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Expedient Approach to Novel N-Unprotected Bicyclic Azapyrimidine and Pyridine Structures

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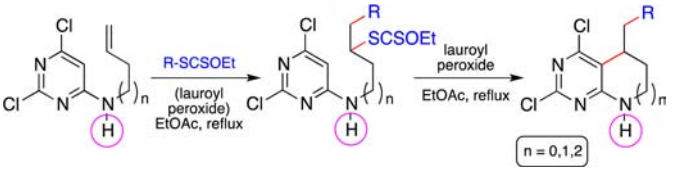
ABSTRACT

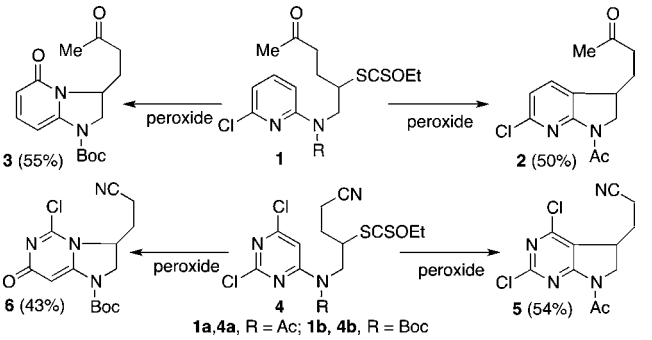


A direct route to novel bicyclic *N*-unprotected azapyrimidine structures including fused five-, six-, and seven-membered rings is described involving radical addition and cyclization of xanthates; this approach could be partially extended to pyridines.

Heterocyclic and heteroaromatic compounds constitute by far the largest proportion of drugs in clinical use. It is therefore not surprising that access to novel heterocyclic and heteroaromatic derivatives remains at the heart of research in medicinal chemistry.[1] As part of our ongoing exploration of the scope of the radical addition-transfer of xanthates, we have established their unique potential for the construction of very diverse heterocyclic and heteroaromatic structures.[2,3] In the course of this study, we uncovered a dramatic effect of the protecting group on nitrogen on the regioselectivity of the radical cyclization in the pyridine and pyrimidine series.[4]

A sample of our observations is displayed in Scheme 1. When an acetyl (or a sulfonyl) group is present on the nitrogen of the side chain, as in **1a** and **4a**, the cyclization proceeds as expected to give aza- or diazaindolines **2** and **5**; however, in the presence of a carbamate, such as the Boc group in **1b** and **4b**, the radical attack takes place on the ring nitrogen. This hitherto unprecedented reaction pathway ultimately leads to pyridinone and pyrimidone structures such as **3** and **6**. The remarkable, and totally unexpected, effect of the nitrogen substituent raised the question as to what would be the outcome in the *absence* of a substituent. Cyclizations on aromatic or heteroaromatic rings starting with a naked extranuclear nitrogen, such as **1** and **4** with R = H, had never been performed as far as we are aware; we were therefore curious to explore the regiochemistry of the cyclization.

Scheme 1. Divergent Radical Cyclizations



(1) (a) Ward, R. A.; Kettle, J. G. *J. Med. Chem.* **2011**, *54*, 4670. (b) Pitt, W. R.; Parry, D. M.; Perry, B. G.; Groom, C. R. *J. Med. Chem.* **2009**, *52*, 2952. (c) Lovering, F.; Bikker, J.; Humblet, C. *J. Med. Chem.* **2009**, *52*, 6752.

(2) For reviews on the xanthate radical transfer reaction, see: (a) Zard, S. Z. *Angew. Chem., Int. Ed.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Chem.—Eur. J.* **2006**, *12*, 6002. (c) Quiclet-Sire, B.; Zard, S. Z. *Top. Curr. Chem.* **2006**, *264*, 201. (d) Zard, S. Z. *Aust. J. Chem.* **2006**, *59*, 663. (e) Quiclet-Sire, B.; Zard, S. Z. *Pure Appl. Chem.* **2011**, *83*, 519.

(3) For a review, see: El Qacemi, M.; Petit, L.; Quiclet-Sire, B.; Zard, S. Z. *Org. Biomol. Chem.* **2012**, *10*, 5707.

(4) (a) El Qacemi, M.; Ricard, L.; Zard, S. Z. *Chem. Commun.* **2006**, *42*, 4422. (b) Laot, Y.; Petit, L.; Zard, S. Z. *Chem. Commun.* **2010**, *46*, 5784.

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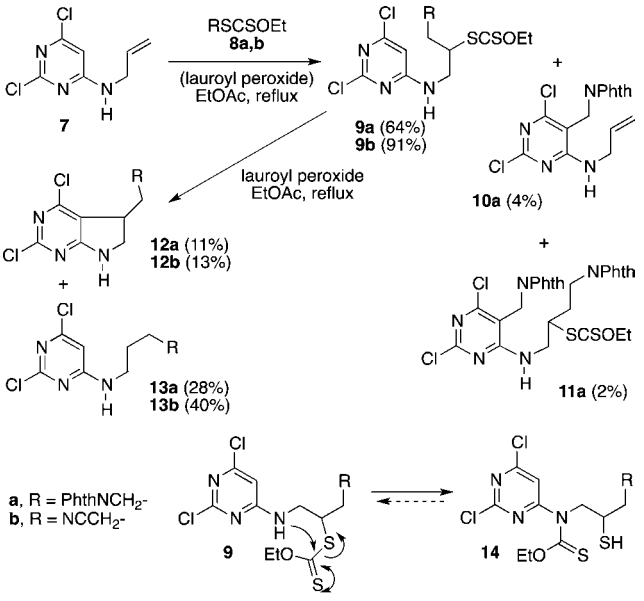
Previously, the protecting group on the extranuclear nitrogen (and also the chlorine atoms on the ring) was introduced to avoid any inter- or intramolecular attack on the xanthate by a nucleophilic nitrogen, resulting in the formation of thiols, which are inhibitors of the radical chain.[5] It seemed to us, at least in the dichloropyrimidine series, that the heteroaromatic ring would exert a sufficient electron pull on the extranuclear nitrogen to obviate the need for a protecting group, thus allowing both radical addition and cyclization to be performed directly on the parent compound.

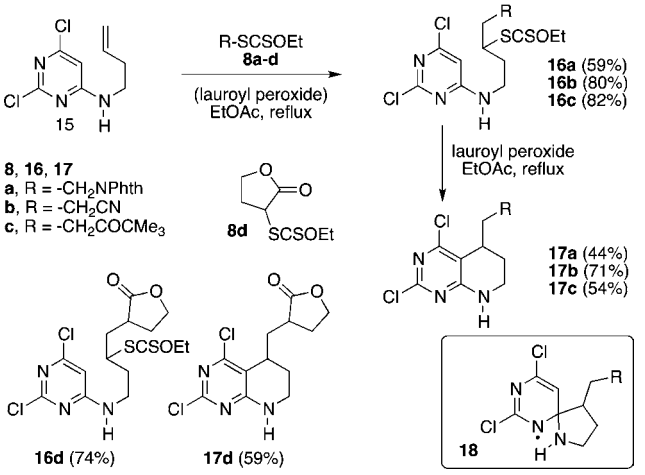
Scheme 2. Inefficient Route to Diazaindolines (PhthN− = Phthalimido)



Lauroyl peroxide initiated addition of both *S*-phthalimidomethyl- and cyanomethylxanthates **8a** an **8b** on unprotected *N*-allylaminodichloropyrimidine **7** to give **9a** and **9b** indeed proceeded in good yield (Scheme 2).[6] In the case of the former, very minor amounts of compounds **10a** and **11a** were observed, resulting from direct addition to the heteroaromatic nucleus.[7] However, the subsequent radical cyclization step proved disappointing and furnished only a very modest yield (10−15%) of diazaindolines **12a**,**b**. Varying amounts of prematurely reduced material **13a**,**b** were also isolated from a rather complex reaction mixture, but no cyclization on the nitrogen atom of the pyrimidine was observed.

Although the little cyclization that took place proceeded on the carbon atom of the pyrimidine ring, it was initially surprising that the cyclization of xanthates **9** should be so much less efficient in comparison to that of the protected analogues **4**, especially since there was no particular problem in principle arising from slow rotation and unfavorable rotamer population, as in the well-known case of unsubstitued amides.[8] Nevertheless, one positive aspect of these preliminary experiments is that the feared *S*- to *N*-migration of the alkoxythiocarbonyl group leading to the unwanted thiol **14**, a serious inhibitor of the radical chain, was indeed not a complicating factor in this case.

Scheme 3. Synthesis of Tetrahydroazanaphthyridines



Notwithstanding this setback, we explored the homologous series and were pleased to find that a similar sequence starting with unprotected (*N*-butenylamino)-dichloropyrimidine **15** furnished the desired cyclized products in much higher yield (Scheme 3). Thus, addition of xanthates **8a**−**d** to **15** gave the corresponding adducts **16a**−**d** in 59% to 82% yield. Further treatment with stoichiometric amounts of lauroyl peroxide afforded tetrahydroazanaphthyridines **17a**−**d** in synthetically useful yield. Interestingly, no side products derived from an *ipso* radical substitution (cf. **18**) were observed in these cyclizations. Such radical Smiles rearrangements on related structures are known.[9] Even more surprising, unprotected pyrimidoazepines **21a**,**b**,**e**,**f** could be readily obtained by subjecting (*N*-pentenylamino)dichloropyrimidine **19** to the same sequence (Scheme 4). In the case of **20f** and **21f**, the two diastereoisomers were separable. The formation of a seven-membered ring by direct radical cyclization on an aromatic ring is quite rare, and all approaches essentially rely on xanthate technology.[5,10] The fact that the cyclization could

(5) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 3671.

(6) In Schemes 2−7, placing lauroyl peroxide in parentheses indicates that it is used as the initiator in substoichiometric amounts. No parentheses means that the peroxide is used both as initiator and as a stoichiometric oxidant.

(7) Osornio, Y. M.; Cruz-Almanza, R.; Jimenez-Montano, V.; Miranda, L. D. *Chem. Commun.* **2003**, 2316.

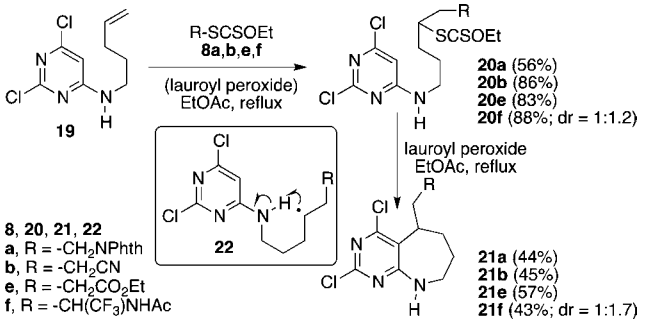
(8) Yamasaki, R.; Tanatani, A.; Azumaya, I.; Saito, S.; Yamaguchi, K.; Kagechika, H. *Org. Lett.* **2003**, *5*, 1265and references cited therein.

(9) (a) Studer, A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds; Wiley-VCH: Weinheim, 2001; Vol. 2, p 44. (b) Studer, A.; Bossart, M. *Tetrahedon* **2001**, *57*, 9649. (c) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Org. Lett.* **2005**, *7*, 3817.

(10) (a) Kaoudi, T.; Quiclet-Sire, B.; Seguin, S.; Zard, S. Z. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 731. (b) Petit, L.; Botez, I.; Tizot, A.; Zard, S. Z. *Tetrahedron Lett.* **2012**, *53*, 3220. (c) Charrier, N.; Liu, Z.; Zard, S. Z. *Org. Lett.* **2012**, *14*, 2018. (d) Bacqué, E.; El Qacemi, M.; Zard, S. Z. *Heterocycles* **2012**, *84*, 291. (e) Quiclet-Sire, B.; Tran, N. D. M.; Zard, S. Z. *Org. Lett.* **2012**, *14*, 5514.

be accomplished with an unprotected extranuclear nitrogen atom is certainly not trivial because of the likelihood of an intramolecular abstraction of the aminyl hydrogen (cf. **22**). The strength of the N−H in anilines is comparable to that of a benzylic C−H, and aniline derivatives are sometimes used as radical chain inhibitors.[11]

Scheme 4. Synthesis of Pyrimidoazepines



We observed a more complicated trend in the pyridine series. Thus, while the intermolecular addition to *N*-alkenylfluoropyridines **23**, **26**, and **30** proceeded reasonably efficiently, treatment of the resulting adducts with stoichiometric amounts of peroxide in the usual manner furnished a moderate yield of tetrahydronaphthyridine **28** from **27** but did not produce any of the corresponding azainoline **25** or pyridoazepine **32** from adducts **24** and **31a**, respectively. Prematurely reduced compounds **29** and **33a** were the main side products in the cyclization of xanthates **27** and **31a**. These results are summarized in Scheme 5.

It is unusual for radical cyclizations leading to six- and seven-membered rings to prove more efficient than those leading to five-membered rings. The reasons underlying the inefficiency in the formation of diazaindolines **12** are not clear but may be related to unfavorable bond angles resulting in increased strain in the transition state leading to the fused five-membered ring. The small size of the hydrogen atom allows the opening of C−N−C bond angle and thus favors the formation of the larger ring. This phenomenon is well documented in radical cyclizations.[12] While no values are available for the compounds at hand, the C−N−C bond angle in the closely related 4-methylaminopyridine **34*t***, even with a small methyl substituent, has been calculated to be 124.2°. This value is larger than the 120° expected for a completely sp^2-hybridized extranuclear nitrogen atom (Scheme 6).[13] Interestingly, the *trans*-rotamer **34*t***, with a conformation propitious for cyclization, was found to be 1.4 kcal/mol *more stable* than the *cis*-rotamer **34*c***.

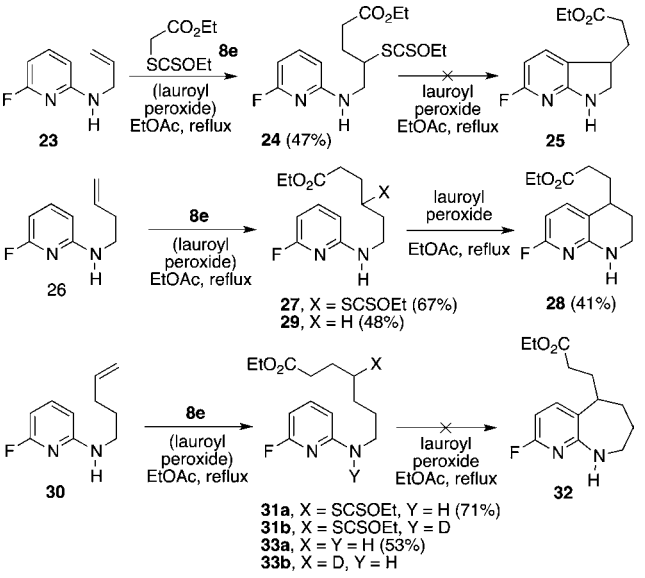
The lack of cyclization leading to a seven-membered ring in the pyridine series was nevertheless puzzling. Although the feared 1,5-hydrogen atom transfer (cf. **22**) did not

(11) Pratt, D. A.; DiLabio, G. A.; Mulder, P.; Ingold, K. U. *Acc. Chem. Res.* **2004**, *37*, 334.

(12) Broeker, J. L.; Houk, K. N. *J. Org. Chem.* **1991**, *56*, 3651.

(13) Akai, N.; Ohno, K.; Aida, M. *J. Photochem. Photobiol. A* **2007**, *187*, 113.

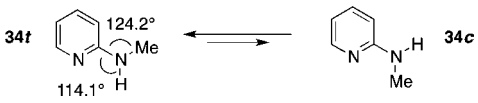
Scheme 5. Synthesis of a Tetrahydronaphthyridine



materialize to any significant extent in the case of the pyrimidine derivatives, it could nevertheless prevail with the less electrophilic pyridine ring. Polar effects are known to influence considerably the rate of hydrogen atom abstractions.[14] We therefore repeated the cyclization experiment with deuterated substrate **31b** and indeed observed partial intramolecular deuterium abstraction. About 20−25% (by MS) of reduced deuterated product **33b** was formed (see the Supporting Information for details). The proportion of intramolecular abstraction in the case of the nondeuterated analogue **33a** must be much higher because of the kinetic isotope effect (an N−H bond is slightly weaker than an N−D bond).[15]

The competition with the untoward radical translocation is further compounded by an intrinsically slower ring-closure step due to the greater aromaticity and lower electrophilicity of the 2-fluoropyridine nucleus. With the more electrophilic dichloropyrimidine, not only is the rate of ring-closure increased, because of a polarity match with the mildly nucleophilic carbon radical, but the hydrogen atom shift is also slowed down. The net result is a clean formation of the seven-membered ring.

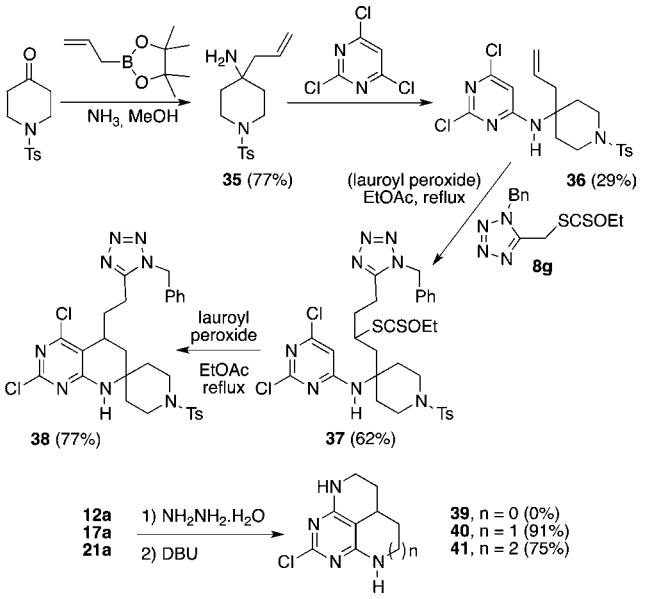
Scheme 6. Bond Angles in 2-(*N*-Methylamino)pyridine



The present approach is modular, flexible, and concise. Indeed, both the intermolecular addition and cyclization can be combined in a one-pot procedure, since the same

(14) Tedder, J. M. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 401.

Scheme 7. Access to Spirocyclic and Fused Tricyclic Structures



peroxide and solvent are used in both steps; only the concentration differs. Thus, **17b** and **21b** were obtained in comparable overall yield, 41% and 34% respectively, by simply diluting the reaction medium, once TLC monitoring indicated that the intermolecular addition of xanthate **8b** to alkenes **15** and **19** was essentially complete, and adding portionwise a stoichiometric amount of lauroyl peroxide.

Bicyclic pyrimidine derivatives such as **17** and, especially, **21** are rare and hitherto not readily available core structures.[16] The expedient access to complex derivatives, only tediously available by conventional ionic or organometallic routes, is further illustrated by the synthesis of spiro derivative **38** from xanthate **37** displayed in Scheme 7. The radical cyclization step proved remarkably efficient in this case, and the precursor alkenes **35** and **36** are readily available using known chemistry.[17]

Finally, the incorporation of various functional groups contained in the xanthate partner and the presence of the two chlorines on the pyrimidine ring provide a simple means for constructing another ring by an ionic process. Compounds **17a** and **21a** may thus be converted into the novel tricyclic compounds **40** and **41** after cleavage of the phthalimido group with hydrazine. This cyclization failed with **12a** presumably because of increased strain in the expected product **39**.

In summary, apart from highlighting a facile route to polycyclic pyrimidine and, to a lesser extent, pyridine derivatives, this study has revealed a relatively rare situation where the formation of a five-membered ring is much less efficient than the corresponding ring closure leading to six- and seven-membered rings.[18]

Acknowledgment. This paper is dedicated with respect to the memory of Professor Alessandro Degl'Innocenti (University of Florence). We thank Ecole Polytechnique and Master Ile-de-France/Fudan University for scholarships to Z.L. and L.Q.

Supporting Information Available. 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.

(15) The slower abstraction of deuterium, because of the primary kinetic isotope effect, has been exploited to circumvent synthetic hurdles caused by unwanted intramolecular hydrogen atom shifts: (a) Wood, M. E.; Bissiriou, S.; Lowe, C.; Norrish, A. M.; Sénéchal, K.; Windeatt, K. M.; Coles, S. J.; Hursthouse, M. B. *Org. Biomol. Chem.* **2010**, *8*, 4653. (b) Wood, M. E.; Bissiriou, S.; Lowe, C.; Windeatt, K. M. *Org. Biomol. Chem.* **2008**, *6*, 3048. (c) Clive, D. L. J.; Cantin, M.; Khodabocus, A.; Kong, X.; Tao, Y. *Tetrahedron* **1993**, *49*, 7917. (d) Clive, D. L. J.; Tao, Y.; Khodabocus, A.; Wu, Y. -J.; Angoh, A. G.; Bennett, S. M.; Boddy, C. N.; Bordeleau, L.; Kellner, D.; Gleiner, G .; Middleton, D. S.; Nichols, C. J.; Richardson, S. R.; Vernon, P . G. *J. Am. Chem. Soc.* **1994**, *116*, 11275.

(16) (a) El Kaïm, L.; Grimaud, L.; Oble, J. *J. Org. Chem.* **2007**, *72*, 5835. (b) LaLonde, R. T.; El-Kafrawy, A.; Muhammad, N.; Oatis, J. E., Jr. *J. Org. Chem.* **1977**, *42*, 1808. (c) Kuyper, L. F.; Garvey, J. M.; Baccanari, D. P.; Champness, J. N.; Stammers, D. K.; Beddell, C. R. *Bioorg. Med. Chem.* **1996**, *4*, 593. (d) Gossett, L. S.; Habeck, L. L.; Shackelford, K. A.; Mendelsohn, L. G.; Gates, S. B.; Worzalla, J. F.; Self, T. D.; Theobald, K. S.; Andis, S. L.; Schultz, R. M.; Shih, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 75. (e) St-Denis, Y.; Di Fabio, R.; Bernasconi, G.; Castiglioni, E.; Contini, S.; Donati, D.; Fazzolari, E.; Gentile, G.; Ghirlanda, D.; Marchionni, C.; Messina, F.; Micheli, F.; Pavone, F.; Pasquarello, A.; Sabbatini, F. M.; Zampori, M. G.; Arban, R.; Vitulli, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3713. (f) Provins, L.; Christophe, B.; Danhaive, P.; Dulieu, J.; Durieu, V.; Gillard, M.; Lebon, F.; Lengelé, S.; Quéré, L.; van Keulen, B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1834. (g) Morita, K.; Kobayashi, S.; Shimadzu, H.; Ochiai, M. *Tetrahedron Lett.* **1970**, *11*, 861. (h) Boger, D. L.; Kochanny, M. J. *J. Org. Chem.* **1994**, *59*, 4950.

(17) (a) Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182. (b) Dhudshia, B.; Tiburcio, J.; Thadani, A. N. *Chem. Commun.* **2005**, *41*, 5551The modest yield of precursor **36** is due to competing substitution at the 2-position of the 2,4,6-trichloropyrimidine ring.

(18) For another related instance, see ref 10e.

The authors declare no competing financial interest.