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A Convergent Approach to Indolines and Indanes

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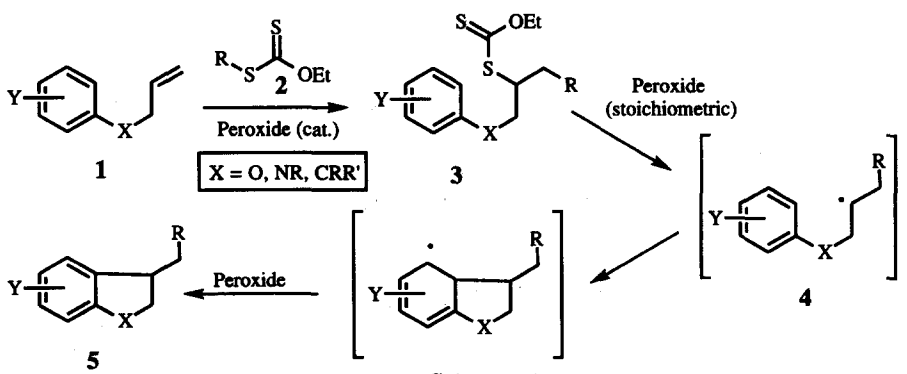
Abstract : Radical addition of a xanthate to an N-allylanilide or to a substituted 4-aryl-1-butene followed by cyclisation onto the aromatic ring provide the corresponding indoline or indane respectively.

Indolines and, but to a much lesser extent, indanes are substructures present in a large number of natural products and in compounds of pharmaceutical importance.[1] Indolines, being also immediate precursors to the ubiquitous indoles, are especially interesting synthetic intermediates.[2] It is not surprising that numerous routes have been devised to access these structures. Most approaches, however, employ ionic or organometallic intermediates; only a few make use of radicals.[3] Even then, a large proportion of the latter synthetic schemes rely on stannane chemistry to generate an aromatic radical which is captured by an internal olefin.[4] Radical cyclisation *onto the aromatic nucleus* has rarely been applied, largely because such additions are relatively slow (on a radical reaction time scale) and hence difficult to accomplish with stannane technology.[5] We have recently found that it is relatively easy to perform such radical cyclisations if the intermediate radicals are given a long enough lifetime through the use of xanthates as radical precursors. We have thus succeeded in constructing oxindoles, α-tetralones, and dihydroisoquinolinones.[6] In the present Letter, we describe preliminary, but very encouraging results related to an expedient and versatile synthesis of indolines and — but with less generality— indanes, and also some interesting observations concerning the extension of this approach to the case of dihydrobenzofurans.



Scheme 1

Our approach is summarised in a simplified form in Scheme 1. Radical addition and xanthate transfer

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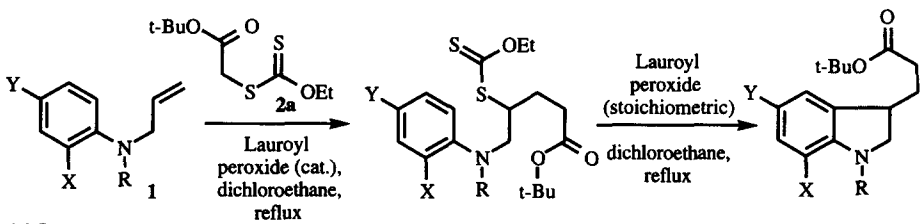
from a suitable xanthate **2** to an olefinic trap of general structure **1** gives an adduct **3** where a new carbon-carbon and carbon-sulfur bonds have been formed.[7] In addition to simplicity, cheapness, absence of heavy metals, ease of scale-up, and the possibility of operating under quite concentrated conditions, this process has one further useful feature in that the end product **3** is also a xanthate that can be used as a starting point for another radical sequence. Thus, upon further exposure to peroxide, radical **4** is regenerated and can now cyclise (possibly reversibly) onto the aromatic ring to give a cyclohexadienyl radical which should be easily aromatised into compound **5**.



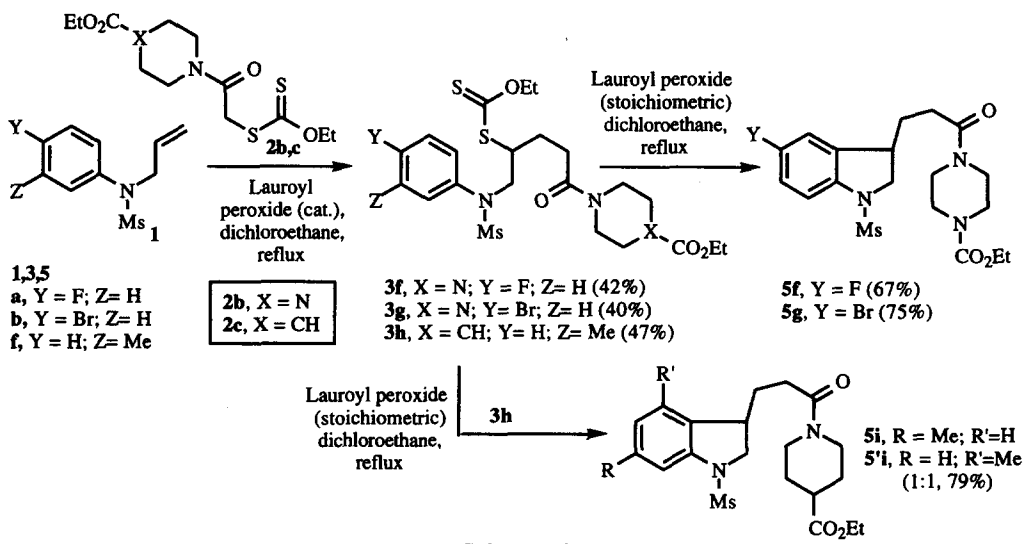
1,3,5
a, X = H; Y = F; R = Ms
b, X = H; Y = Br; R = Ms
c, X = H; Y = OMe; R = Ms
d, X = Y = H; R = Ac
e, X = Y = Cl; R = Ms

3a (81%)
3b (83%)
3c (83%)
3d (57%)
3e (79%)

5a (79%)
5b (76%)
5c (70%)
5d (70%)
5e (—)

Scheme 2

Indeed, radical addition of a number of xanthates **2a-e** to various substituted N-allyl anilides **1a-h** resulted in the formation of the expected adducts **3a-j** which, upon gradual treatment with stoichiometric amounts of lauroyl peroxide xanthates in refluxing dichloroethane,[8] furnished in most cases the corresponding indolines **5a-i** in quite acceptable yields (Schemes 2-4). A small amount of the cyclised product (5-10%) was already formed in the first intermolecular addition, so that the overall yields are in fact slightly better than those indicated.



1,3,5
a, Y = F; Z= H
b, Y = Br; Z= H
f, Y = H; Z= Me

2b, X = N
2c, X = CH

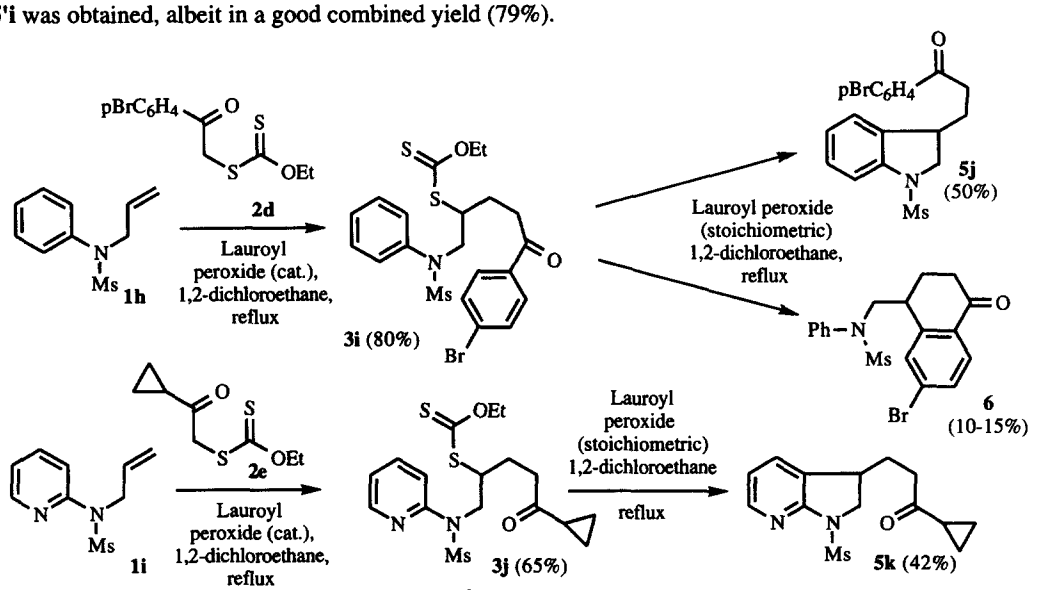
3f, X = N; Y = F; Z= H (42%)
3g, X = N; Y= Br; Z= H (40%)
3h, X = CH; Y= H; Z= Me (47%)

5f, Y = F (67%)
5g, Y = Br (75%)

Scheme 3

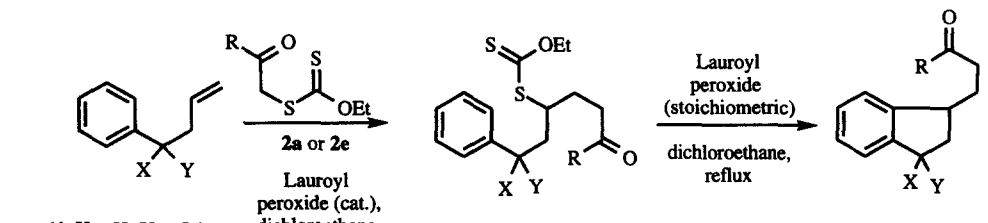
Both electron-withdrawing and electron donating substituents on the aromatic ring are tolerated, allowing access to a great variety of structures and, even if an N-mesyl group was used in most cases for

convenience, a more easily removable N-acyl protection (as in **1d**--> **5d**) is also suitable. However, there appears to be two limitations in the cyclisation step. The first concerns the presence of an ortho-substituent, as in **3e**, which did not undergo the desired ring closure. It is still not clear if this will turn out to be a general observation. The second relates to a meta substituent which, at least in the case of a methyl group in **3h**, did not exert any control of the regiochemistry and an essentially 1:1 mixture of regioisomers **5i** and **5'i** was obtained, albeit in a good combined yield (79%).



Scheme 4

Two examples are shown in Scheme 4 which are worthy of further comments. In xanthate **3i**, the presence of the carbonyl group could in principle activate the bromoaromatic nucleus, thus favouring the six-membered α–tetralone **6** over indoline **5j**. In the event, however, it is the latter that strongly dominated. The second example, **5k**, shows that this sequence is also applicable to aza-indolines, a pharmaceutically important but somewhat inaccessible class of derivatives.[9]



1j, X = H; Y = OAc
1k, X =Y = CO_2Et

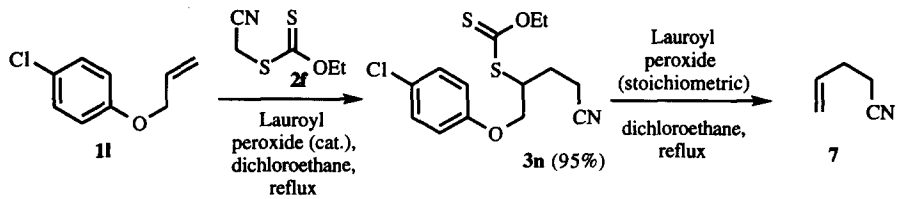
3k, X = H; Y = OAc;
R= Cyclopropyl (97%)
3l, X =Y = CO_2Et;
R=-COO^tBu (56%)
3m, X =Y = CO_2Et;
R=-Cyclopropyl (62%)

5l, X = H; Y = OAc;
R= Cyclopropyl (<10%)
5m, X =Y = CO_2Et;
R=-COO^tBu (56%)
5n, X =Y = CO_2Et;
R= Cyclopropyl (46%)

Scheme 5

When we attempted to extend this approach to the synthesis of indanes, the results were mixed. Only a poor yield of **5l** was isolated from a complex reaction mixture upon treatment of adduct **3k** with

stoichiometric amounts of lauroyl peroxide (Scheme 5). Placing two carbethoxy groups resulted in a much cleaner transformation and the yield of the corresponding indane **5m** rose to 56%. In a similar way, indane **5n** with the interesting cyclopropyl ketone group was prepared in 46% yield respectively. It is possible that the geminal ester groups exert a Thorpe-Ingold type effect which favours cyclisation.



Scheme 6

Finally, we examined the possibility of elaborating dihydrobenzofurans by the same route and thus carried out the radical addition of xanthate **2f** onto *O*-allyl p-chlorophenol **11**. This addition proved especially efficient, giving adduct **3n** in 95% yield. However, when this compound was exposed to lauroyl peroxide in the usual manner, no cyclisation was observed; instead, elimination of a *p*-chlorophenoxy radical occured to give 4-pentenenitrile **7**, as ascertained by nmr and by GC-MS (Scheme 6).

In summary, we have outlined a convergent, flexible route to indolines and indanes which employs readily available and cheap starting materials. Many of the compounds we have prepared are relatively inaccessible otherwise. Success in our case hinges on the possibility of using the xanthate group twice: first, in the intermolecular addition to a non-activated olefin and, second, in the cyclisation to the aromatic ring. Both of these radical steps, which in principle can be combined into one operation, are generally difficult to perfom with most traditional radical processes.

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