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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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From a Remarkable Manifestation of Polar Effects in a Radical Fragmentation to the Convergent Synthesis of Highly Functionalized Ketones

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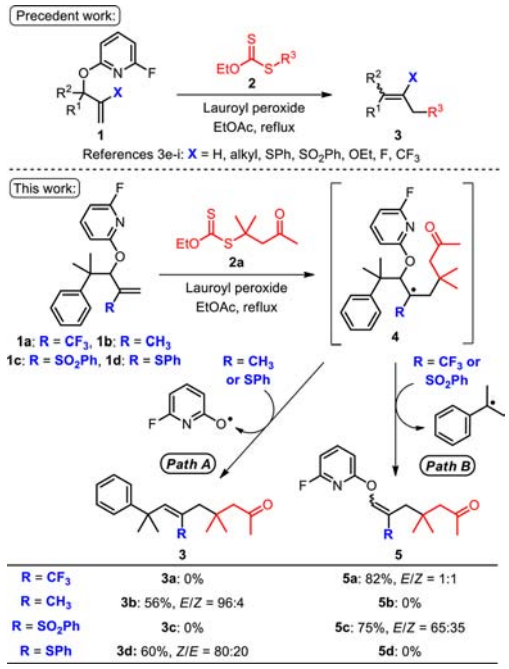
Supporting Information

ABSTRACT: A new radical addition/C−C bond fragmentation process is reported. Vinyl carbinols derived from 2-methyl-2-phenylpropanal react with radicals generated from xanthates to give the corresponding ketones. The radical cleavage reaction proceeds under mild conditions, in good to high yield, and in the presence of the unprotected carbinol. Highly functionalized 1,5-diketones and pyridines are readily available using this approach.

Radical fragmentations represent powerful synthetic processes that have been used for the creation of structurally diverse alkenes. In practice, these are limited to scissions of C−Sn,[1] C−S,[2] and C−O bonds.[3] While homolytic cleavage of C−C bonds is quite common for strained ring structures, especially cyclopropanes and cyclobutanes,[3a] synthetically useful C−C bond fragmentations triggered by ordinary carbon radicals (in contrast to highly energetic alkoxy radicals) in open chain, unstrained derivatives are rare.[4]

We recently reported that xanthates **2** react with various fluoropyridyl ethers **1** *via* a radical addition/C−O bond homolytic scission to yield the corresponding alkenes.[3e−i] In the context of our study on trifluoromethyl-alkenes,[3i] we were surprised to find that the reaction between fluoropyridyl ether **1a**, derived from 2-methyl-2-phenylpropanal, and xanthate **2a** gave enol ether **5a** in good yield instead of the expected alkene **3a** (Scheme 1, Path B). This unexpected result prompted us to search for the origin of this unusual reactivity. We thus decided to study the effect of the R substituent on the fragmentation process. We found that substitution of the trifluoromethyl moiety by a methyl group in **1a** completely modified the course of the reaction and delivered the corresponding olefin **3b** (Scheme 1, Path A). A similar divergence of behavior was observed with sulfone **1c** and sulfide **1d**, with the former leading to C−C bond cleavage to give **5c** and the latter undergoing C−O rupture to yield **3d** (Scheme 1). This sharp difference of reactivity emphasizes the dramatic effect of an electron-withdrawing group on the β-fragmentation of the intermediate radical **4**. Indeed, σ-bond acceptors such as CF_3 and SO_2Ph lower the SOMO energy level of the intermediate radical **4** and therefore increase the interaction between the SOMO of the intermediate radical **4** and the HOMO of the cumyl benzylic C−C bond. This enhanced interaction causes the preferential scission of the comparatively weak benzylic C−C bond and the extrusion of a stabilized cumyl radical to yield enol ethers **5a** and **5c**. Such a clear-cut distinction between two radical leaving groups is very rare at best and has interesting synthetic implications.[5] We have indeed explored these observations to develop a new route to synthetically useful ketones, and our preliminary results are described herein.

Scheme 1. Polar Effects in C−C Bond *versus* C−O Bond Homolytic Cleavages

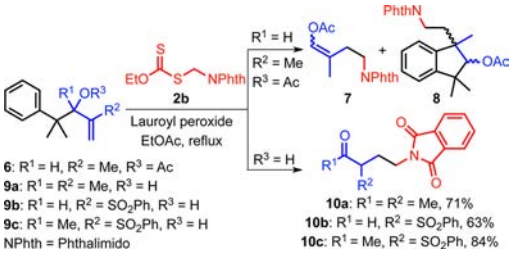


We first examined the possibility of replacing the fluoropyridoxyl moiety with an acetoxy group that is unable to act as a radical leaving group under normal circumstances, so as to force the extrusion of the cumyl radical, whatever the electronic nature of the substituent. Thus, as depicted in Scheme 2, addition of xanthate **2b** to allylic acetate **6** resulted in the formation of the expected enol acetate **7**, but it was heavily contaminated with indane **8** formed by cyclization of the intermediate radical onto the phenyl ring.[6] Moreover, the separation of these two products proved to be difficult by standard purification methods. This undesired cyclization is no doubt favored by the Thorpe−Ingold effect exerted by the germinal dimethyl substituents. Clearly, the

Received: January 26, 2013
Published: February 20, 2013

dx.doi.org/10.1021/ja400831w | J. Am. Chem. Soc. 2013, 135, 3808−3811

Scheme 2. Design of an Adequate Olefinic Partner



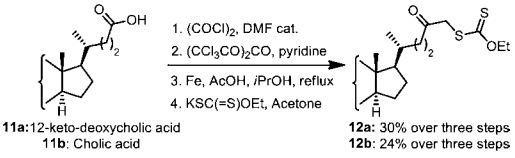
β-scission of the benzylic C−C bond is a sluggish process that competes only poorly with the radical cyclization onto the phenyl ring. Unfortunately, the solution consisting of blocking the unwanted cyclization by substituting the aromatic ring at the ortho-positions was not practical.

Hence, we decided to accelerate the desired fragmentation by weakening further the benzylic bond by increasing the interaction between the lone pair of the oxygen atom and the σ^* orbital of the benzylic C−C bond (an anomeric type effect). In practice, we found that removing the acetyl group and simply using the parent allylic alcohol **9a** as the olefinic partner eliminate the side reaction leading to indanes by significantly increasing the rate of the desired fragmentation. Thus, reaction of xanthate **2b** with olefin **9a** using stoichiometric amounts of lauroyl peroxide furnished the corresponding ketone **10a** *via* its transient enol. In a similar fashion, aldehyde **10b** and ketone **10c** were obtained from vinyl sulfones **9b** and **9c**. The sharp contrast between the reactivity of olefin **1b** (Scheme 1) and olefin **9a** (Scheme 2) is noteworthy.

With these successful preliminary results in hand, we explored the scope of the reaction. As indicated by the examples displayed in Figure 1, this process is particularly adapted for the synthesis of highly functionalized 1,5-diketones.[7] Indeed, α-keto-xanthates are particularly competent and versatile partners in radical reactions[8] and are easily accessible from the corresponding α-haloketones.[9] One of the keto groups is thus present in the xanthate partner, and the second is generated through the fragmentation process. A broad variety of functional groups and substitution patterns are tolerated, and both starting materials are readily available.[9,10] Noteworthy is the possibility of forming complex trifluoromethyl ketones such as **10n** and **10o**, which would be quite tedious to make by more conventional approaches. The presence of a sulfonyl group in example **10h** is also synthetically interesting, since it allows the modulation of the acidity of the various acidic protons in the molecule and can later be reductively removed.[11] In most of the examples, 2 equiv of alkene were used, as this generally allowed reactions to go to completion and simplified the purification, but an excess of xanthate (2 equiv) may also be employed if necessary, without adversely impacting the reaction yield (*e.g.* **10k**, Figure 1).

As highlighted by adducts **10f**, **10i**, and **10n**, our method is well suited for the modification of the steroid side chains. In particular, product **10i** stemming from 9-fluorohydroxycortisone derived xanthate testifies to the wide functional group tolerance of the reaction. Xanthates **12a** and **12b** used to make **10f** and **10n** were respectively prepared from bile acids **11a** and **11b**, using a method we developed some years ago (Scheme 3).[12] The steroid

Scheme 3. Preparation of Bile Acid Derived Xanthates



examples, as well as some of the other examples of 1,5-diketones in Figure 1, contain functional groups that would not be compatible with the conditions needed for the ionic Michael type additions commonly employed to assemble 1,5-diketones.

Complexity may be introduced by taking advantage of the fact that the "normal" addition of a xanthate to an alkene leads to another xanthate, which could then be subjected to this new ketone forming reaction. One example of this modular approach is depicted in Scheme 4. Thus, addition of xanthate **2c** to *N*-vinylphthalimide[13] furnishes xanthate **13**, and this, in turn, can be

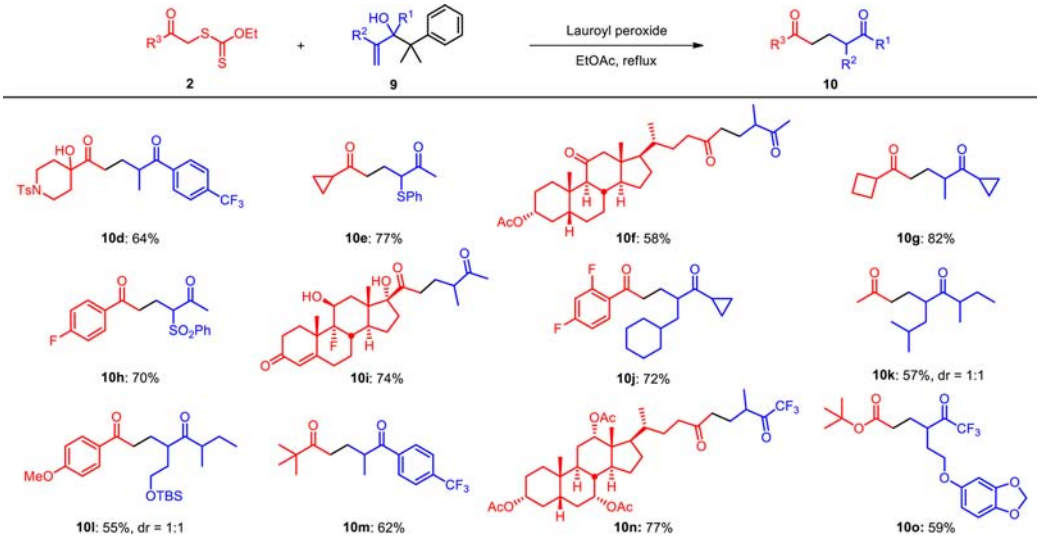
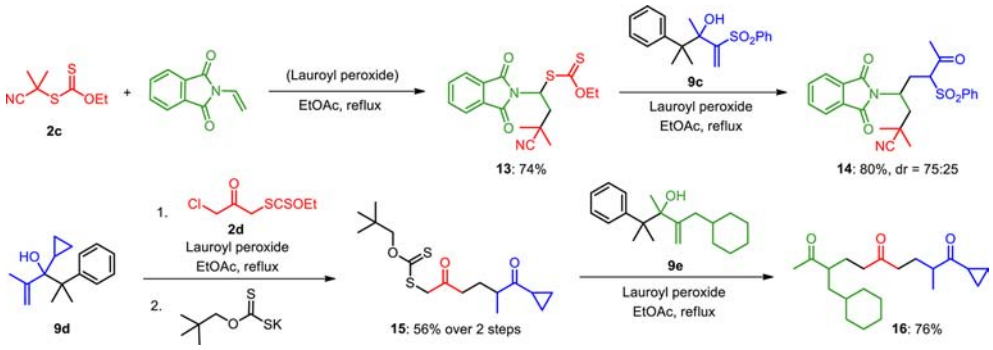


Figure 1. Scope of the radical addition/C−C bond fragmentation reaction. Reaction conditions: Olefin (2.0 equiv), xanthate (1.0 equiv), addition of lauroyl peroxide 30 mol %/h with respect to the xanthate (1.8−2.1 equiv of lauroyl peroxide, 6−7 h). For **10i**, a 1:1 mixture of trifluoroethanol and 1,2-dichloroethane was used as solvent. Reaction conditions for **10k**: Olefin (1.0 equiv), xanthate (2.0 equiv), addition of lauroyl peroxide 30 mol %/h with respect to the olefin (2.1 equiv of lauroyl peroxide, 7 h).

dx.doi.org/10.1021/ja400831w | *J. Am. Chem. Soc.* 2013, 135, 3808−3811

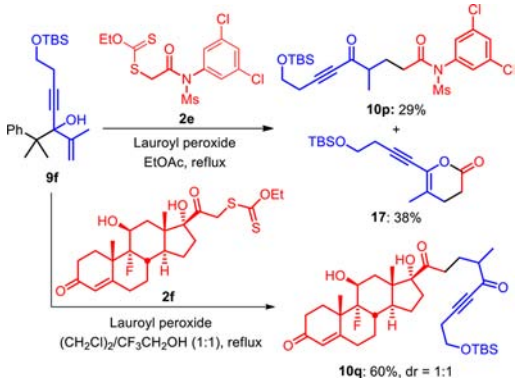
Scheme 4. Modular Construction of Complex Ketones by Sequential Radical Reactions



made to react with vinyl sulfone **9c** to give densely functionalized phenylsulfonyl ketone **14** in good yield. An alternative route to complex polyketones, also shown in Scheme 4, is to start with chloroacetonyl xanthate **2d**. After the first addition−fragmentation to alkene **9d**, the chlorine atom may be substituted by potassium *O*-neopentyl xanthate to give a new xanthate **15**, which in turn can be engaged in an addition−fragmentation on another alkene **9e** to finally give triketone **16** (Scheme 4).

The mildness of the experimental conditions and the general tolerance of the process are further demonstrated by the synthesis of ynones. Thus, reaction of xanthate **2e** with propargylic alcohol **9f** furnished the expected product **10p**, accompanied by lactone **17** in a good overall yield (Scheme 5).

Scheme 5. Preparation of Ynones



The latter is the result of ring closure of the enol of **10p** onto the activated anilide. Indeed, *N*-mesyl-3,5-dichloroaniline is a respectable leaving group.[14] On the other hand, when xanthate **2f** was used as a partner, ynone **10q** was readily obtained in good yield (Scheme 5).

As a class, 1,5-diketones are of special importance since they are immediate precursors for a variety of carbo- and heterocycles.[15] Pyridines, in particular, are readily obtained from 1,5-diketones by a number of classical procedures. In the present case, pyridines with unusual substitution patterns become easily accessible. This is illustrated by the examples in Figure 2, where 1,5-diketones **10j**, **10n**, and **10g** are converted into pyridines **18a**, **18b**, and **18c** respectively upon treatment with excess ammonium acetate in refluxing acetic acid.[7e]

During our study, we wondered about the fate of the cumyl radical **20** after its extrusion from intermediate **19** (Scheme 6, step c). Based on our experience,[16] we first envisioned that lauroyl peroxide would act as an oxidant for the cumyl radical **20** to give undecylate ester **21**. However, careful analysis of a typical

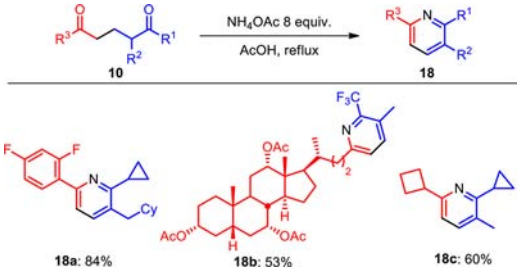
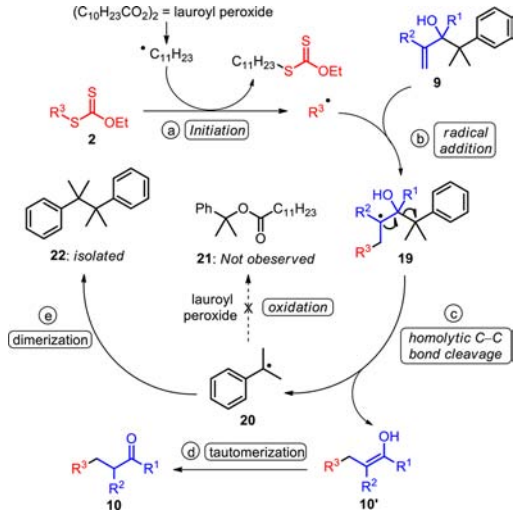


Figure 2. Synthesis of trisubstituted pyridines.

Scheme 6. Proposed Mechanism



reaction mixture showed that ester **21** was not formed under the present conditions.[17] 2,3-Dimethyl-2,3-diphenylbutane **22** resulting from the dimerization of two cumyl radicals **20** could nevertheless be isolated from the crude mixture. This allows the formulation of the mechanism depicted in Scheme 6. Radical R^3 generated from xanthate **2** and lauroyl peroxide (step a) reacts with olefin **9** to give intermediate radical **19** (step b), which undergoes *β*-fragmentation (step c) to give enol **10′** and a stabilized cumyl radical **20**. Enol **10′** tautomerizes to the desired ketone **10** (step d) while the cumyl radical combines to give the observed dimer **22** (step e, Scheme 6).[18]

In summary, we have established a powerful and convergent route to ketones which involves a rare cleavage of a C−C bond in a nonstrained open chain structure. This new radical addition/elimination process is tolerant of numerous functional groups and provides a particularly easy access to 1,5-diketones.

dx.doi.org/10.1021/ja400831w | *J. Am. Chem. Soc.* 2013, 135, 3808−3811

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures as well as a compilation of spectral and analytical data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This article is dedicated to Professor Keith U. Ingold. Financial support provided by the ANR is gratefully acknowledged.

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