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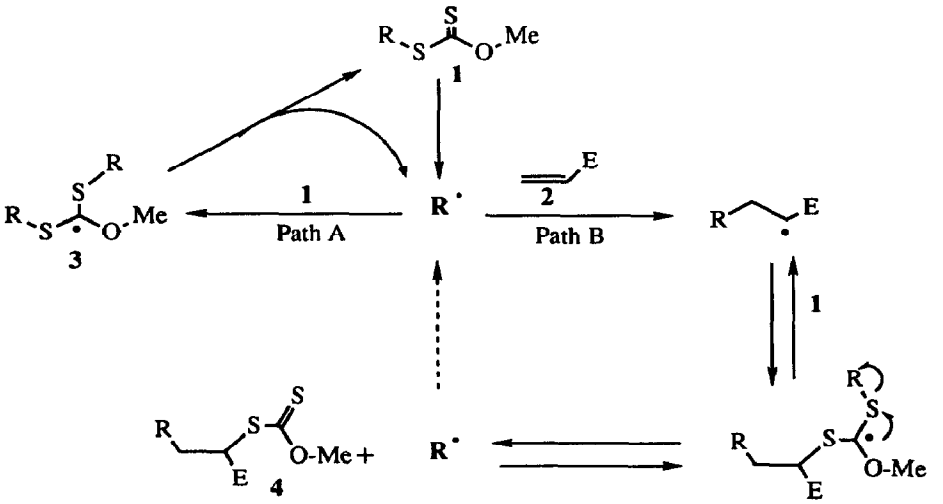
A New Radical Based Synthesis of Lactams and Indolones from Dithiocarbonates (Xanthates)†.

Jonathan Axon, Laurent Boiteau, Jean Boivin, Judith E. Forbes and Samir Z. Zard*
Laboratoire de Synthèse Organique Associé au C. N. R. S.,
Ecole Polytechnique, F-91128 Palaiseau, France.

Abstract. N,N-disubstituted α-(xanthyl)-acetamides with an olefin on one of the substituents undergo cyclisation to a lactam by a radical chain reaction involving transfer of the xanthate group; anilides lead to the corresponding indolones.

In a recent series of papers we have shown that xanthates such as **1** constituted a convenient and practical source of a variety of radicals including alkyl, acyl, alkoxycarbonyl, alkoxythiocarbonyl and even tin centred radicals.[1] The mechanistic reasoning upon which this work hinges is outlined in the scheme below. Thus, a radical R• generated from **1** by chemical or photochemical initiation can be captured by an internal or external olefin **2** to give an intermediate which reacts with the starting material in a dithiocarbonate group transfer propagation step to give finally a new xanthate **4** (scheme, path B).

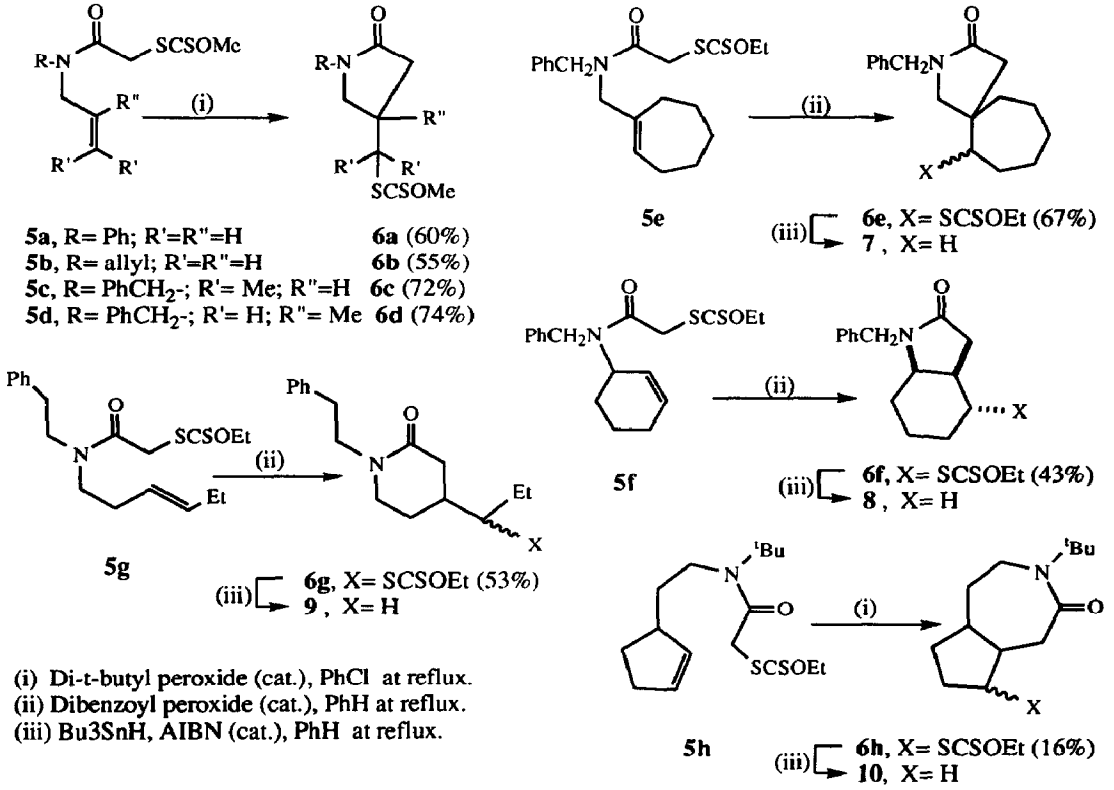


One important advantage of this system is that if radical R• adds to its xanthate precursor before reacting with the trap (i.e path A), the intermediate adduct **3** is symetrical and can only fragment to give back the same radical R• and the starting xanthate **1**. The degeneracy of path A therefore allows the use of relatively unreactive olefinic traps since R• is not consumed by what otherwise would have been a major competing pathway. We now wish to describe the application of this method for the synthesis of various lactams[2] and indolones from the corresponding α-(S-xanthyl)-acetamides and anilides.

† *Dedicated to the memory of Olivier Cyrot, a budding chemist of outstanding talent.*

The key radical cyclisation step leading to the lactam is a relatively slow process due to an unfavourable conformation and restricted rotation around the carbonyl group of the amide[3]. Bulky substituents on the nitrogen and substituents α- to the carbonyl group (especially heteroatoms and electron withdrawing groups) have been found to increase the rate of cyclisation. This can cause a dramatic improvement in the yield of lactams in the case of tin hydride based procedures where premature irreversible hydrogen abstraction from the stannane is a serious competing side reaction.[2] A more interesting approach involves the use of halogen transfer methods (Kharasch type reactions) since the intermediate radicals have intrinsically a longer effective lifetime[4] allowing them to undergo more difficult cyclisations. Our novel process involving xanthates belongs to the latter class and possesses therefore all its inherent advantages.

The precursor xanthates **5a-h** are easily prepared from the appropriate α-haloacetamide by treatment with potassium methyl or ethyl xanthate. Upon heating in chlorobenzene in the presence of a small amount of di-t-butyl peroxide as initiator[8] a smooth reaction occured over several hours to give the desired lactam **6a-h** in the yields indicated.



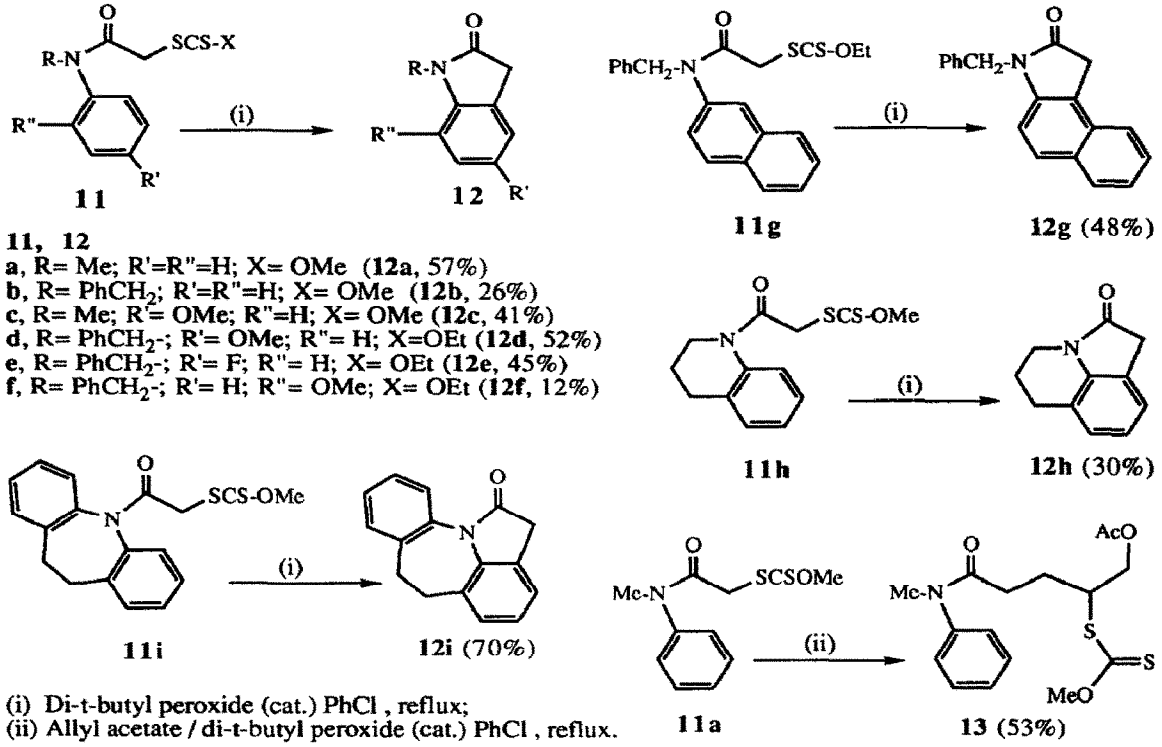
5a, R= Ph; R'=R"=H **6a** (60%)
5b, R= allyl; R'=R"=H **6b** (55%)
5c, R= $PhCH_2$-; R'= Me; R"=H **6c** (72%)
5d, R= $PhCH_2$-; R'= H; R"= Me **6d** (74%)

(i) Di-t-butyl peroxide (cat.), PhCl at reflux.
(ii) Dibenzoyl peroxide (cat.), PhH at reflux.
(iii) Bu3SnH, AIBN (cat.), PhH at reflux.

A variety of γ lactams, including spiro and bicyclic structures such as **6e** and **6f**, could be prepared by this procedure in fair to good yield. Dibenzoyl and dilauryl peroxides were also found to be suitable initiators allowing the use of lower boiling solvents such as cyclohexane or benzene. Compound **6f** was obtained as essentially one stereomer. In contrast, spiro lactam **6e** was isolated as a mixture of diastereoisomers. In both cases, for characterisation purposes, the xanthate group was removed with tributyl stannane to give derivatives **7** and **8** in high yield. Six and seven membered ring lactams are also accessible,

although the latter only in poor yield. The xanthate groups were again reductively removed with tributylstannane to give **9** and **10** respectively.

Indolone formation by radical cyclisation onto an aromatic ring is a much more difficult process[5] that has hardly been used in practice. It is therefore with some scepticism that we explored the possibility of using the xanthate approach for the construction of such compounds. We were however delighted to find that a variety of indolones **12a-i** could indeed be obtained in reasonable yield from anilides **11a-i**, even though the reactions were sluggish and required several additions of initiator to go to completion. It is clear that with these systems, the radical chains are short due to the inefficiency of the propagation steps. A number of ring substituents such as a para fluoro (**12e**) or methoxy groups (**12c,d,f**) are tolerated. An ortho group, however, has a deleterious effect on the yield (e.g.**12f**), presumably resulting from an unfavourable steric interaction with the substituent on the nitrogen in the transition state. Polycyclic indolones, as examplified by **12g-i**, are also accessible. The regioselectivity in the case of the naphthalene derivative **12g** is in line with earlier observations.[6]

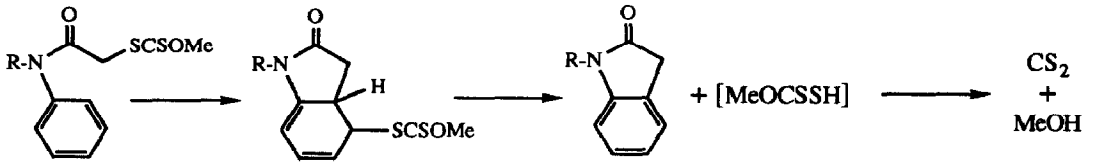


11, 12
a, R= Me; R'=R"=H; X= OMe (**12a**, 57%)
b, R= $PhCH_2$; R'=R"=H; X= OMe (**12b**, 26%)
c, R= Me; R'= OMe; R"=H; X= OMe (**12c**, 41%)
d, R= $PhCH_2$-; R'= OMe; R"= H; X=OEt (**12d**, 52%)
e, R= $PhCH_2$-; R'= F; R"= H; X= OEt (**12e**, 45%)
f, R= $PhCH_2$-; R'= H; R"= OMe; X= OEt (**12f**, 12%)

(i) Di-t-butyl peroxide (cat.) PhCl , reflux;
(ii) Allyl acetate / di-t-butyl peroxide (cat.) PhCl , reflux.

From a mechanistic standpoint, the case of the indolones raises some interesting questions. The cyclisation step is as expected a relatively slow process. For instance, if five equivalents of allyl acetate are incorporated into the reaction mixture, hardly any indolone is formed. The compound that is produced instead is **13** (53%) arising by intermolecular radical addition to the allyl acetate[1g]. Moreover, the aromatisation step occurs by elimination of xanthic acid which is itself a good radical trap in principle since it contains both a thiocarbonyl group and a thiol subunit which can act as a hydrogen atom donor. Its presence

would certainly have suppressed the already short radical chain. Fortunately, xanthic acids are thermally unstable[7] and decompose to carbon disulfide and the corresponding alcohol (methanol or ethanol in our case). These volatile side products are continously removed under our experimental conditions (refluxing chlorobenzene), and thus rendered harmless. This is certainly crucial to the success of the cyclisation.



In summary, this approach to lactams and indolones allies cheapness and simplicity in terms of reagents and experimental procedure[8]. None of the reported yields has been optimized and room for improvement certainly exists. In the case of lactams, a very useful xanthate "handle" is introduced, allowing further elaboration through the exceptionally rich radical or ionic chemistry of organosulfur derivatives.

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4. For an excellent discussion of this point, see: Curran, D. P. *Synthesis* **1988**, 417-439; 489-513.
5. For an example of a related photochemical cyclisation to indolone, see: Hamada, T.; Okuno, Y.; Ohmori, M.; Nishi, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1981**, *29*, 128-136.
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8. Typical experimental procedure: A degassed solution of starting xanthate (1 mmole) and di-t-butyl peroxide (ca 0.05 mmole) in chlorobenzene (5ml) was heated to reflux until thin layer chromatograghic analysis indicated essentially complete reaction (from several hours for lactams to 2-3 days for some indolones; in the case of the latter, a fresh batch of initiator was added every few hours). The reaction mixture was then concentrated and the residue purified by flash chromatography.

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