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A New Synthesis of α-Tetralones.

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Abstract : α–tetralones **8a-j** can be prepared by radical cyclisation, in the presence of stoichiometric amounts of lauroyl peroxide, of xanthates **5a-j** obtained by an intermolecular addition of substituted S-phenacyl xanthates **4a-c** to various olefins.
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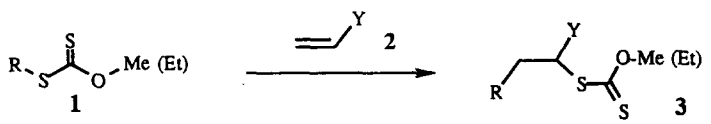
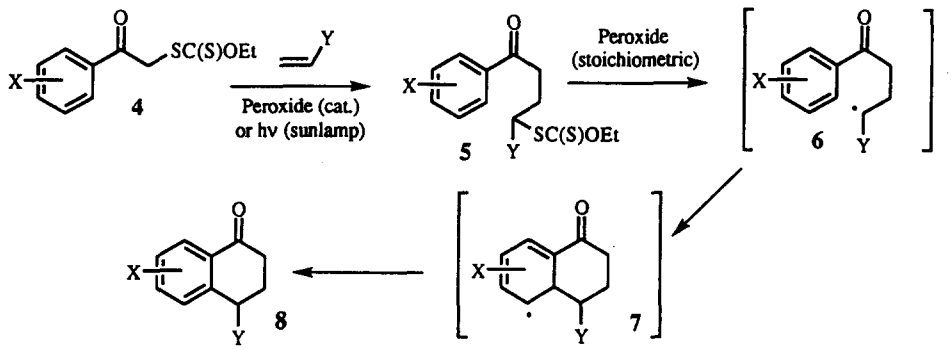
α–Tetralones represent an important class of starting materials and intermediates for the synthesis of biologically active substances such as the anthracyclines (e. g. daunomycinone,[1a] aklavinone[1b]), the tetracyclins,[2] estrone derivatives,[3] or the carcinogenic polyaromatic hydrocarbons and their metabolites.[4] Access to a number of medicinally useful derivatives also relies on tetralones.[5] Synthethic routes to α–tetralones remain however extremely limited, the most general being still the intramolecular Friedel-Crafts reaction of arylbutyric acids and its variants.[6] The need to use strongly acidic conditions, especially when the aromatic ring is deactivated by electron withdrawing substituents, restricts severely the variety of functional groups that are tolerated. In addition to the elaboration of simpler tetralones, a few less direct routes may be found in the literature, aimed mostly at a specific target and lacking the simplicity and flexibility necessary for a general process. These include for instance the oxidation of tetrahydronaphthalenes,[7] the photolysis of 1-*o*-methylaryl-1,3-diketones,[8] or the Michael addition of the anion derived from an *o*-toluate to an α,β-unsaturated ester followed by a Dieckmann condensation.[9] As part of our work on the radical chemistry of xanthates,[10] we now report an alternative and fairly general route to substituted α–tetralones involving an intramolecular radical addition to an aromatic ring.



Scheme 1

We had shown that xanthates such as **1** could undergo a radical chain addition to a great variety of olefinic traps **2** to give an adduct **3** where a new carbon-carbon and carbon-sulfur bonds have been formed. 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. It seemed therefore conceivable to take advantage of the last property in order to construct the 6-membered ketonic ring of α–tetralones as outlined in Scheme 2. Precursors **5** are readily available by a radical transfer reaction of S-phenacyl xanthates such as **4** with an olefin.



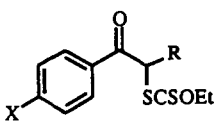
Scheme 2

When exposed to dilauroyl peroxide, xanthates such as **5** give rise to radicals **6** quite efficiently since the thermal decomposition of the peroxide generates ultimately primary undecyl radicals which rapidly add to the thiocarbonyl group and the intermediate collapses preferentially in the direction of the more stable secondary radical, i. e. **6** (or tertiary if a further substituent geminal to Y- is present). Although radical **6** can and does react with its precursor **5**, this process is degenerate. As a consequence, **6** should acquire a sufficiently long lifetime to allow it to add to the aromatic ring to give **7**. Cyclisations of this type are comparatively slow and thus difficult to accomplish by other radical generating methods such as those based on the now popular tin hydride chemistry. Radical **7** is too stabilised to propagate the chain but its conversion into the final product can occur either through dismutation or by oxidation and loss of a proton through reaction with the peroxide. Thus, unlike the first step in scheme 2 where catalytic amounts of peroxide are sufficient to produce **5**, the cyclisation to tetralone **8** will require stoichiometric quantities.

These considerations were easily put to practice: portionwise addition of dilauroyl peroxide to a refluxing 0.26 M solution of **5a** in 1,2-dichloroethane over 37 hours resulted in the formation of the corresponding tetralone **8a** in 56% yield.[11] Compound **5a** was itself prepared by reaction of xanthate **4a** with allyl cyanide in 77% yield. Two- and four-fold dilution did not alter significantly the yield. Moreover, the bromine in the aromatic ring, which would have been in principle incompatible with a tin hydride based process, did not seem to affect the reaction; its presence is however a synthetic asset in allowing further elaboration of the tetralone.

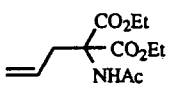
Various other tetralones **8b-j** were prepared by modifying the olefinic trap (**2b-g**) and the substitution pattern of the aromatic ring in the xanthate (**4a-c**). These further examples, including the intermediate adducts **5b-j**, are displayed in figures 1 and 2 with the yields (unoptimised) shown next to the structures. It is clear that the process is compatible with a large number of functional groups on the olefinic partner, ranging from ester groups (**8b,c,f,g**) to protected amine (**8d**) or amino acid (**8e**) and certainly many others which we have not examined in this instance but which we have learnt to handle in related studies on the radical chemistry of xanthates. Example **8g** illustrates furthermore the possibility of generating a quaternary centre. As for substituents on the starting acetophenone moiety, both electron donating (e.g. methoxy) and electron withdrawing groups (bromides, fluorides, etc.) appear to be tolerated, thus considerably expanding the utility of this approach, especially as regards the latter type which normally deactivates the aromatic ring towards a classical Friedel-Crafts mode of cyclisation. One further important

aspect that emerges from inspection of the examples is that practically all the positions of the tetralone structure may be functionalised by the appropriate choice of the initial xanthate and olefin components or by subsequent modification of the product.

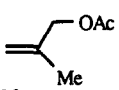


4a, X = Br; R = H
4b, X = OMe; R = H
4c, X = F; R = Me

2a, R = -CN
2b, R = -OAc
2c, R = -NPhth
2e, R = $-CH_2OCOCMe_3$

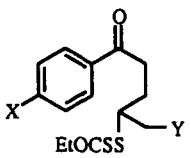


2d

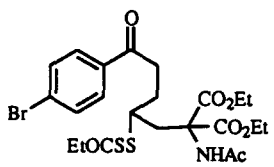


2f

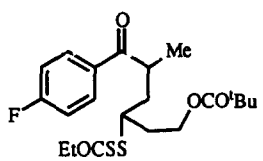
Phth- = phthalimido-;
yields in italics are based on recovered starting material.



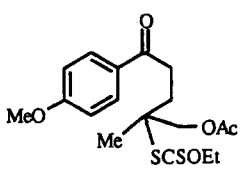
5a, X= Br; Y= CN (77%)
5b, X= Br; Y= OAc (78%)
5c, X= OMe; Y= OAc (77%)
5d, X= Br; Y= NPhth (72%)



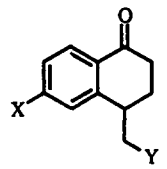
5e (87%)



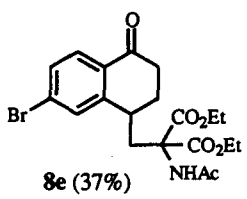
5f (60%; *89%*)



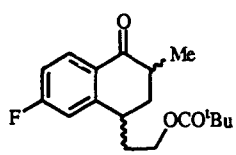
5g (36%; *94%*)



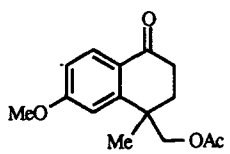
8a, X= Br; Y= CN (56%)
8b, X= Br; Y= OAc (45%)
8c, X= OMe; Y= OAc (48%)
8d, X= Br; Y= NPhth (62%)



8e (37%)



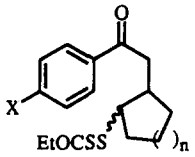
8f (65%)



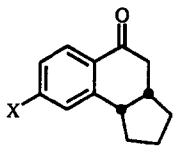
8g (67%)

Figure 1

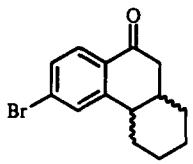
Access to polycyclic derivatives is also possible if a cycloalkene is employed; however, these are generally less efficient radical traps (especially cyclohexenes, which moreover give a mixture of isomeric tetralones, c.f. **8j**) as compared with unhindered terminal olefins. An alternative way of accomplishing the cyclisation step is to heat the intermediate xanthate **5** in refluxing chlorobenzene and adding the peroxide over a period of 30-60 minutes.[11] At this temperature, the half life of lauroyl peroxide is much shorter[12] allowing a speedier operation and the yields are usually comparable. However, special care must be taken to monitor the reaction in order to avoid the use of excess peroxide as it tends to destroy the product, once the starting xanthate has been depleted.



4h, X = Br; n =1 (61%)
4i, X = OMe; n =1 (52%)
4j, X = Br; n =2 (31%)



8h, X = Br (66%)
8i, X = OMe (62%)



8j (53%)

Figure 2

In summary, this novel xanthate chemistry provides a simple, expedient, yet veratile and flexible route to highly functionalised tetralones that are otherwise accessible only with difficulty. Apart from being interesting in their own right, such tetralones can act as springboards to a plethora of aromatic and even non aromatic derivatives through the powerful Birch reduction.

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11. Typical experimental procedure: To a degassed, refluxing solution of xanthate **5** in 1,2-dichloroethane (0.1 mmole / ml) is added dilauoyl peroxide in 5 mole% portions every hour until consumption of the starting material (1-1.5 mole-equivalents are usually needed). Alternatively, the higher boiling chlorobenzene can be used and a 0.1M peroxide added over 0.5-1 hour. In both cases, the reaction is regularly monitored for the disappearance of the starting material by thin-layer chromatography. Upon completion, the solvent is removed under partial vacuum and the residue purified by chromatography.
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