A Convergent and Flexible Approach to Hydroxylamines, Hydrazines and Related Structures

Béatrice Quiclet-Sire, Benoît Sortais, Samir Z. Zard*

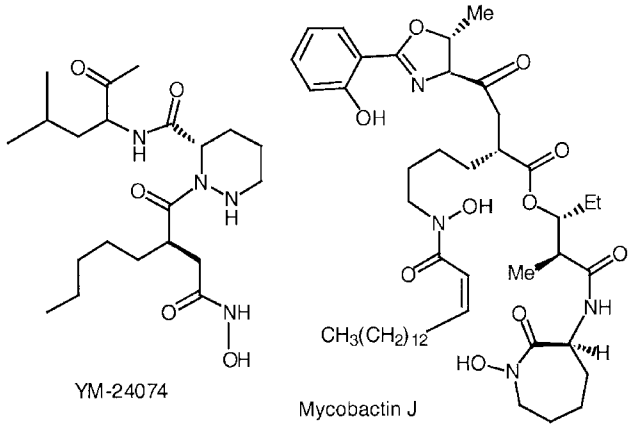
Laboratoire de Synthèse Organique associé au CNRS, Ecole Polytechnique, 91128 Palaiseau, France
Fax +33(169)333851; E-mail: zard@poly.polytechnique.fr

Received 22 March 2002

Abstract: Intermolecular xanthate transfer radical addition to protected allyl hydroxylamine or hydrazine provides a new, flexible, and convergent route to adducts which can be readily elaborated into complex aromatic or heterocyclic hydroxylamine or hydrazine derivatives.

Key words: hydrazines, hydroxylamines, xanthates, radical reactions

Hydroxylamine and hydrazine based functions, especially hydroxamic acids and hydrazides, are present in a number of biologically active natural products.[1] These include siderophores, such as mycobactin J (Figure),[1f] matrix metalloproteinase inhibitors, and some antibiotics and antifungals, such as compound YM-24074,[1g] a peptide antibiotic, which contains both a hydroxamic and a cyclic hydrazide subunit (Figure; only two of the three asymmetric centers have been determined).



Figure

Traditional routes to such compounds have relied mostly on the alkylation and acylation of simple hydroxylamine or hydrazine derivatives and on the partial reduction of, or addition of organometallic reagents to oximes, nitrones, and hydrazones.[2] Except for the acylation, where a complex acylating agent may be used, these methods are often limited to simple structures and are intolerant of many functional groups, which have to be protected beforehand.

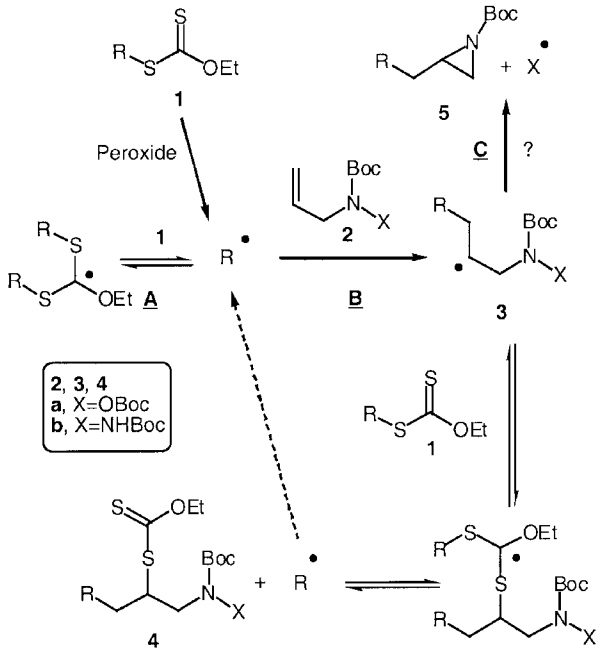
We have, over the past few years, shown that xanthates (and related dithiocarbonic acid derivatives) readily undergo a group transfer radical addition, allowing the intra- and especially inter-molecular creation of new C–C bonds even on unactivated olefins.[3] The superiority of this technology derives from its generality, mildness, and absence of heavy metals and other ecologically unacceptable ingredients. As part of our ongoing study, we have now found that complex hydroxylamine and hydrazine structures can be readily assembled through a radical addition to Boc protected *N*-allyl-hydroxylamine **2a** or hydrazine **2b**.[4]

The general mechanism outlining the principle of the process is shown in Scheme 1. Radical R$^{\bullet}$, generated from xanthate **1**, has a relatively long effective lifetime in the medium, since it is not consumed by reaction with its precursor (path **A** is reversible and degenerate), and can therefore add to the unactivated olefinic bond of the trap (path **B**). Reversible exchange of xanthate finally produces the adduct **4** and regenerates R$^{\bullet}$ to propagate the chain. In the present case, we were concerned by the possibility that intermediate radical **3** might undergo an S_H2 substitution on the nitrogen to give an aziridine **5** by cleavage of relatively weak N–O or N–N bond (path **C**). Such a behaviour has indeed been observed in the case of allylic peroxides, which readily produce epoxides.[5]

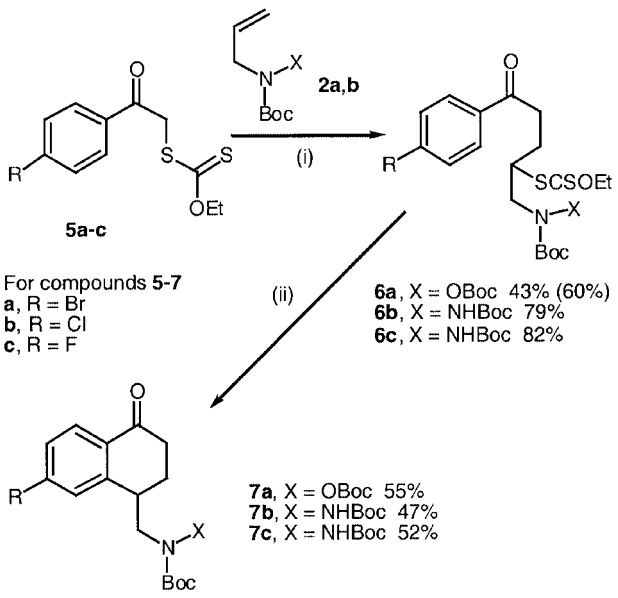
In the event, our worries about an S_H2 side reaction via path **C** were unfounded. We first tested this approach by the synthesis of α-tetralones **7a**–**c**, as depicted in Scheme 2. Thus, heating a solution of *S*-*p*-bromophenacyl xanthate **5a** and protected allylhydroxylamine **2a** in refluxing 1,2-dichloroethane with the periodic addition of a small amount of lauroyl peroxide, resulted in the formation of the expected adduct **6a** in 43% yield (60% based on recovered starting material). Exposure of this compound to a stoichiometric amount of the peroxide (added portion-wise) induced a second C–C bond formation through ring closure onto the aromatic ring to give tetralone **7a** in 55% yield.[6] In a similar fashion, protected allylhydrazine **2b** was converted first into adducts **6b** and **6c** in 79% and 82% yield respectively, then into the corresponding tetralones **7b** and **7c** by treatment with stoichiometric amounts of peroxide.

Synlett 2002, No. 6, 04 06 2002. Article Identifier:
1437-2096,E;2002,0,06,0903,0906,ftx,en;D06502ST.pdf.

ISSN 0936-5214

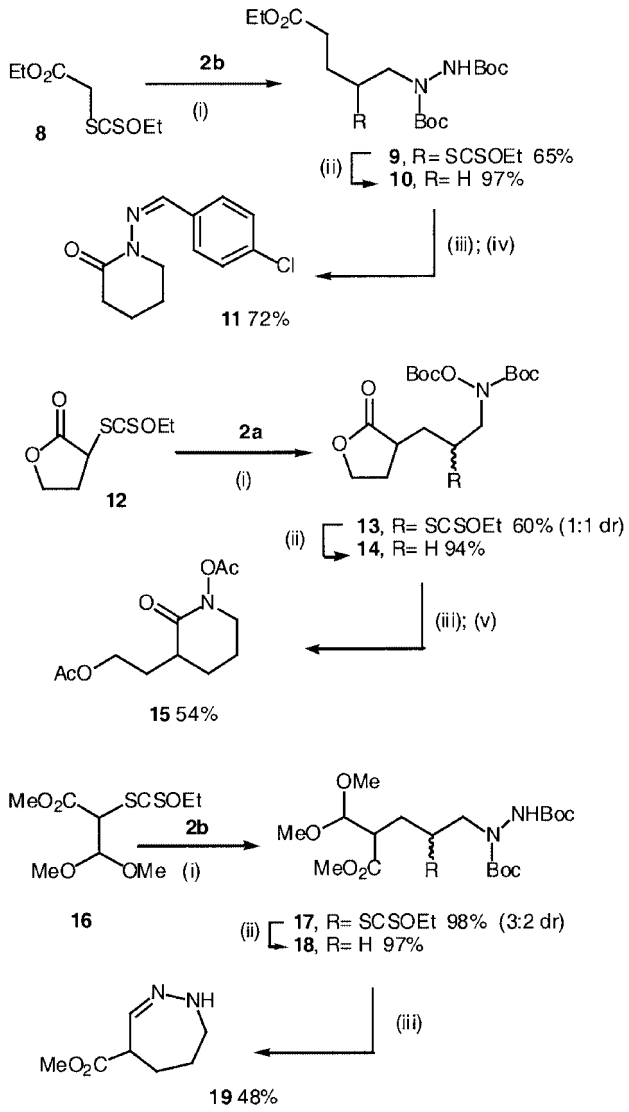


Scheme 1



Scheme 2 (i) Lauroyl peroxide (10–15 mol%), $(CH_2Cl)_2$, reflux. (ii) Lauroyl peroxide (1–1.15 equiv), $(CH_2Cl)_2$, reflux. (yield in parenthesis is based on recovered starting material).

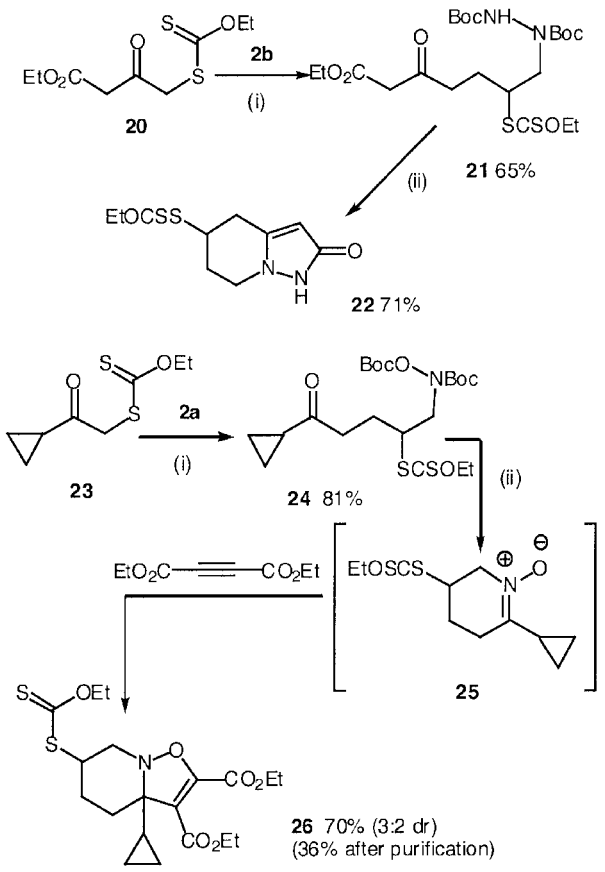
This methodology could be easily extended to the synthesis of useful heterocycles, as illustrated by the examples in Scheme 3. Thus, addition of xanthate **8** to olefin **2b** gave the expected addition product **9**, from which the xanthate group was reductively removed with tri-*n*-butylstannane in nearly quantitative yield. Exposure of the resulting product **10** to the action of trifluoroacetic acid in 1,2-dichloroethane, followed by triethylamine afforded *N*-amino-2-piperidone in 75% yield. To facilitate isolation and characterization, this was converted into the known hydrazone **11**[7] by condensation with *p*-chlorobenzaldehyde. A similar sequence starting from lactone **12** and olefin **2a** provided first adduct **13**, then a cyclic hydroxamic acid, characterized as its diacetate **15** in reasonable overall yield.



Scheme 3 (i) Lauroyl peroxide (10–15 mol%), $(CH_2Cl)_2$, reflux. (ii) Bu_3SnH (AIBN), toluene, reflux. (iii) TFA, $(CH_2Cl)_2$; TEA, $(CH_2Cl)_2$. (iv) *p*-Chlorobenzaldehyde, EtOH, reflux. (v) Ac_2O, pyridine.

The versatility of this convergent approach to heterocyclic ring construction was further demonstrated by varying the functions present in the xanthate partner. Addition of compound **16** to olefin **2b** occurred with remarkable efficiency, giving the corresponding adduct **17** in almost quantitative yield. Reductive removal of the xanthate then treatment with trifluoroacetic acid followed by buffering with triethylamine gave rise to the seven membered ring hydrazone **19**. As anticipated, the aldehyde reacted in preference to the ester group to give the relatively rare [1,2] diazepine structure.[8]

The xanthate group, in the preceding examples was removed for convenience. More densely functionalized structures may be constructed by omitting the reduction step. For instance, reaction of xanthate **20** with protected allyl hydrazine **2b** afforded the corresponding addition product **21**, which underwent acid mediated deprotection and double ring closure to furnish bicyclic pyrazolone **22** in a useful overall yield (Scheme 4). It is interesting to note that the formation of compound **21** represents ultimately an elongation at position 4 of ethyl acetoacetate, performed under neutral conditions. Using ionic chemistry, the creation of new C–C bonds at this position requires the prior formation of either the strongly basic dianion of the acetoacetate or the bis-(silyl enol ether) under Lewis acid catalysis.[9] Xanthate **20**, trivially made by displacing the chloride from commercially available ethyl 4-chloroacetoacetate with potassium *O*-ethyl xanthate, is thus a very convenient reagent, which complements by its reactivity the more common ionic processes.



Scheme 4 (i) Lauroyl peroxide (15–40 mol%), $(CH_2Cl)_2$, reflux. (ii) TFA, $(CH_2Cl)_2$, reflux.

Finally, the expedient generation and capture of a complex nitrone is illustrated by the second example in Scheme 3. Addition of xanthate **23** to olefin **2a** proceeded efficiently to adduct **24** in 81% yield. Deprotection with trifluoroacetic acid was followed by spontaneous cyclisation to nitrone **25**, which was not isolated but trapped by addition of diethyl acetylenedicarboxylate to give bicyclic hydroxylamine **26** in 70% crude yield. Some decomposition occurred upon purification by distillation.

In summary, we have described a simple, yet highly efficient and flexible route to a variety of hydroxylamine and hydrazine derivatives, many of which would be difficult to obtain by more conventional methods.[10] The reagents are cheap and readily available, and the reaction conditions sufficiently mild to tolerate many of the functional groups encountered in modern organic synthesis.

References

(1) (a) Surnam, M. D.; Miller, M. J. *J. Org. Chem.* **2001**, *66*, 2466; and numerous references there cited. (b) Miller, M. J. *Chem. Rev.* **1989**, *89*, 1563. (c) Michaelides, M. R.; Curtin, M. L. *Curr. Pharm. Des.* **1999**, *5*, 787. (d) Nikam, S. S.; Kornberg, B. E.; Johnson, D. R.; Doherty, A. M. *Tetrahedron Lett.* **1995**, *36*, 197. (e) Karunartne, V.; Hoveyda, H. R.; Orvig, C. *Tetrahedron Lett.* **1992**, *33*, 1827. (f) Schwartz, B. D.; De Voss, J. J. *Tetrahedron Lett.* **2001**, *42*, 3653. (g) Sato, T.; Takebayashi, Y.; Tokunaga, T.; Ozasa, T. *J. Antibiot.* **1996**, *49*, 811.

(2) (a) Wroblonsky, H.-J.; Andree, R.; Kluth, J. F. In *Methoden der Organischen Chemie (Houben-Weyl)*, Vol. E16a; Klamann, D., Ed.; Georg Thieme Verlag: Stuttgart, **1990**, 1. (b) Jensen-Korte, U.; Müller, N. In *Methoden der Organischen Chemie (Houben-Weyl)*, Vol. E16a; Klamann, D., Ed.; Georg Thieme Verlag: Stuttgart, **1990**, 421. (c) Chang, Z.-Y.; Coates, R. M. *J. Org. Chem.* **1990**, *55*, 3464. (d) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. *J. Org. Chem.* **1996**, *61*, 9028; and references there cited.

(3) (a) Zard, S. Z. *Angew.Chem., Int. Ed. Engl.* **1997**, *36*, 672. (b) Quiclet-Sire, B.; Zard, S. Z. *Phosphorus, Sulfur, Silicon* **1999**, 153. (c) Zard, S. Z. *Angew.Chem., Int. Ed. Engl.* **1997**, *36*, 137. (d) Zard, S. Z. *J. Chin. Chem. Soc.* **1999**, *46*, 139. (e) For addition of xanthates to allyl amines, see: Boivin, J.; Pothier, J.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 3701.

(4) (a) Staszak, M. A.; Doecke, C. W. *Tetrahedron Lett.* **1993**, *34*, 7043. (b) Mellor, S. L.; Chan, W. C. *Chem. Commun.* **1997**, 2005. (c) Genet, J. P.; Thorimbert, S.; Touzin, A. M. *Tetrahedron Lett.* **1993**, *34*, 1159. (d) Maëorg, U.; Ragnarsson, U. *Tetrahedron Lett.* **1998**, *39*, 681.

(5) (a) Ramon, F.; Degueil-Castaing, M.; Maillard, B. *J. Org. Chem.* **1996**, *61*, 2071. (b) Ramon, F.; Degueil-Castaing, M.; Maillard, B. *Tetrahedron* **1998**, *54*, 11489; and references there cited.

(6) Liard, A.; Quiclet-Sire, B.; Saicic, R. N.; Zard, S. Z. *Tetrahedron Lett.* **1997**, *38*, 1759.

(7) Smith, P. A. S.; Pars, H. G. *J. Org. Chem.* **1959**, *24*, 1325.

(8) For some examples see: (a) Kane, J. M.; Stewart, K. T. *J. Heterocycl. Chem.* **1988**, *25*, 1471. (b) Kalyanam, K. G.; Likhate, M. A. *Synth. Commun.* **1988**, *18*, 2183. (c) Zimmerman, H. E.; Eberbach, W. *J. Am. Chem. Soc.* **1973**, *95*, 3970.

(9) (a) Huckin, S. N.; Weiler, L. *J. Am. Chem Soc.* **1974**, *96*, 1082. (b) Chan, T.-H.; Brownbridge, P. *J. Chem. Soc., Chem. Commun.* **1979**, 578. (c) Hagiwara, H.; Kimura, K.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1992**, 693.

(10) **Typical Procedure for 19**: Lauroyl peroxide (10–15 mol%) was added portion-wise (in 3–4 portions over several hours) to a degassed, refluxing solution of 800 mg (2 mmol) of xanthate **16** and 1.1 g (4.0 mmol) of olefin **2b** in 2 mL of 1,2-dichloroethane under argon. The reaction was regularly monitored for the disappearance of the starting material by thin layer chromatography. Upon completion, the solvent

was removed under reduced pressure and the residue purified by chromatography on silica gel (heptane/EtOAc 98/2–95/5) to give compound **17** (1.58 g, 98%) as a colourless oil; it consisted of a 3:2 mixture of diastereoisomers, which were used without further purification in the next step. ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): δ = 6.72 (bs, 1 H, NH), 4.62 (q, 2 H, OCH_2, *J* = 6.5 Hz), 4.52 (d, 1 H, CH, *J* = 7.2 Hz), 4.01–3.79 (m, 3 H, CH_2N, CHS), 3.71 (s, 3 H, $COOCH_3$), 3.35 (s, 3 H, OCH_3), 3.31 (s, 3 H, OCH_3), 3.08–3.02 (m, 0.6 H, CHCOO), 2.99–2.91 (m, 0.4 H, CHCOO), 2.14–1.79 (m, 2 H, CH_2), 1.60 (s, 18 H, $6CH_3$), 1.59 (t, 3 H, CH_3, *J* = 6.5 Hz); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): δ = 211.6 (CS), 172.4 (COO), 154.5–154.4 (2 COO), 104.1/104.0 (CH), 81.2–80.9 (2 Cq, Boc), 69.9 (OCH_2), 54.4–54.2 (2 CH_3), 53.0/52.9 (NCH_2), 51.8 (CH_3), 47.7/46.7 (CHS), 45.2 (CHCOO), 46.1 (CH_2), 27.9 (CH_3), 13.5 (CH_3); IR (CCl_4): 3326 (m), 1736(vs), 1479 (m), 1443 (m), 1394 (m), 1368 (m), 1220 (s), 1155 (s), 1051 (s)cm^{-1}.

A solution of xanthate **17** (800 mg, 1.5 mmol), Bu_3SnH (0.75 mL), and AIBN (22 mg) in benzene (15 mL) was heated to reflux for 2 h under an inert atmosphere. The solvent was then removed under reduced pressure and the residue was purified by chromatography on silica gel (pentane→heptane–EtOAc, 7:3) to give **18** (602 mg, 97%) as a colourless oil. This material was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz, ppm): δ = 6.58 (s, 1 H, NH), 4.50 (d, 1 H, CH), 3.69 (s, 3 H, $COOCH_3$), 3.53–3.34 (m, 2 H, CH_2N), 3.35 (s, 3 H, OCH_3), 3.34 (s, 3 H, OCH_3), 2.76–2.72 (m, 1 H, CH), 1.68–1.37 (22 H, 2 CH_2 and 6 CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz, ppm): δ = 173.3 (COO), 155.3–155.2 (2 COO), 104.6 (CHO) 80.8–80.7 (2 Cq), 54.5–54.4 (2 CH_3), 52.6 (CH), 51.5 (NCH_2), 48.7 (OCH_3), 28.1 (CH_3), 25.2–25.0 (2 CH_2); IR (CCl_4): 3329 (broad), 1735(vs), 1454 (m), 1398 (m), 1369 (m), 1253 (m), 1161 (s), 1067 (m)cm^{-1}.

A solution of **18** (280 mg, 0.7 mmol) in 1,2-dichloroethane (2 mL) and trifluoroactic acid (2 mL) was stirred for 1 h at r.t. under argon. The mixture was then evaporated under reduced pressure and the residue dissolved in a mixture of 1,2-dichloroethane (2 mL) and triethylamine (2 mL) and kept at r.t. for 48 h. The solvent was removed and the crude residue was extracted with dichoromethane and distilled water. The organic layer was dried over sodium sulfate. Evaporation under reduced pressure and purification by chromatography on silica gel (heptane–EtOAc, 1:1) afforded **19** as a colourless oil (50 mg, 48%). ^{1}H NMR ($CDCl_3$, 250 MHz, ppm): δ = 6.25 (d, 1 H, CH=, *J* = 7.3 Hz), 3.68 (s, 3 H, $OOCH_3$), 3.04 (m, 1 H, CH), 2.52–2.34 (m, 1 H, NH), 2.34–2.25 (m, 2 H, CH_2N), 2.24–2.12 (m, 2 H, CH_2), 1.94–1.89 (m, 2 H, CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz, ppm): δ = 173.1 (COO), 153.1 (CH=), 53.9 (CH_2N), 51.8 ($OOCH_3$), 46.8 (CH), 27.6 (CH_2), 23.8 (CH_2); IR (CCl_4): 3432, 2947, 1735, 1670, 1322, 1266, 735 cm^{-1}. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74%. Found: C, 53.69; H, 7.51%.