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Carbon Radical Attack on a Pyrimidine Nitrogen. An Unusual Entry into Polycyclic Aminopyrimidones

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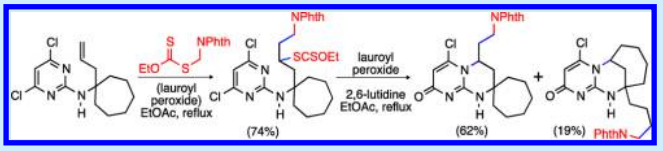
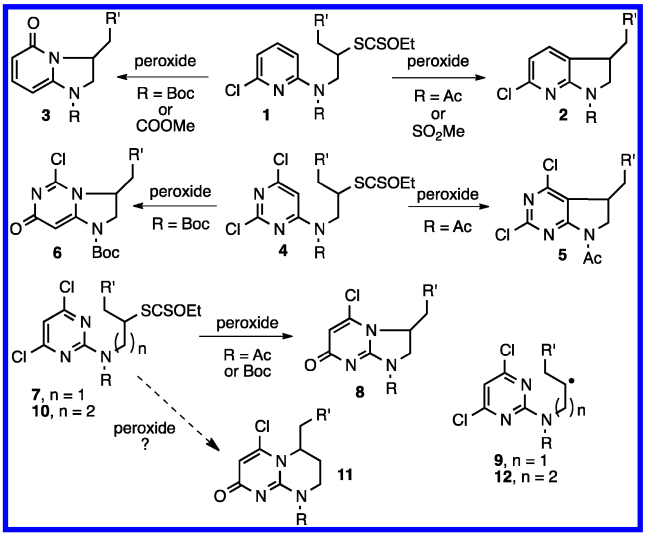
Supporting Information

ABSTRACT: Unprecedented examples of a synthetically useful radical ring closure onto a pyrimidine nitrogen leading to novel, highly functionalized bi- and tricyclic pyrimidone structures are reported. An unexpected hydrogen atom translocation prior to the cyclization step was observed in some cases.



We recently observed the dramatic effect a protecting group exhibited on the regioselectivity and outcome of a radical cyclization on a pyridine ring.[1] We found that the radical derived from xanthate **1**, with an acetyl or a mesyl group on the extranuclear nitrogen (R = Ac or SO_2Me), cyclizes in the usual manner to give ultimately the expected azaindoline product **2** (Scheme 1). In striking contrast, and for reasons still not clear,[2]

Scheme 1. Unexpected Cyclizations



the mere replacement of the nitrogen protection by a Boc group or any other carbamate (R = Boc or COOMe) results in the formation of a totally unexpected pyridone product **3** through a hitherto unprecedented radical ring closure *on the nitrogen atom of the pyridine nucleus*. The presence of the chlorine (or a fluorine) atom adjacent to the nitrogen is necessary; otherwise, the reaction is not clean.

We have been able to extend this chemistry to the pyrimidine series, where two possibilities arise, depending on the position of the nitrogen substituent.[3] In the case of derivatives **4**, the acetyl-protected substrate **4** (R = Ac) furnishes diazaindoline **5**, whereas carbamate analogue **4** (R = Boc or COOMe) undergoes attack on the pyrimidine nitrogen leading to bicyclic pyrimidone **6** as the major product, under otherwise identical experimental conditions. In the case of symmetrical precursor **7**, the bicyclic pyrimidone **8** is obtained, despite the nature of the protecting group on the extranuclear nitrogen. The symmetrical intermediate carbon radical **9** is able to attack *either of the pyrimidine nitrogens* to finally give the same pyrimidone **8**.

Not surprisingly, the process in this last instance is significantly more efficient in terms of yield. This tempted us to extend the cyclization to the more difficult case of a six-membered ring formation, by starting with the homologous precursor **10**. This would allow us to attain the more elusive bicyclic pyrimidone **11** through cyclization of radical **12** (Scheme 1).

The synthesis of the requisite precursors **16a,b**, outlined in Scheme 2, is trivial. It simply involves the protection of aminopyrimidine **13**, itself derived by the reaction of 2,4,6-trichloropyrimidine with 3-butenylamine, by acetylation (**14a**) or by *tert*-butoxycarbonylation (**14b**). Lauroyl peroxide (DLP) mediated radical addition of *S*-cyanomethyl xanthate **15** affords the respective adducts **16a** and **16b** in high yield.[4] Disappointingly, no cyclized product **17a** or **17b** was formed upon exposure of either precursor to stoichiometric amounts of DLP in refluxing EtOAc. A rather complex mixture of products was formed in each case, in which the prematurely reduced uncyclized substances could be identified as the main components by NMR spectroscopy.

In the hope of diminishing the degrees of freedom in the side chain and perhaps encourage cyclization on one of the two pyrimidine nitrogens, we examined the behavior of adduct **19** derived by addition of the same xanthate **15** to alkene **18** (Scheme 2). The latter was available to us as a side product in a previous study, in which we had found that cyclization on *the*

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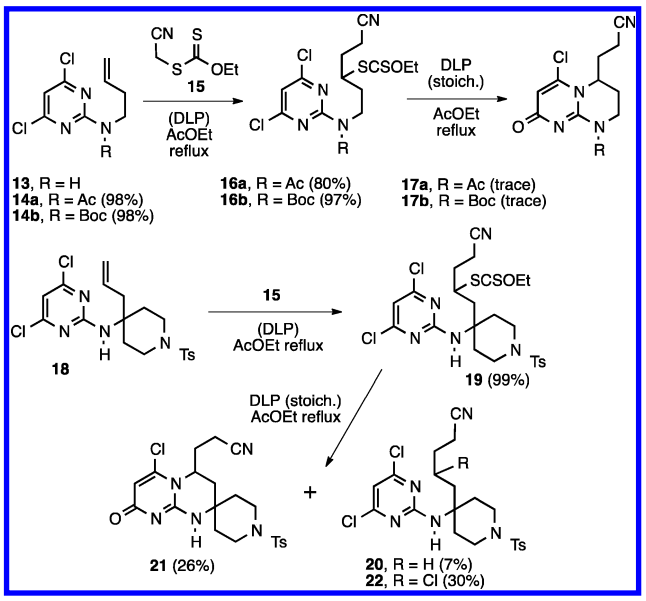
Scheme 2. Synthesis of a Bicyclic Pyrimidone

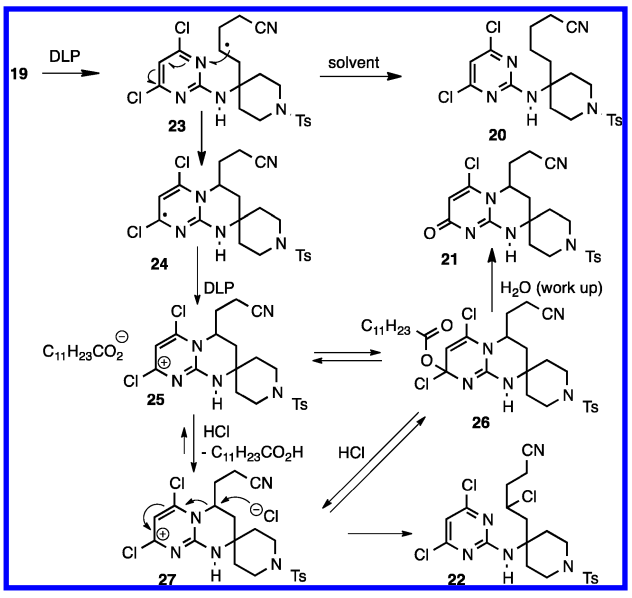


carbon of pyridines and pyrimidines was possible even with a naked extranuclear nitrogen.[5]

We therefore subjected compound **19** to the action of stoichiometric amounts of DLP in refluxing ethyl acetate and isolated three main products from the reaction mixture (Scheme 2). The minor component (7%) was the reduced, uncyclized compound **20**, but the next main product turned out to be the desired bicyclic pyrimidone **21** (26%). More surprisingly, the third product proved to be the totally unexpected chloride **22** (30%).

This last compound presumably arises from the ring opening of intermediate **27** by the chloride anion, as depicted in Scheme 3. This reactive intermediate would result from the action of hydrogen chloride on ion-pair **25**, which has a laurate counteranion. This ion pair is produced upon oxidation of the cyclized radical **24** by electron transfer to the peroxide and combines rapidly but also reversibly into neutral structure **26**.

Scheme 3. An Unexpected Chloride Formation



The equilibrium almost certainly favors the latter in a nonpolar medium with a low dielectric constant. Hydrolysis of **26** upon workup furnishes the desired pyrimidone **21**. Capture of cationic species **25** and **27** by adventitious water also gives pyrimidone **21**.

Removal of the HCl from the medium would limit the formation of cationic species **27** from either precursor **25** or **26** and consequently hinder the undesired generation of chloride **22**. Since both the desired pyrimidone **21** and chloride **22** arise from the same precursors, suppression of the latter would increase the yield of the former to synthetically respectable levels.

We therefore repeated the cyclization in the presence of calcium carbonate as a harmless solid scavenger of HCl Unfortunately, the yield of pyrimidone **21** improved only marginally to 34%. In contrast, the addition of 2,6-lutidine, a sterically hindered base we knew from past experience to be generally compatible with the radical chemistry of xanthates, had an almost dramatic effect: the yield nearly doubled to 53% and became almost comparable to the yields we had observed in the formation of five-membered rings. Clearly, the soluble, hindered lutidine is a faster scavenger for HCl and thus efficiently blocks the formation of unwanted chloride **22**.

With a potential route to an interesting family of heterocycles, we next briefly explored its scope. Using the same alkene, we first varied the xanthate component. The results are presented in Scheme 4. In addition to the nitrile present in pyrimidone **21**, an ester (**29**), a ketone (**31**), a trifluoromethyl group (**33**), and a phthalimido-protected amine (**35**) could also be introduced. While the yields for the intermolecular addition were generally high, those of the cyclization step were fair to modest, reflecting the inherently difficult ring-closure process. In the case of the trifluoromethyl substituted product **33**,[6] the slow cyclization is further aggravated by a polarity mismatch between the intermediate carbon radical, the SOMO of which is lowered by the presence of the strongly electron-withdrawing CF_3-group, and the electrophilic dichloropyrimidine ring.[7] We found that lowering the concentration in this case from 0.05 to 0.01 M increased the yield to 50%.

The piperidine could be replaced without loss of efficiency by a simple cyclohexyl (**38**) or a cyclopentyl ring (**41** and **43**), or even by a *geminal* diethyl motif (**46**). However, when substrate **48**, derived from alkene **47** and possessing a cycloheptane ring, was examined, we were surprised to find that the reaction gave two products in high combined yield (Scheme 5). The major product was the expected pyrimidone **50**, formed in a typical yield of 62%, whereas the minor product turned out to be bridged tricyclic compound **52**, isolated in 19% yield.

Clearly, because of the greater flexibility of the seven-membered ring and the sluggish cyclization step, intermediate radical **49** is able to abstract a hydrogen to give isomeric radical **51**, which can also ring-close on the nitrogen of the pyrimidine to give rearranged product **52**. While the translocation step is in principle reversible, in view of the similar stabilities of radicals **49** and **51**, it is not clear if an equilibrium is indeed established under the reaction conditions.[8]

Interestingly, we found that the addition of *S*-trifluoromethyl-*O*-octadecyl xanthate to alkene **47** furnished, in addition to the expected adduct **53**, a small amount of the translocated isomer **54**. Further exposure to lauroyl peroxide gave rise to the linear and bridged tricyclic derivatives **55** (27%) and **56** (26%), respectively (Scheme 5). Because of the strongly electron-withdrawing nature of the CF_3-group, the hydrogen abstraction

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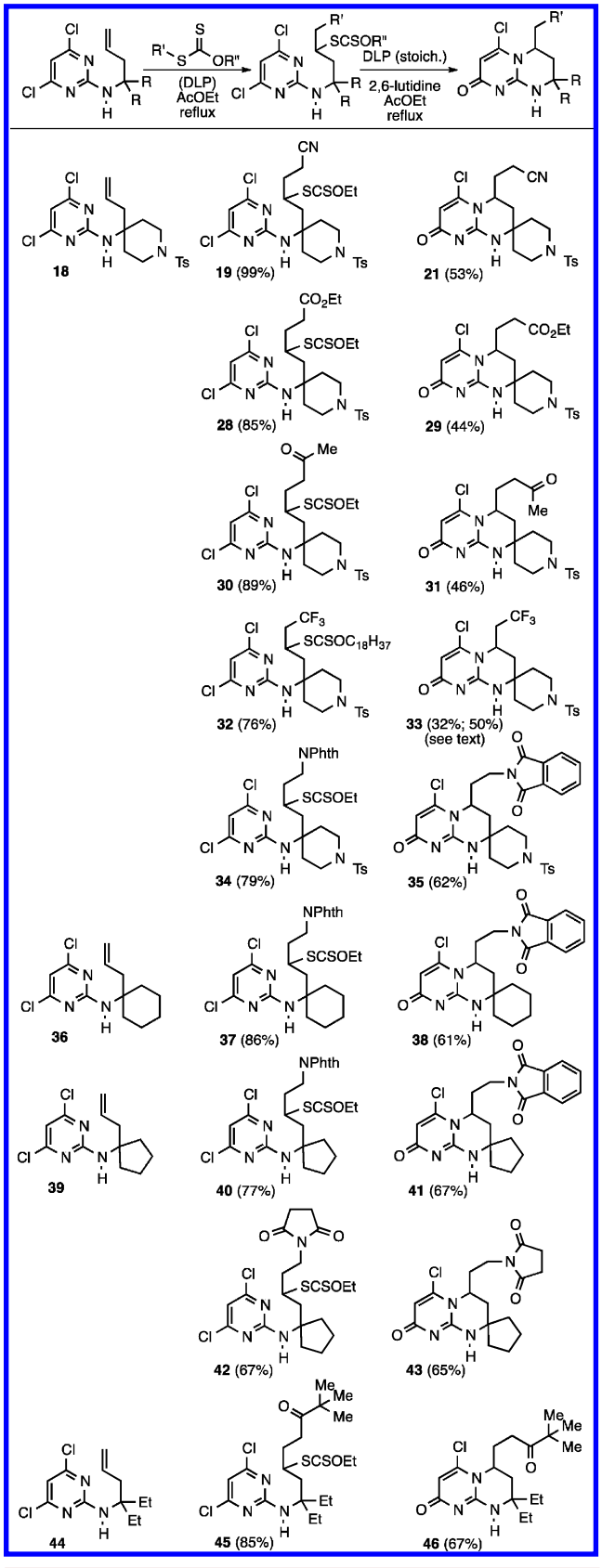
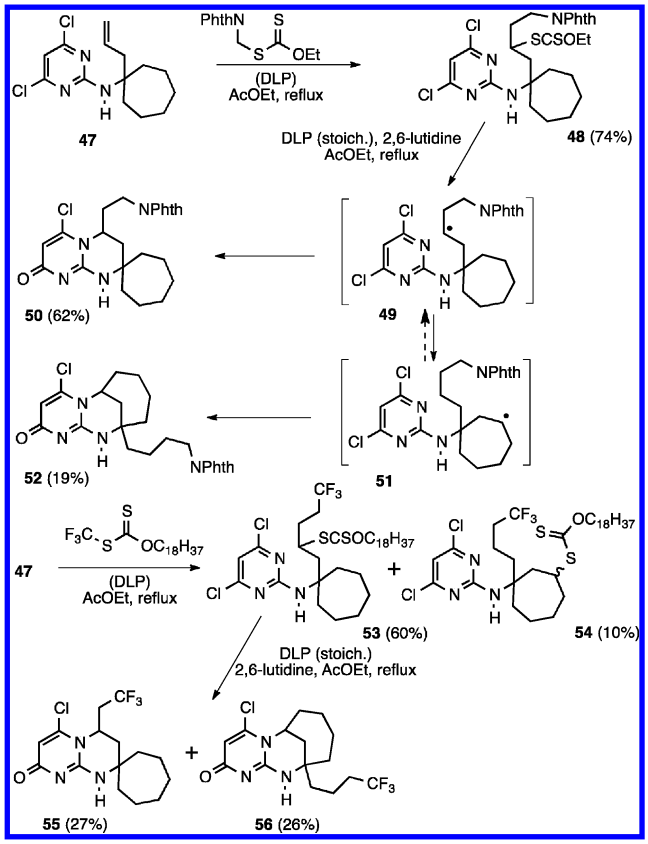
Scheme 4. Synthesis of Bicyclic Pyrimidones



becomes significantly faster, allowing the observation of uncyclized isomeric xanthate **54**. We have exploited in the past these accelerating polar effects to cheaply prepare various

Scheme 5. Unexpected Hydrogen Atom Transfer and Cyclization



deoxysugars and to accomplish deiodination of iodolactones using cyclohexane as the hydrogen atom source.[9]

In the case of xanthate **58**, derived from isobutyl-substituted alkene **57**, the reaction furnished rearranged bicyclic pyrimidone **62**, accompanied by some reduced, uncyclized material **60** and, surprisingly, by the radical Smiles rearranged product **65** (Scheme 6). No significant "normal" cyclized product was observed. Presumably, with only one substituent next to the extranuclear nitrogen atom, the Thorpe−Ingold effect is not as effective in promoting the ring closure of intermediate radical **59**, resulting in a competition between hydrogen abstraction from the solvent and intramolecular abstraction of the tertiary hydrogen in the isobutyl side chain. The latter pathway culminates in the formation of rearranged bicyclic pyrimidone **62**. A third competing pathway involves formation of spiro radical **63** followed by fragmentation to give aminyl radical **64**, which abstracts a hydrogen from the solvent and then reacts ionically with lauroyl peroxide to give the final rearranged lauramide **65**. While well-documented, radical Smiles rearrangements leading to the direct formation of nitrogen centered radicals are relatively uncommon.[10]

The present study reports several examples of the hitherto exceedingly rare radical attacks on a nitrogen atom leading to the formation of six-membered rings, and the first involving a heteroaromatic nitrogen. Much remains to be done to better delineate the scope of the process, in particular as regards the effect of substituents and possible extension to other nitrogen heteroaromatic systems. Nevertheless, the compounds presently accessible by this expedient approach would be very difficult to obtain by other routes. Indeed, the bicyclic aminopyrimidone core skeleton has rarely been described in

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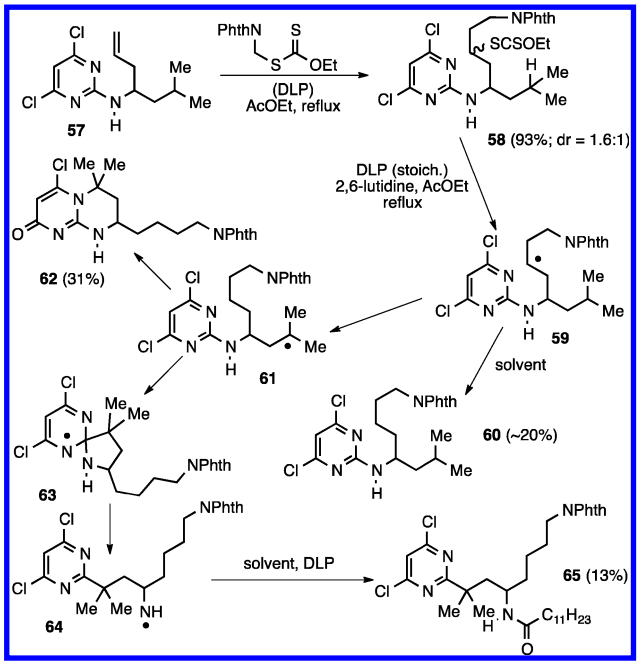
Scheme 6. Further Examples of Hydrogen Atom Transfers and Cyclizations



the literature, with most examples being derived from a modification of uridine and thymidine.[11] Recently, plant protection chemists at BASF patented the parent structure with a simple benzyl group on the extranuclear nitrogen as an agent for pest control.[11h] The present synthesis is modular, metal-free, and tolerant of various functional groups and, thus, offers numerous opportunities for postmodification and for the construction of diverse libraries for biological testing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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