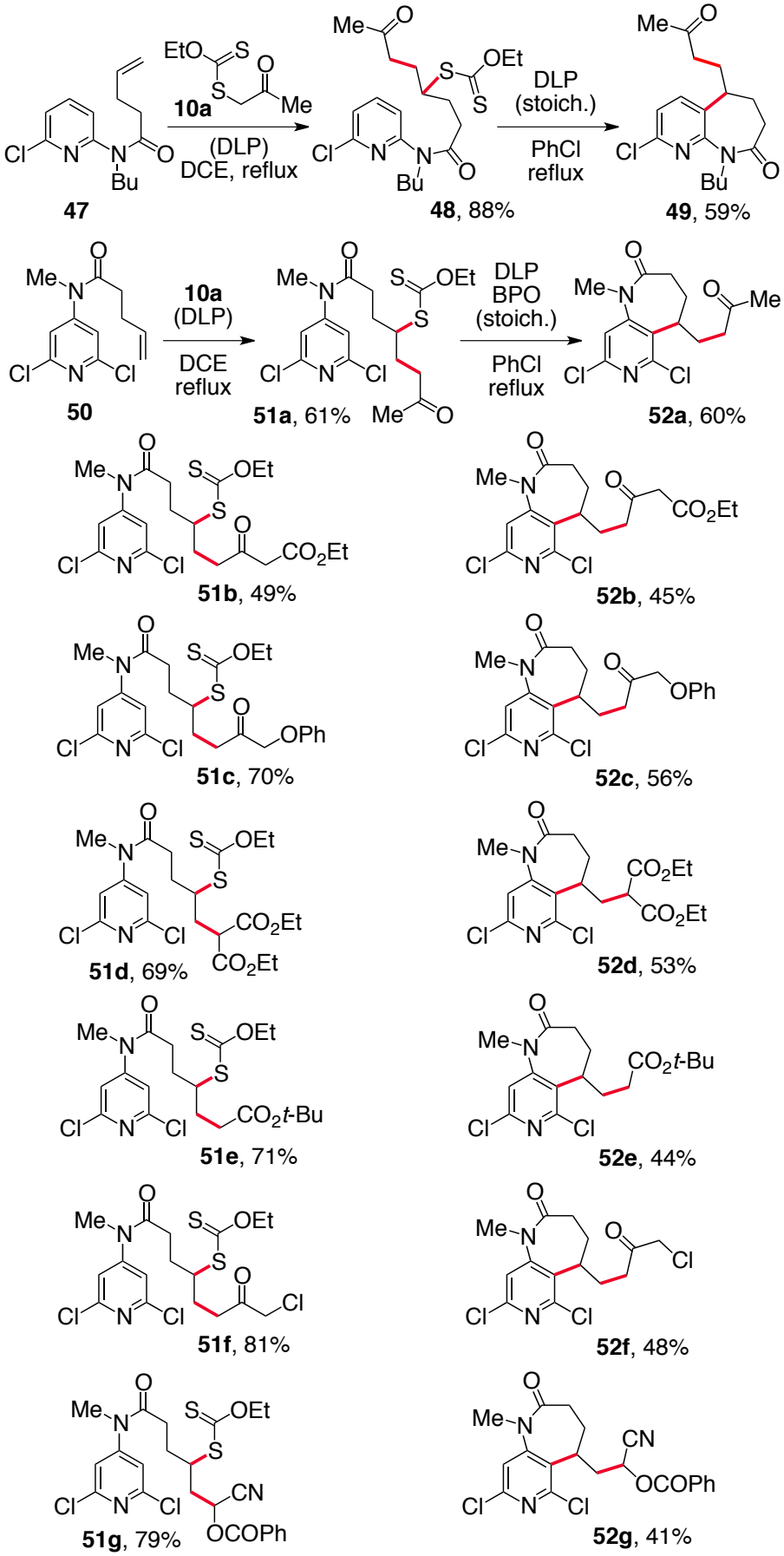
This approach can be readily extended to heteroaromatic substrates, as demonstrated by the transformations in Scheme 8. Carbazole derived xanthates **40a-c** react efficiently with allyl acetate and *N*-allylphthalimide to give adducts **41a-d**.[21,28] Symmetrical carbazole adducts **41a** and **41d** furnish only one carbazolazepinone, **42a** and **42d** respectively, upon exposure to stoichiometric amounts of DLP in chlorobenzene. In contrast, methylsulfide and methylsulfone substituted xanthates **41b** and **41c** give rise to two regioisomeric carbazolazepinones, **42b** and **42'b** from the former and **42c** and **42'c** from the latter. There is only a slight but, interestingly, opposite regioselectivity. Unmasking of the primary amine in compound **42d** with trifluoroacetic acid (TFA) followed by addition of triethylamine induces a transamidation leading to carbazole-substituted piperidone **43** in good yield.[28]



Scheme 8. Synthesis of Carbazolazepinones and Pyridoazepinones

Extension of this strategy to aminopyridine derived xanthate **44** proved feasible, allowing the two-step synthesis of pyridoazepinone **46** via intermediate adduct **45**.[29] While only allyl acetate and *N*-allylphthalimide were used as the alkene partners in Scheme 8, numerous other alkenes bearing various functionalities are compatible and could be incorporated in principle. This tolerance will be illustrated in the following section. Furthermore, it is possible to place the olefinic moiety on the lactam and generate the required cyclisation precursors by an intermolecular radical addition of various functional xanthates. This alternative approach is exemplified in Scheme 9.

Addition of acetonyl xanthate **10a** to alkene **47** produces expected adduct **48** in high yield.[30] Further treatment with DLP in the higher boiling chlorobenzene induces cyclisation to furnish pyridoazepinone **49** in a useful yield. The isomeric pyridoazepinone **52a** was prepared in a similar manner from amide **50** via adduct **51a**.[31] In this case, however, the oxidation of the cyclized radical necessary for rearomatization is more difficult, but it was found that it could be improved by combining benzoyl peroxide (BPO) with

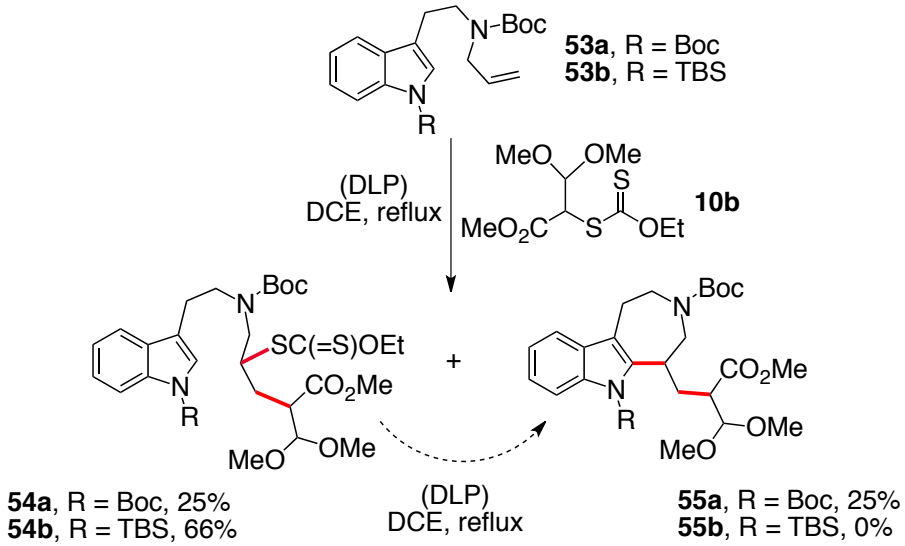


Scheme 9. An Alternative Route to Pyridoazepinones

DLP. The former is at the same time slightly more thermally stable and a slightly stronger oxidant as compared to DLP. Thus, the formation of the radical from adduct xanthate **51a** is accomplished by the thermolysis of DLP and the oxidation of the cyclized radical is achieved by the mostly intact BPO that remains in the medium.

By simply modifying the xanthate partner, analogous pyridoazepinones **52b-g** were prepared from the corresponding adducts **51b-g**.[31] This allows the introduction of various synthetically useful functional groups, most notably a ketoester (**52b**), an α-chloroketone (**52f**), and a cyanohydrin benzoate (**52g**). The last is in fact a masked aldehyde and α-chloroketones are precursors of various heteroaromatics by application of a number of classical named reactions such as the Hantzsch pyrrole and thiazole syntheses, the Feist-Benary furan synthesis, the Tschitschibabin (Chichibabin) indolizine condensation, the Bischler-Möhlau indole synthesis, etc.[32]

A conceptually related formation of an indoloazepine was found as an unwanted side reaction in a model study towards the eburna alkaloids (Scheme 10).[33] Thus, addition of xanthate **10b** to Boc-protected *N*-allyltryptophan **53a** furnished both the desired adduct **54a** and indoloazepine **55a** in comparable yields. The formation of the latter could be suppressed by starting with compound **53b**, bearing the bulkier TBS group on the indole nitrogen, which furnished essentially only adduct **54b**. In principle, the cyclization to indoloazepine **55a** could be forced by exposing adduct **54a** to further amounts of peroxide. It is worth noting that xanthate **10b** also allows the convenient introduction of a protected aldehyde group.

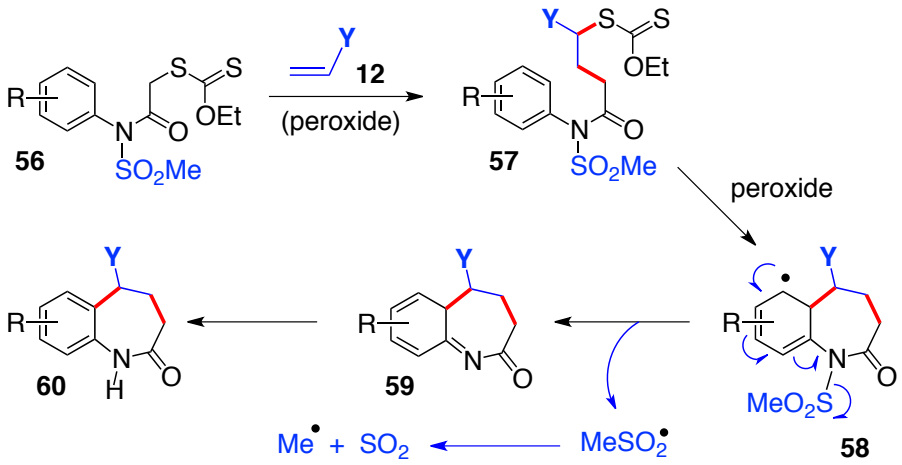


Scheme 10. An Example of an Indoloazepine

4. SYNTHESIS OF *N*-UNSUBSTITUTED BENZAZEPINONES

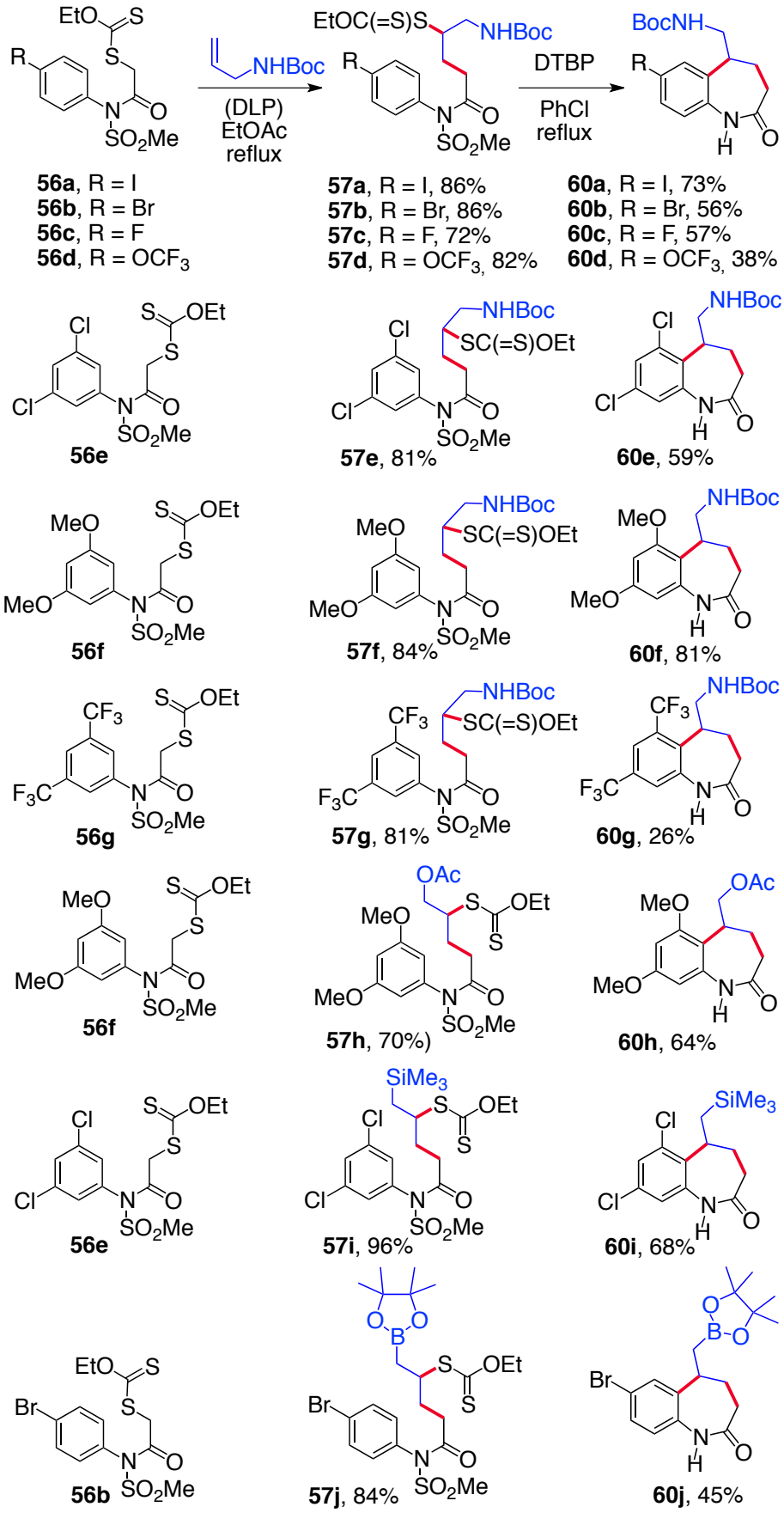
In all the above examples, the nitrogen of the azepinone motif is substituted. This is necessary for the cyclization because unsubstituted amides adopt almost exclusively the (*Z*) conformation that is not favorable for ring closure.[34] This constraint could in principle be circumvented by placing a suitable

temporary group on the nitrogen atom and removing it once the cyclization has been accomplished. Another difficulty that was briefly mentioned concerns the oxidation step needed for rearomatization (e.g., **37** → **38** in Scheme 6) that could be too slow in the case of electron-poor aromatics or heteroaromatics resulting in the formation of side-products and low yields. This hurdle was addressed in the transformations in Scheme 9 by using a combination of two different peroxides, DLP and BPO. We found that both difficulties could be solved in a simple manner by starting with *N*-sulfonylamides **56** (Scheme 11).[28] The usual intermolecular radical addition to alkene **12** furnishes the expected adduct **57** and the cyclization leads first to cyclohexadienyl radical **58**, which now is able to undergo elimination of a methylsulfonyl radical to give intermediate **59**. Finally, a prototropic shift provides the desired *N*-unsubstituted benzazepinone **60**. As for the methylsulfonyl radical, it can extrude sulfur dioxide to give a methyl radical that can participate in the initiation of the sequence and thus limit the amount of peroxide needed to complete the transformation.



Scheme 11. An Approach to *N*-Unsubstituted Benzazepinones

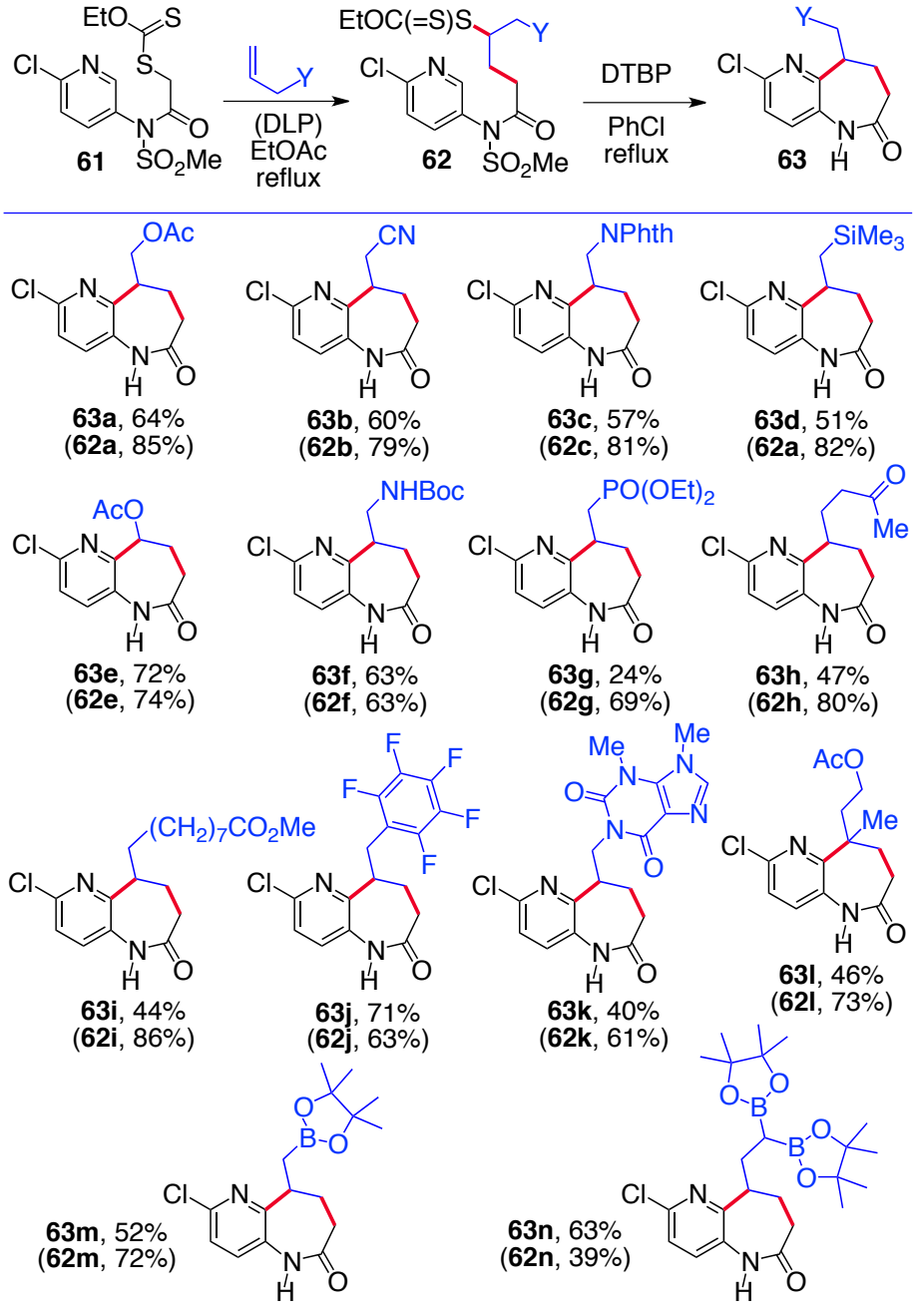
This strategy proved quite successful and opened access to a large variety of *N*-unsubstituted benzazepinones, as can be gauged by inspection of the examples in Scheme 12.[28] Because of the electron-withdrawing effect of the sulfonyl substituent, the radicals derived from xanthates **56a-g** acquire additional electrophilic character, and the improved polarity matching results in highly effective additions leading to intermediates **57a-j**. The conversion into benzazepinones **60a-j** is best accomplished at the higher temperature of refluxing chlorobenzene, using the slow decomposition of di-*t*-butyl peroxide (DTBP; half-life at 130 °C is about 10 hours[35]) to initiate the radical sequence. The high temperature is needed to speed the scission of the sulfonamide, which would otherwise be too sluggish to be useful. Nevertheless, these neutral thermal conditions remain quite mild and tolerate a broad variety of functional groups. One notable example is boronate **60j**, which would be fairly inaccessible by other more conventional approaches. The modest yield of benzazepinones **60d** and, especially, **60g**, bearing strongly



Scheme 12. Examples of *N*-Unsubstituted Benzazepinones

electrophilic substituents on the aromatic ring, is probably the result of a particularly sluggish fragmentation of the sulfonamide caused by a polarity mismatch between the SOMO of cyclohexadienyl radical (cf., **58**) and the σ* of the nitrogen-sulfur bond. Probably a higher reaction temperature would have been better in these cases.

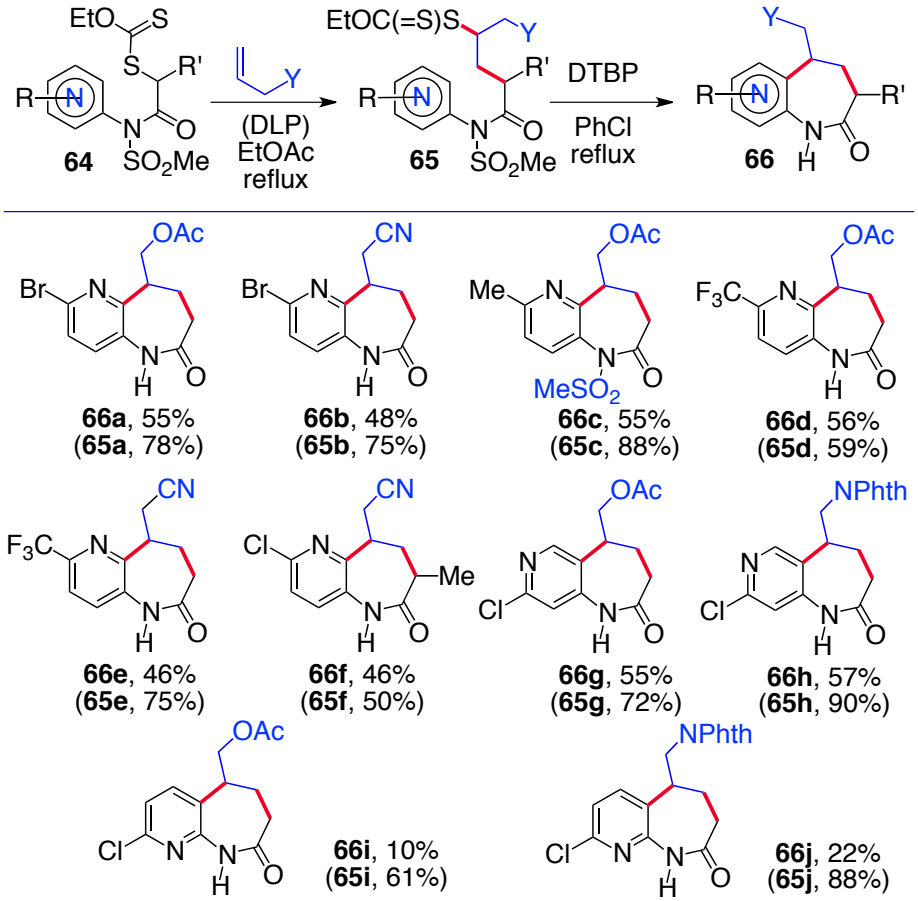
This practical route to *N*-unsubstituted benzazepinones hinging on the elimination of methylsulfonyl radicals could be extended to the preparation of the generally less accessible pyridoazepinones. Several examples **63a-n** starting from xanthate **61** are displayed in Scheme 13.[36] The yield of intermediate adducts **62a-n** is indicated but the corresponding structures are not shown. Furthermore, as for the examples in the preceding Scheme, the yield of the addition is generally higher than that of the



Scheme 13. *N*-Unsubstituted Pyridoazepinones

cyclization step. Numerous substituents on the alkene partner are tolerated, including esters (**63a**, **63e**, **63i** and **63l**), cyanide (**63b**), protected amine (**63c** and **63f**), silane (**63d**), phosphonate (**63g**), ketone (**63h**), aromatic and heteroaromatics (**63j** and **63k**), and boronates and even bis-boronates (**63m** and **63n**).

Further examples are compiled in Scheme 14, illustrating variations in the substituents on the pyridine fragment (examples **66a-e**) and in the position adjacent to the lactam group (methyl group in **66f**).[36] Thus, the chlorine can be replaced by a bromine (**66a** and **66b**), a methyl (**66c**) or a trifluoromethyl (**66d** and **66e**). The presence of the bromine atom in the first two is particularly interesting from a medicinal chemistry perspective since it allows the automated attachment of myriad aromatics, heteroaromatics, and indeed many other motifs, through transition metal catalyzed couplings, especially the exceedingly powerful Suzuki reaction, and the creation of vast libraries of diverse compounds for testing.

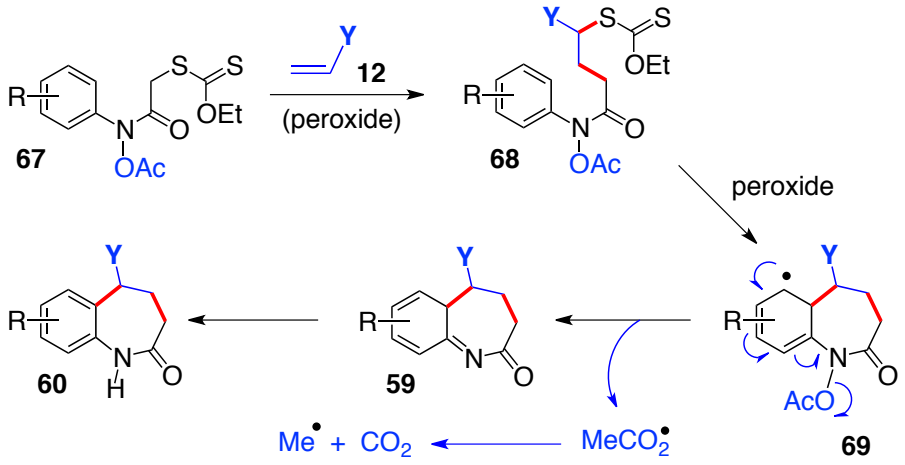


Scheme 14. Further Examples of *N*-Unsubstituted Pyridoazepinones

Modification of the position of the pyridine nitrogen in the starting xanthate **64** is also possible, as indicated by the formation of pyridoazepinones **66g-j** in the same Scheme.[36] This constitutes a further dimension for introducing diversity in a simple, expedient manner. The reason for the low yield in the case of compounds **66i** and **66j** is not yet clear but could also be due to a sluggish loss of methylsulfonyl radical. More work is needed to clarify this puzzling observation. The yields for intermediates **65a-j** are

given for all the examples in Scheme 14 but, again, the structures are not shown. It can also be noticed that these yields are in all cases higher than those of the ring closure step reflecting, as stated above, the general difficulty of forming a seven-membered ring by radical cyclization.

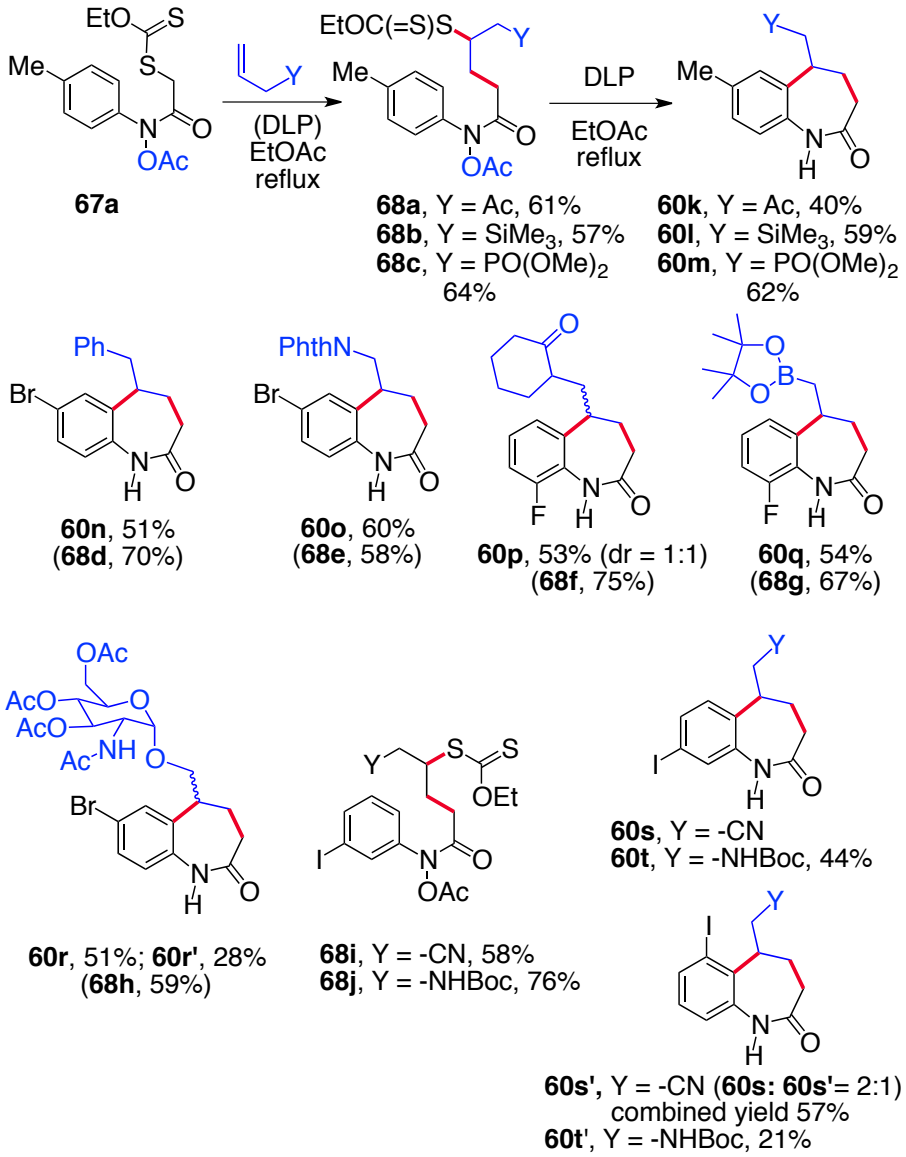
An alternate route to benzazepinones of general structure **60** is outlined in Scheme 15. It hinges on the easy cleavage of a nitrogen-oxygen bond and starts with xanthates **67**.[37] The addition to alkene **12** gives adducts **68** which, upon exposure to further peroxide, undergo ring closure onto the aromatic ring to provide the corresponding cyclohexadienyl radicals **69**. These species readily fragment to generate acetyloxy radicals and the same intermediates **59** pictured in Scheme 11 that rapidly proceed to benzazepinones **60** by a prototropic shift. The acetyloxy radicals instantly expel carbon dioxide to give methyl radicals which, as for the sulfonamides above, can participate in initiating the process.



Scheme 15. An Alternative Approach to *N*-Unsubstituted Benzazepinones

The sequence in Scheme 15 obviously parallels closely the one in Scheme 11. From a practical standpoint, xanthates **67** are less readily available than their sulfonamide analogs **56** but, because of the much weaker N—O bond in the former, as compared to the N—S bond in the sulfonamide, the fragmentation is orders of magnitude faster. Both the addition and cyclization steps can be performed in refluxing ethyl acetate using DLP as the initiator. Examples **60k-t** of this second approach are displayed in Scheme 16.[37] Again, a variety of substituents can be present on the alkene and on the aromatic ring. An interesting example is the 2-acetamido-glucose substituted product **60r**,**r'**. The two diastereoisomers could be separated by chromatography and the good combined yield is a strong testimony to the mildness of this procedure. The yields for intermediate adducts **68a-j** are indicated in Scheme 16, but the structures are not shown, except for **68i** and **68j** possessing an iodide in the meta position. As would be expected, the cyclization of both these precursors leads to two regioisomers in approximately 2:1 ratio. These were inseparable in the case of nitriles **60s** and **60s'** but separable in the case of Boc-protected amines **60t** and **60t'**. The compatibility

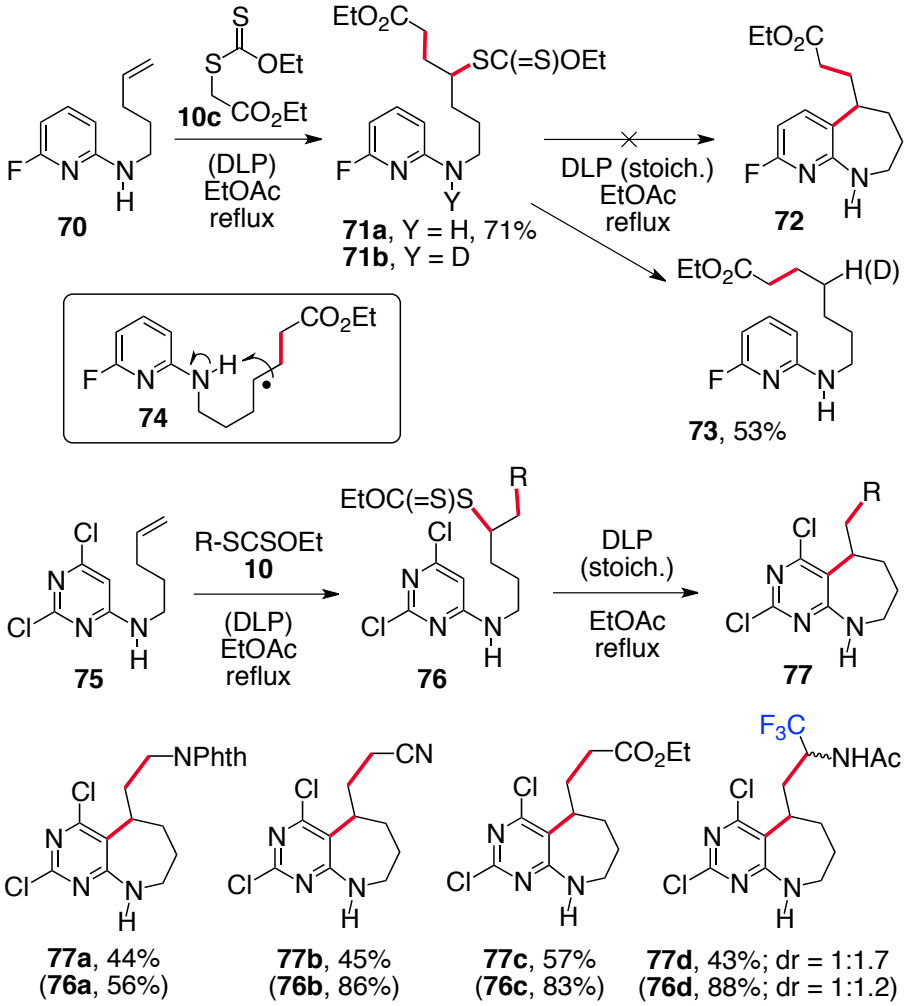
with aromatic iodides is remarkable and, along with aromatic bromides, provides, as stated above, a convenient handle for further derivatization through powerful organometallic couplings.



Scheme 16. Further Examples of *N*-Unsubstituted Benzazepinones

This second approach to *N*-unsubstituted benzazepinones has not yet been extended to the pyridine series, in part because of the lower accessibility of the hydroxamate precursors, even though there is no a priori reason it would not proceed in the same manner. One attempt was made to obtain the desired pyridoazepinones by cyclization of *N*-unsubstituted precursors such as **71a** (Scheme 17). Normally, the xanthate addition is incompatible with the presence of nucleophilic amines because they cause aminolysis of the xanthate group. Amines therefore need to be protected, most conveniently as amides, carbamates, or sulfonamides. It was surmised, however, that in the case of alkene **70**, the nucleophilicity of the secondary amine is strongly subdued by delocalization of the nitrogen lone pair into the

electron-withdrawing pyridine ring and would thus not interfere with the radical addition.[38] Indeed, the reaction of alkene **70** with xanthate **10c** proceeded normally to give adduct **71a** in good yield. Unfortunately, further exposure to peroxide did not give any pyridoazepinone **72** but resulted instead in the formation of reduced compound **73**. Intramolecular hydrogen atom abstraction from the secondary amine by intermediate carbon radical **74** seems to be the main problem as demonstrated by starting with deuterated precursor **71b**.

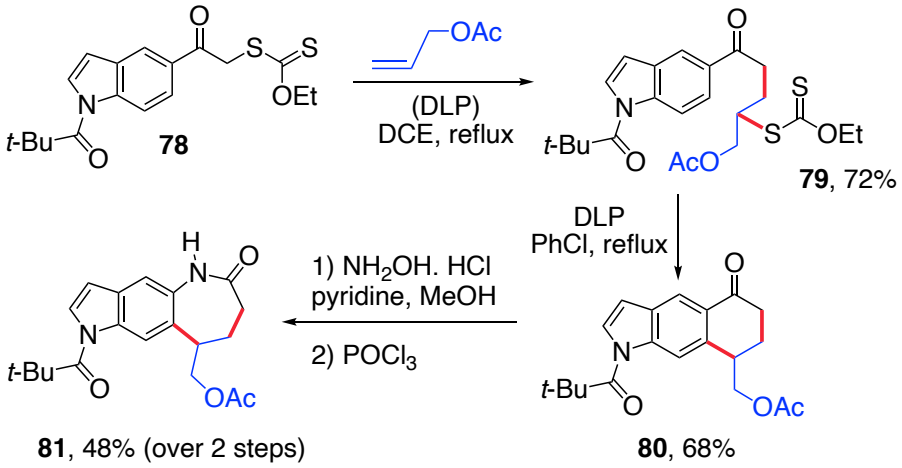


Scheme 17. Synthesis of *N*-Unsubstituted Pyrimidinoazepines

Despite this initial setback, an analogous sequence starting from the pyrimidine analog **75** was examined in the hope that with the more electrophilic heteroaromatic ring the hydrogen atom abstraction would be slowed down and the cyclization step speeded up.[38] This, pleasantly, turned out to be the case and olefin **75** could be converted into pyrimidinoazepinones **77a-d** via adducts **76a-d**. The presence of a CF_3 group in the last example is particularly noteworthy.

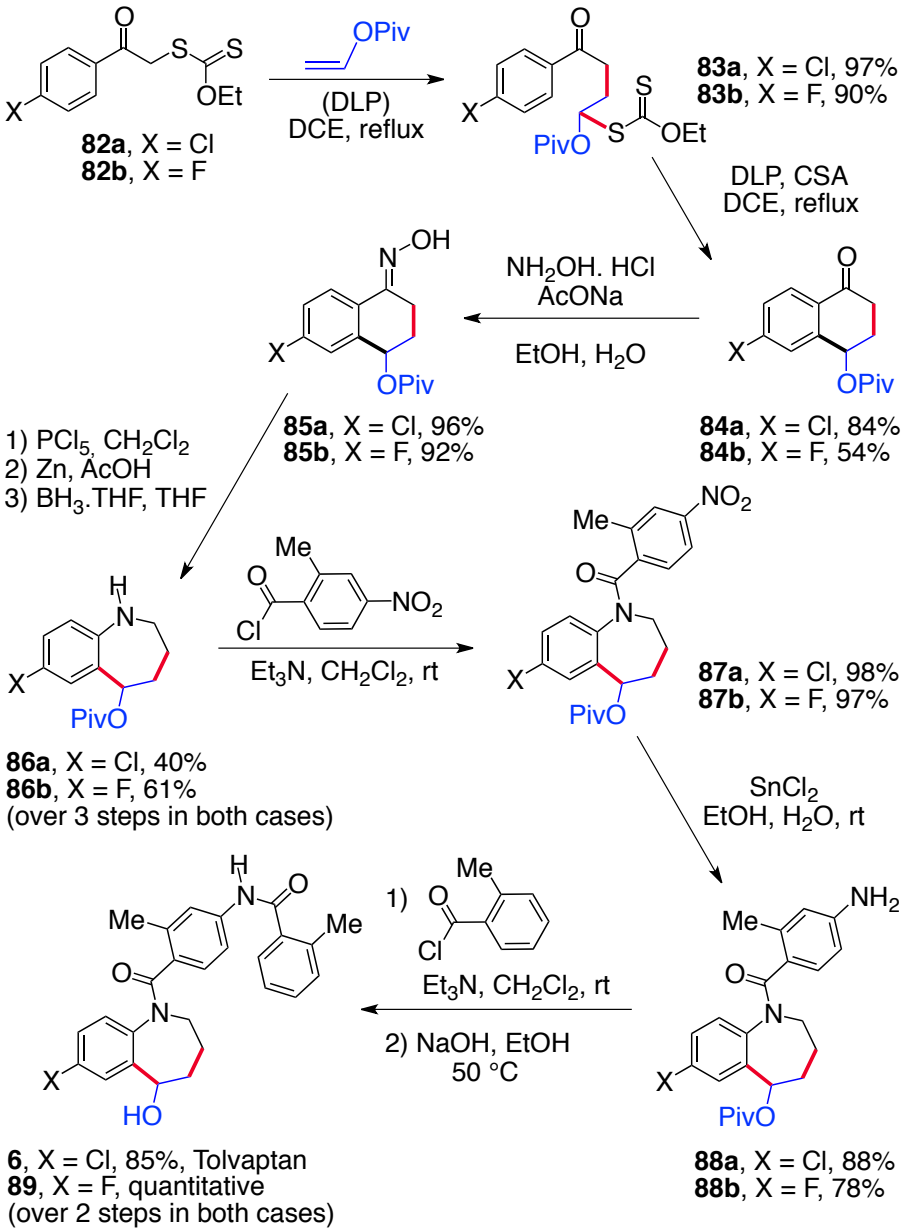
One classical route to *N*-unsubstituted benzazepinones is by a Beckmann ring expansion of tetralone oximes.[15] This approach has hitherto been handicapped by the limited availability of the required

tetralones. It turns out that xanthate chemistry also solves to a large extent the synthesis of tetralones and thus provides an entry to numerous otherwise inaccessible benzazepinones.[39] One such example is displayed in Scheme 18.[40] Thus, addition of α-keto xanthate **78** to allyl acetate furnishes adduct **79** and further heating with DLP in refluxing chlorobenzene induces cyclization onto the aromatic ring to give tetralone **80**. Treatment of the corresponding oxime with phosphorus oxychloride produces unusual indoloazepinone **81**.



Scheme 18. An Indoloazepinone via the Beckmann Rearrangement

This alliance of tetralone formation and Beckmann rearrangement was used in an improved preparation of Tolvaptan (**6**, Figure 1). Its synthesis, along with that of its fluoro analog **89b**, is outlined in Scheme 19.[31] Starting with *S*-(*p*-chlorophenacyl)-xanthate **82a**, radical addition to vinyl pivalate (piv = pivaloyl) gives adduct **83a** in excellent yield. Subsequent ring closure to tetralone **84a** and treatment with hydroxylamine leads to oxime **85a**. A modified Beckmann rearrangement using phosphorus pentachloride (see discussion in next section) followed by dechlorination with zinc/acetic acid and reduction of the lactam with borane-THF complex in THF as the solvent furnishes benzazepine **86a** without purification of the intermediates. Interestingly, the pivalate group remains intact throughout all these transformations. This allows a completely regioselective N-acylation to afford nitrobenzoate **87a**. Finally, reduction to aminobenzoate **88a**, acylation with *o*-toluoyl chloride, and saponification of the pivalate complete the synthesis of Tolvaptan **6**. An identical sequence starting from *S*-(*p*-fluorophenacyl)-xanthate **82b**, provides fluoro analog **89** in comparable overall yield.[41]

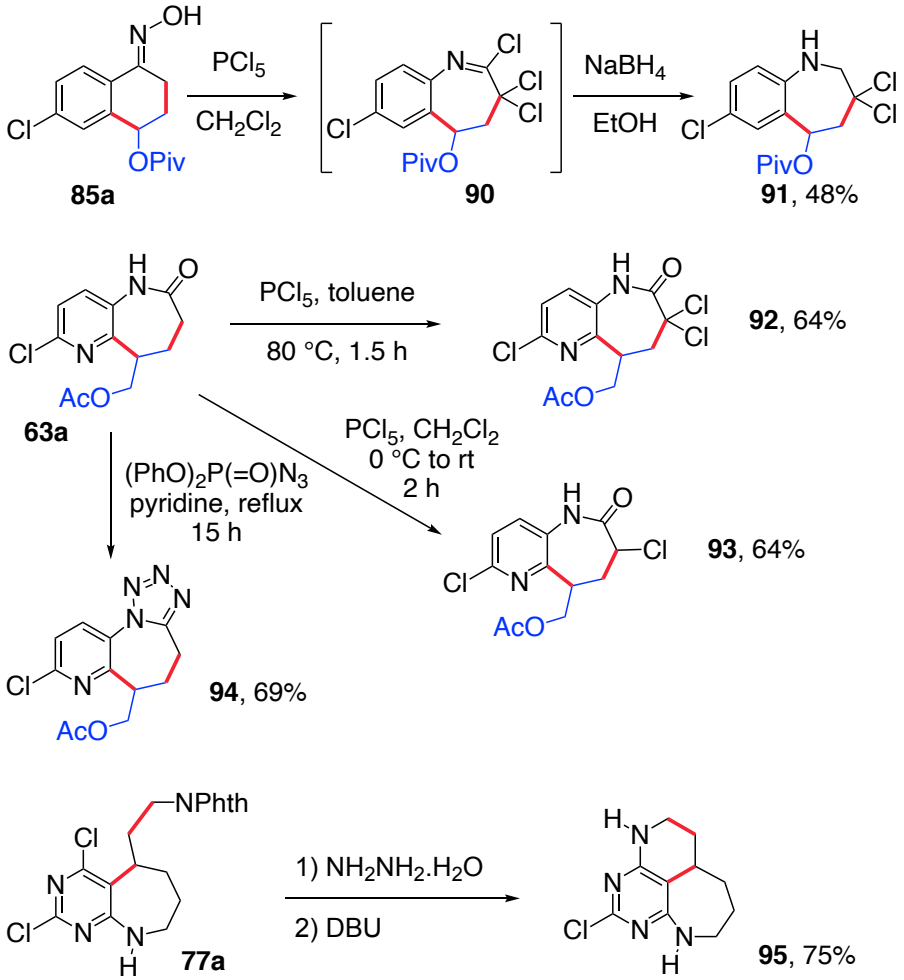


Scheme 19. Synthesis of Tolvaptan and its Fluoro Analogue

5. CONCLUDING REMARKS AND FURTHER PERSPECTIVES

The transformations discussed in the present review show how this unique radical chemistry of xanthates enables various strategies for the synthesis of benzazepinones, benzazepines and their aza congeners. The simplicity of the experimental procedures, the cheap and readily available reagents, the remarkable tolerance for numerous functional groups, and the modularity and convergence of some of the approaches are valuable features that need to be underscored. In alliance with other well-established reactions, such as the Suzuki coupling mentioned above, an almost infinite diversity of structures can be constructed for testing by medicinal and plant protection chemists. A few other modifications are depicted in Scheme 20.

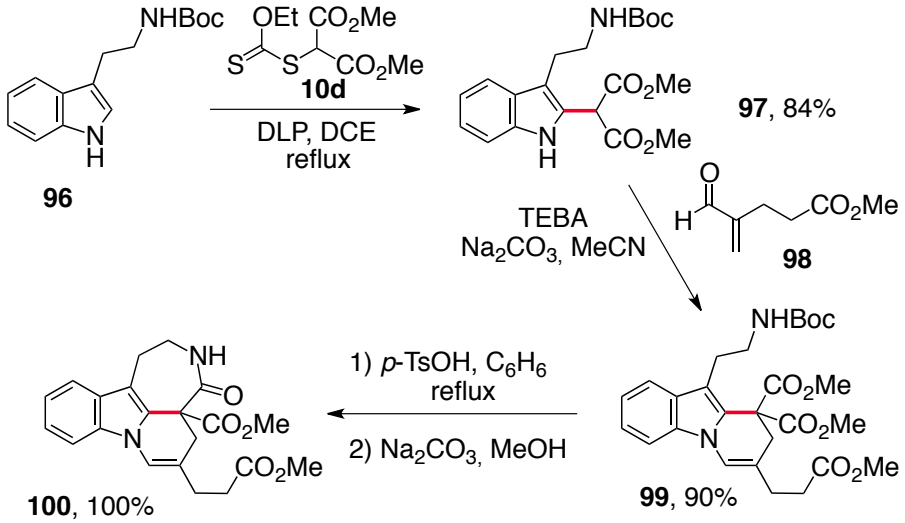
The phosphorus pentachloride induced Beckmann rearrangement used in the synthesis of Tolvaptan in fact leads first to dichloroimidoyl chloride **90** which is hydrolyzed to the corresponding dichlorolactam before dechlorination with zinc and acetic acid (cf., Scheme 19). Reduction with sodium borohydride instead of hydrolysis furnishes dichlorobenzazepine **91**.[41] This compound could in principle be processed into a dichloro analog of Tolvaptan. Treatment of pyridinoazepinone **63a** with phosphorus pentachloride and hydrolysis provide the dichloro congener **92**.[36] Interestingly, operating at 0 °C results in the formation of the monochloride **93** in the same yield, whereas treatment with diphenylphosphonyl azide in pyridine produces fused tetrazole **94**. Finally, in the case of pyrimidinoazepinone **77a**, liberation of the amine followed by exposure to DBU induces an ionic substitution of one chlorine atom to give novel tricyclic structure **95**.[38]



Scheme 20. Further Transformations of Benzazepinones, Pyridoazepinones, and Pyrimidinoazepinones

One last route to benzazepinones fused to an indole ring that deserves further exemplification was reported by Martinez.[41] It consists in using xanthate **10d** to introduce a malonate on C-2 of tryptamine **96**. The malonate in the resulting product **97** was then used to install a piperidine motif by reaction with enal

98. Deprotection of the amino group in tricylic derivative **99** and treatment with sodium carbonate in methanol induces intramolecular aminolysis of one of the esters of the malonate to create the azepinone subunit in product **100**. This sequence was destined to provide the pentacyclic core of the alkaloid tronocarpine, but could constitute an attractive route to benzazepinones fused to various heteroaromatic rings. The intermolecular addition of xanthates to heteroaromatics, such as pyridines, indoles, thiophenes, and furans, is quite versatile and allows the placement of the necessary substituents for building the benzazepinone moiety.[42]



Scheme 21. Synthesis of Indoloazepinone by a Radical-Ionic Sequence

In summary, many of the azepinones fused to aromatic and heteroaromatic rings described herein are medicinally relevant and not readily accessible by the more established methods. It is hoped that this review will encourage academic and industrial chemists to add this powerful methodology to their arsenal of synthetic tools.

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Samir Z. Zard 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 Professor Sir 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.