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Access to 1,2-diketones by an unusual radical cascade†‡

Rama Heng* and Samir Z. Zard*

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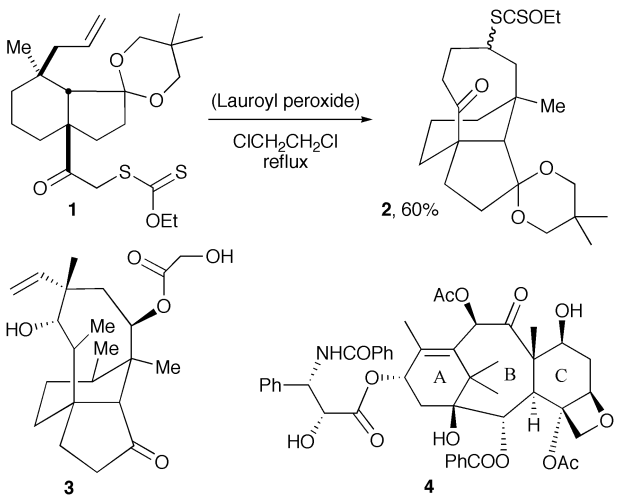
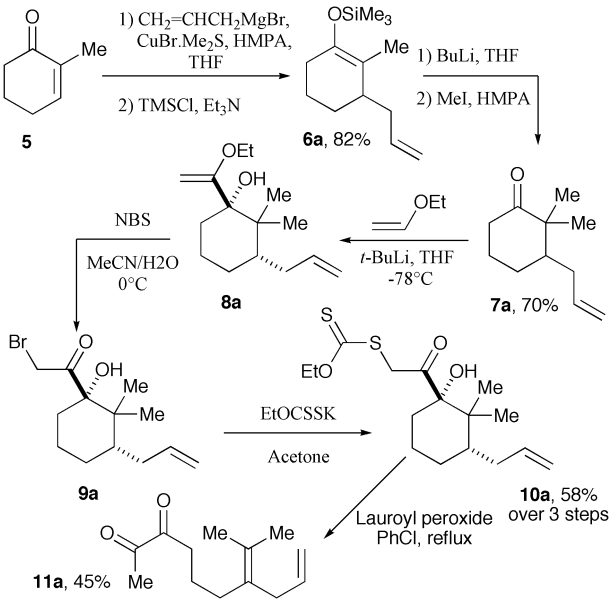
An unusual radical fragmentation of an unstrained cyclohexane structure was observed leading to complex 1,2-diketones.

In an earlier study directed at the synthesis of pleuromutilin **3**, we found that it was possible to construct the bridging eight-membered ring by a radical cyclisation starting with xanthate **1** and leading to product **2** in fairly good yield (Scheme 1).[1,2] Such 8-*endo* radical ring closures are quite rare,[3] but could nevertheless constitute an interesting approach to various polycyclic terpenes containing a cyclooctane sub-unit. In this respect, we examined the possibility of extending this route to a model of the AB ring system found in taxol **4**. While our efforts towards this goal have not yet been successful, we stumbled in the course of this work across a very unusual radical cascade allowing a rapid access to complex 1,2-diketones.

Xanthate **10a** was prepared from 2-methyl-2-cyclohexenone **5** using standard reactions (Scheme 2).[4] The sequence furnished compound **10a** as essentially one diastereoisomer,



Scheme 1 Model 8-*endo* cyclisation in the synthesis of pleuromutilin.



Scheme 2 An unexpected fragmentation leading to a 1,2-diketone.

which proved to be the one with the *undesired* relative stereochemistry. The *trans*- disposition of the allyl group and the side-chain bearing the xanthate precludes any possibility of cyclisation. However, before the relative stereochemistry of **10a** was unambiguously determined, we subjected the compound to the cyclisation conditions, namely refluxing in chlorobenzene in the presence of lauroyl peroxide as an initiator. We were surprised to find that the reaction required stoichiometric amounts of peroxide for complete consumption of the starting material and, moreover, the product was unexpectedly diketone **11a**, isolated in moderate yield (45%).

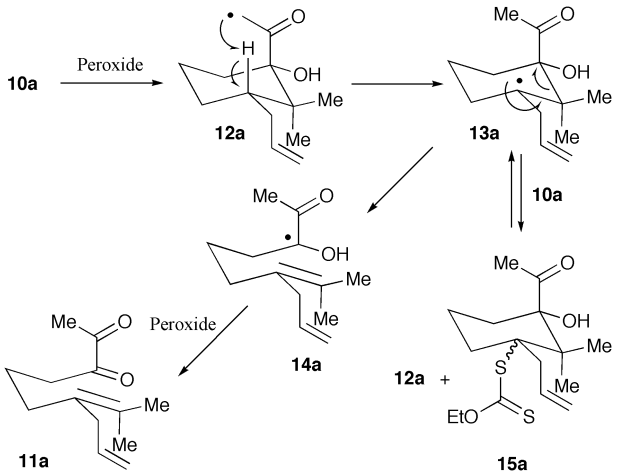
The most logical mechanistic rationale for this transformation is outlined in Scheme 3. Attack by the radicals from the peroxide on xanthate **10a** generates radical **12a**, which is well positioned to abstract a tertiary hydrogen to form **13a**.[5] Fragmentation then furnishes radical **14a**, which ultimately evolves into diketone **11a**. The last step could proceed by electron transfer to the peroxide to give the corresponding cation, followed by loss of a proton. Alternatively disproportionation with radicals derived from the decomposition of the peroxide would also result in the formation of the diketone. Both pathways could in fact be operating since neither excludes the other.

One of the remarkable features of this sequence is the rupture of an unstrained carbon–carbon bond. Such

Laboratoire de Synthèse Organique, CNRS UMR 7652, Ecole Polytechnique, F-91128 Palaiseau, France.
E-mail: heng@dcso.polytechnique.fr, zard@poly.polytechnique.fr;
Fax: +33 169335972; Tel: +33 169335971

† This communication is dedicated with respect to the memory of Professor Heinz Viehe.

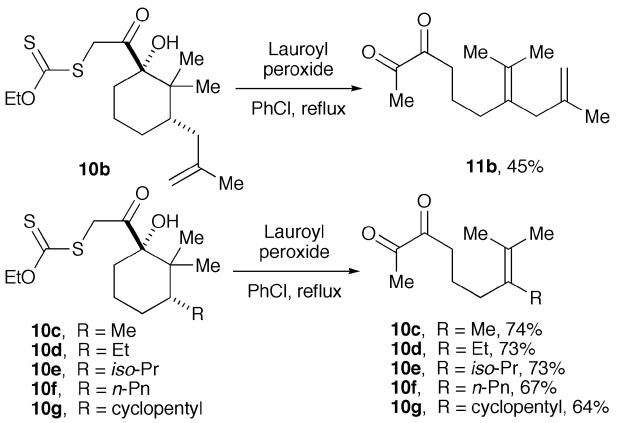
‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c0cc04725b



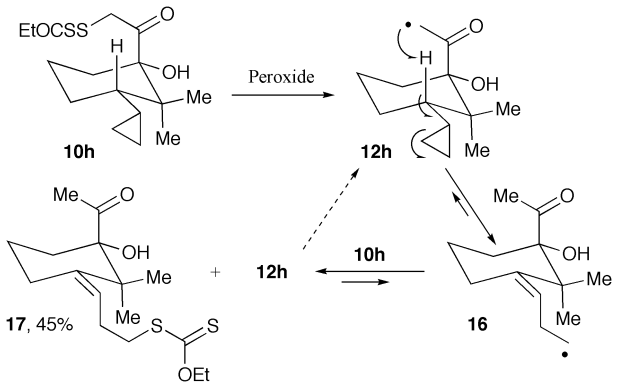
Scheme 3 Mechanistic rationale for the formation of 1,2-diketones.

fragmentations are relatively rare,[6] in contrast to instances where the carbon–carbon bond is part of a strained ring, as epitomised by the case of the cyclopropylmethyl radical.[7] In the present case, the fragmentation is favoured by the high stability of radical **14a**, due to its capto-dative nature, as well as by the relative persistence of intermediate radical **13a**, which gives the presumably slow fragmentation step time to occur. The extended lifetime of radical **13a** is the result of the reversibility of its reaction with the starting xanthate **10a** leading to xanthate **15a** and starting radical **12a**. More generally, the reversible exchange of the xanthate group increases the effective lifetime of most radicals in the medium and often allows transformations that would be very difficult to accomplish by other methods.[2]

Another interesting aspect is the survival of the delicate skipped diene motif to the reaction conditions. In a related example, compound **10b** was converted into **11b** in identical yield (45%; Scheme 4). In both of these transformations, the modest yield could be due to the competing intermolecular addition of radicals **12a** and **12b** (not shown) derived from xanthates **10a** and **10b** to the terminal alkene in the corresponding fragmentation products **11a** and **11b**. Indeed, the efficient intermolecular addition to alkenes, especially unhindered terminal alkenes, is one of the hallmarks of the xanthate transfer process.[2]



Scheme 4 Further examples of an unusual radical fragmentation.



Scheme 5 Modification of the initial radical sequence.

Not unexpectedly, replacing the allyl or methallyl groups by simpler appendages resulted in significantly improved yields for the process. This is illustrated by the transformations of derivatives **10c–g**, which gave the corresponding fragmentation products **11c–g** in yields ranging from 64 to 74% (Scheme 4). Furthermore, by attaching a cyclopropyl sidechain it was possible to modify the course of the reaction and confirm the existence of an intramolecular hydrogen abstraction step. Thus, substrate **10h** furnished product **17**, as one geometrical isomer (presumably the *E* isomer shown, but this was not unambiguously ascertained), through the mechanistic pathway delineated in Scheme 5. Radical **12h** derived from **10h** undergoes translocation and typical opening of the cyclopropyl ring rather than the much more difficult fragmentation of the cyclohexane moiety. This leads to primary radical **16**, which rapidly transfers a xanthate group from the starting material **10h** to give the observed product **17** and radical **12h** to propagate the chain process.

The complete scope of this new radical cascade, as well as its synthetic implications, still remains to be ascertained, but the present preliminary results reveal nevertheless an unusual and rather counterintuitive approach to complex 1,2-diketones. Such 1,2-diketones, which embody a very rich chemistry, would be quite tedious to be obtained by more conventional routes.

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Notes and references

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