Pergamon

Tetrahedron Letters 40 (1999) 3701–3704

TETRAHEDRON LETTERS

A Flexible, Convergent Approach to Piperidines, Pyridines, Azepines, and Related Derivatives

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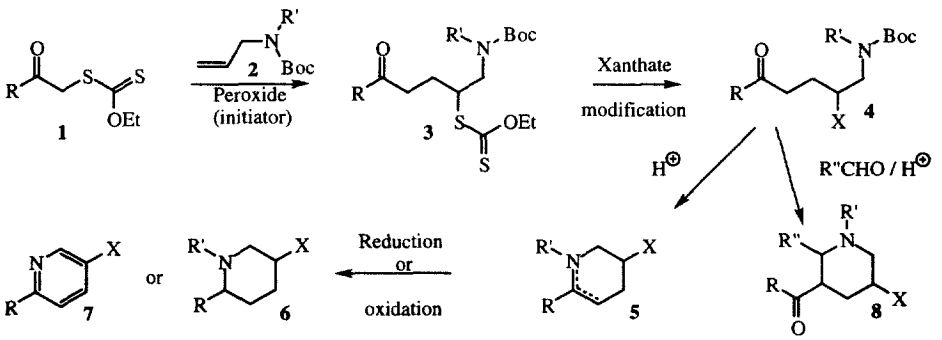
Received 8 February 1999; accepted 18 March 1999

Abstract : A highly convergent approach has been developed for the construction of various nitrogen heterocycles using as the key step the intermolecular addition of an α-ketonyl radical onto a suitably protected allylic or homoallylic amine.

Piperidines, pyridines, azepines, and related structures are ubiquitous in alkaloids and in man-made substances possessing biological activity.[1] The importance of these nitrogen heterocyclic derivatives to the pharmaceutical industry has spurred a great amount of research, and numerous methods have been devised for their construction.[2] In the course of our work on the radical chemistry of xanthates, we have found that radicals with a variety of substituents can be generated and captured in an *intermolecular* fashion with an *unactivated*, preferably unhindered, olefin.[3] We now have found that by combining the intermolecular radical addition with an ionic cyclisation, a convergent and highly flexible approach to a plethora of nitrogen containing 6- or 7-membered heterocyclic structures can be easily implemented.



Scheme 1

If the starting xanthate is derived from a ketone, as in **1**, and if the olefin contains a protected amine in the allylic position as in **2**, then the adduct, **3**, following modification or removal of the xanthate group, can be made to close upon itself, leading in an easy manner to a tetrahydropyridine structure **5**, as summarised in **Scheme 1**. The tetrahydropyridine **5** can then be reduced into a piperidine **6** or oxidised to a pyridine derivative **7**; alternatively, a Mannich reaction on intermediate **4** gives a piperidine **8** with a different

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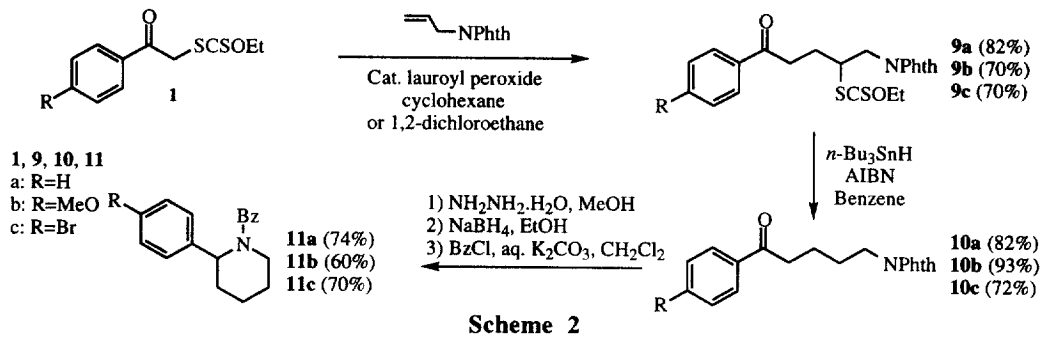
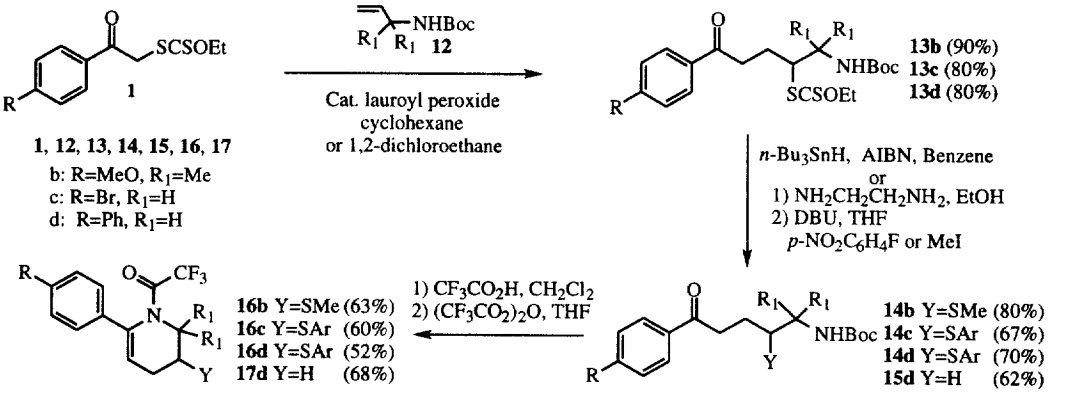
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00592-4

substitution pattern. For simplicity, only a minimum of substituents has been included but the substrates can of course contain many more appendages or ring structures.



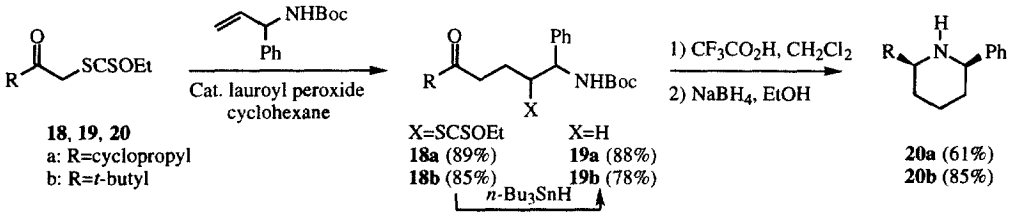
Scheme 2

In a preliminary study adducts **9a-c**[4] were prepared by radical addition of the xanthates derived from the corresponding α-bromoacetophenones onto *N*-allyphthalimide in good yield (**Scheme 2**). The xanthate moiety in the adducts was then reductively removed using *n*-Bu_3SnH in benzene to give **10a-c**. Finally the cleavage of the phthalimide group[5] with hydrazine afforded the corresponding cyclic imines which were reduced in situ to piperidines with sodium borohydride in absolute ethanol, and converted for convenience into benzamides **11a-c** in 60%-75% overall yield.



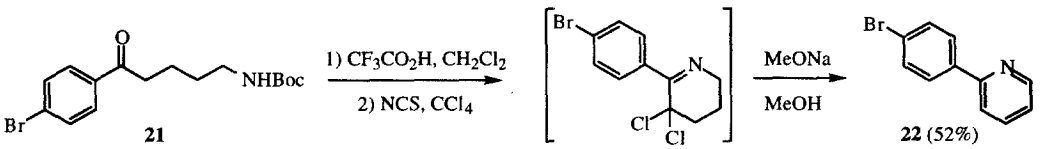
Scheme 3

In a second set of experiments, aiming at the elaboration of more complex structures, three radical adducts **13b-d** were obtained in good yields using the more versatile *N*-Boc protected allylic amines **12** .[7] In one case, the xanthate group was removed with Bu_3SnH leading to **15d**; but for the others, it was cleaved into the corresponding thiol and either alkylated with methyl iodide to give **14b** or converted into *p*-nitrophenylsulfides **14c** and **14d**. Cleavage of the carbamate afforded cyclic imines which were characterized[8] as their *N*-trifluoroacetenamides **16b-d** and **17d**, in fair overall yield. (**Scheme 3**).



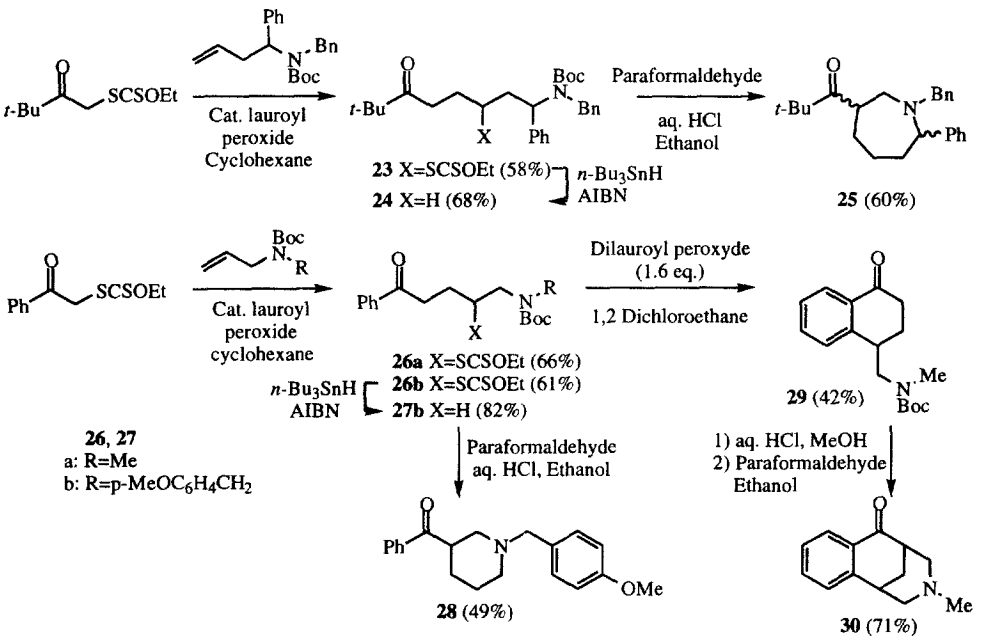
Scheme 4

Although these first experiments were performed using aromatic ketones to show the feasibility of the process, this approach was readily extended to the aliphatic series as demonstrated by the synthesis of piperidines **20a-b**, both obtained as single diastereomers (**Scheme 4**). The stereochemistry in the case of **20a** possessing the interesting cyclopropyl group was confirmed by a NOE experiment.



Scheme 5

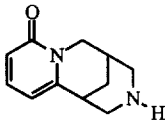
The intermediate imines can also be oxidized into pyridines according to the methodology developed by de Kimpe *et al*.[9] Thus, after dichlorination with N-chlorosuccinimide of the imine derived from **21**, exposure to sodium methoxide in methanol afforded pyridine **22** in 52% yield (**Scheme 5**).



Scheme 6

The flexibility of this strategy was further highlighted by combining the radical process with a Mannich reaction.[10] (**Scheme 6**) In this way azepine **25**[11] was obtained from reduced adduct **24** in 60% yield,

whereas **28** was derived from precursor **27b**, albeit in a lower yield (49%). Finally, the xanthate group in adduct **26a** was used to obtain tetralone **29** by a radical cyclisation onto the aromatic ring.[12] After some experimentation, we found that the Mannich reaction in this example was best accomplished by first forming the hydrochloride salt of the amine following removal of the Boc group before treatment with formaldehyde. This allowed the efficient synthesis of the tricyclic derivative **30** in 71% yield. This compound, which has been made with some difficulty in the past,[13,14] is an analogue of cytisine, a potent acetylcholine receptors agonist.



Cytisine

In summary we have developed a convergent, versatile strategy to access a wide range of cyclic nitrogen structures.[15] The possibility of performing an intermolecular addition provides a simple way to bring together an amine and a ketone function at a suitable distance to allow 6- or 7-membered ring formation.

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15. Selected spectral data: **11c:** ^{1}H NMR ($CDCl_3$): δ 7.48-7.38 (m, 5H); 7.24 (d, *J*=8.6 Hz, 2H); 6.92 (d, *J*=8.8Hz, 2H); 3.82 (s, 3H); 2.90-2.85 (m, 3H); 2.41-2.34 (m, 1H); 2.00-1.85 (m, 1H); 1.85-1.60 (m, 6H); ^{13}C NMR ($CDCl_3$): δ 171.3; 158.6; 136.8; 131.1; 129.4; 128.5; 127.8; 126.5; 114.3; 55.3; 28.1; 26.1; 19.7; two broad peaks at 53.5 and 41.0 (rotamers). Calculated %C 77.25 %H 7.16. Found %C 77.01 %H 7.24. **16b**: ^{1}H NMR ($CDCl_3$): δ 7.18 (d, J=8.4 Hz, 2H); 6.88 (d, J=8.4 Hz, 2H); 5.07 (bs, 1H); 3.81 (s, 3H); 3.09 (dd, J_1=20.9 hz, J_2=10.4 Hz, 1H); 2.69 (s, 1H); 2.24 (s, 3H); 1.43 (s, 3H); 1.29 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 176.2 (q, $J_{C\text{-}F}$=31 Hz); 160.9; 160.2; 130.1; 129.4; 117.9 (q, $J_{C\text{-}F}$= 292Hz); 114.0; 96.4; 55.6; 55.4; 51.0; 28.6; 27.5; 23.9; 16.1. Calculated %C 56.80 %H 5.61. Found %C 56.61 %H 5.63. **20a**: ^{1}H NMR ($CDCl_3$): δ 7.43(d, *J*=7.3 Hz, 2H); 7.35 (t, *J*= 7.3 Hz, 2H); 7.28-7.25 (m, 1H); 3.59 (dd, J_1=10.7 Hz; J_2= 2.3 Hz, 1H); 2.03 (bs, 1H); 1.93-1.91(m, 1H); 1.85-1.75 (m, 4H); 1.47-1.42 (m, 4H); 0.89 (m, 1H); 0.51-0.45 (m, 2H); 0.21-0.19 (m, 1H); 0.14-0.12 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 145.9; 128.5; 127.2; 127.0; 64.1; 62.9; 35.0; 32.0; 25.6; 17.7; 3.0; 2.4. Calculated %C 83.53 %H 9.51. Found %C 83.62 %H 9.39. Three compounds are already known: : **11a**: Sashida, H.; Tsuchiya, T. *Chem. Pharm. Bull.* **1984**, *32*, 4117-4123; **22:** Gutierrez, M.A.; Newkome, G.R.; Selbin, J. *J. Organomet. Chem.*, **1980**, *202*, 341-350; and **30**: refs. 13 and 14.