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Modular Approach to Saturated and α,β-Unsaturated Ketones

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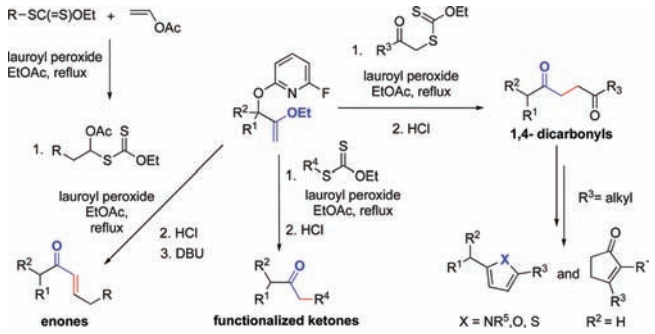
ABSTRACT



2-Fluoro-6-pyridinyloxy derivatives of 2-ethoxyvinyl carbinols react with radicals derived from xanthates by an addition−fragmentation pathway to give highly functionalized ketones after acid hydrolysis. 1,4-Diketones are readily accessible by this approach. α,β-Unsaturated ketones can be obtained by starting with *geminal* acetoxy xanthates prepared by addition of a simpler xanthate to vinyl acetate.

Ketones play a central role in organic chemistry and are key building blocks in modern synthesis. They are involved in many fundamental transformations such as the aldol,[1] the Wittig[2] and the Horner−Wadsworth−Emmons[2] reactions to cite a few and are the direct precursors of numerous organic functionalities such as imines, amines, oximes and alcohols.

Furthermore, 1,4-diketones and, more generally, 1,4-dicarbonyls are substrates of paramount importance for the synthesis of valuable five-membered carbo- and heterocycles such as cyclopentenones,[3] pyrroles,[4] furans,[5] or thiophenes.[6] Indeed, cyclopentenones, furans, and pyrroles are found in many biologically important natural products such as prostaglandins,[7] terpenes[5] and porphyrins.[8] Furans are also versatile dienes and dienophiles for Diels−Alder reactions.[9]

(1) For a review on the aldol and related addition reactions see: Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076.

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(7) For a review on the synthesis of prostaglandins see: (a) Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533. (b) Suzuki, M.; Kiho, T.; Tomokiyo, K.; Furuta, K.; Fukushima, S.; Takeuchi, Y.; Nakanishi, M.; Noyori, R. *J. Med. Chem.* **1998**, *41*, 3084.

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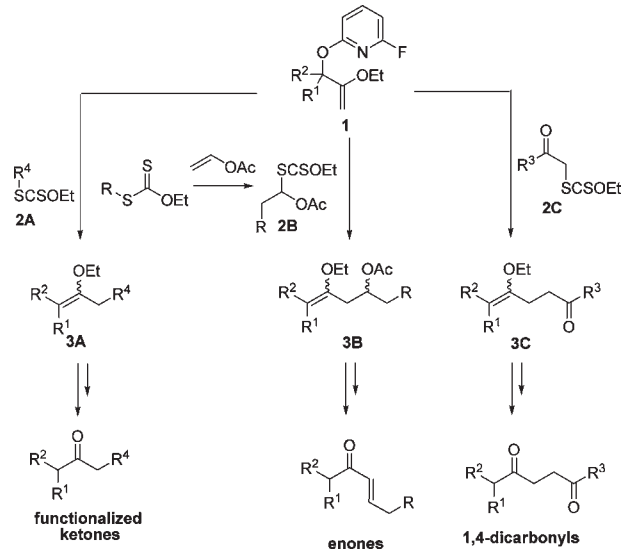
Scheme 1. Synthetic Approach to Functionalized Ketones, Enones and 1,4-Dicarbonyls

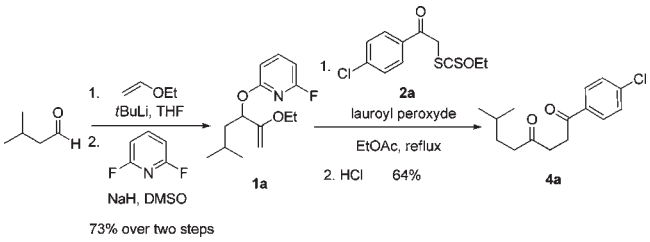


Finally, five-membered heterocycles are useful building blocks for the synthesis of materials with interesting physical and electronic properties.[10]

We report herein a unique, modular, and convergent method for preparing functionalized ketones, including 1,4-dicarbonyls and enones, from other readily available ketones and aldehydes. Recently, we discovered that when a 6-fluoro-pyridin-2-ol moiety is located vicinal to a radical center, it readily undergoes β-elimination, essentially converting an alcohol into a leaving group in a radical sense.[11] Homolysis of the usually strong carbon−oxygen bond is rare and has thus been poorly exploited in organic synthesis. The ability of the alkoxyfluoropyridines to undergo homolytic cleavage of the carbon−oxygen bond under mild conditions offers tremendous synthetic possibilities. Indeed, we demonstrated in a preliminary study the synthetic utility of such an olefination process, which in some cases corresponds to an overall synthetic equivalent of the Wittig reaction.[5]

Our approach relies on the use of xanthates **2** and enol ethers such as **1** as partners in the addition−fragmentation reaction, as outlined in Scheme 1. Tri- and tetra-substituted enol ethers **3A** would thus be obtained and would furnish the corresponding functionalized homologous ketones upon acidic hydrolysis. The use of α-keto-xanthates **2C** would give rise to 1,4-dicarbonyls, via intermediates **3C**, while prior addition of the xanthate to vinyl acetate[12,13] would ultimately furnish α−β-unsaturated ketones after hydrolysis of **3B** and base-induced elimination of the β-acetate moiety. The implementation of this synthetic strategy is detailed hereafter.

Scheme 2. Preliminary Example



In a preliminary experiment, enol ether **1a**, prepared by addition of the vinyl anion derived from ethyl vinyl ether to isovaleraldehyde followed by treatment of the resulting allylic alcohol with 2,6-difluoropyridine in the presence of NaH, was reacted with xanthate **2a** under the reaction conditions previously reported.[5] To our surprise and disappointment, the reaction gave a complex mixture of compounds with only small amounts of the desired ketone being isolated. One possible problem is a sluggish scission of the C−O bond due to a too great stabilization of the intermediate radical by the ethoxy group. This would leave the intermediate radical with enough lifetime to participate in untoward bimolecular processes. Another complication could be due to the premature hydrolysis of the starting and product enol ethers induced by the lauric acid produced during the reaction. After some experimentation, we found that simple moderate dilution of the reaction medium circumvented the difficulty, and the expected 1,4-diketone **4a** could be isolated in 64% yield following acid hydrolysis (Scheme 2).

Having successfully accomplished the desired radical addition, we explored the scope of the reaction. The results are collected in Tables 1 and 2. The three examples in the first Table demonstrate the possibility of isolating the relatively fragile initial enol ethers as mixtures of geometrical isomers and underscore the mildness of the experimental conditions.

If desired, the enol ethers may be further modified regioselectively, for example by bromination or epoxidation, or simply hydrolyzed. In the examples in Table 2, the enol ethers were not isolated but converted directly into the corresponding ketones **4** by treatment with aqueous HCl at room temperature. Thus, masked and free ketones can be rapidly assembled in moderate to good yield. In any case, the process tolerates many useful functional groups and diversity may be introduced both by modifying the xanthate and the starting aldehyde or ketone. Structures

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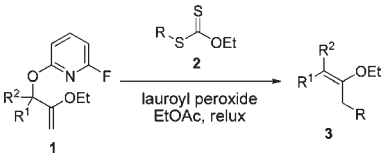
Table 1. Formation of Enol Ethers



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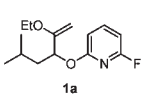
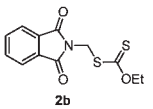
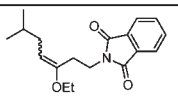
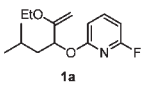
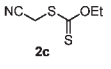
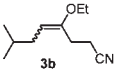
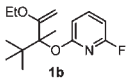
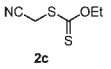
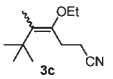
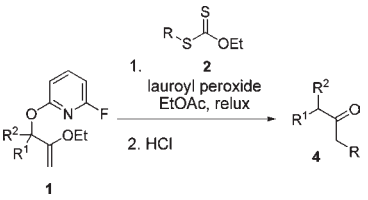
1	 1a	 2b	 3a	51% (95:5)
2	 1a	 2c	 3b	69% (85:15)
3	 1b	 2c	 3c	63% (85:15)

Table 2. Formation of Ketones and 1,4-Dicarbonyls



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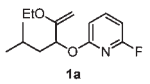
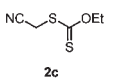
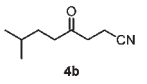
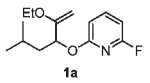
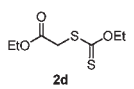
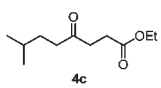
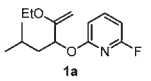
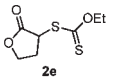
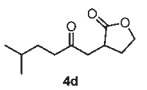
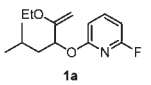
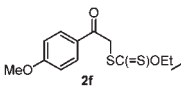
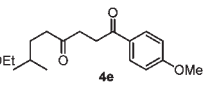
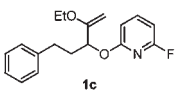
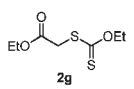
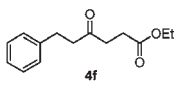
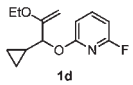
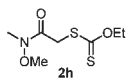
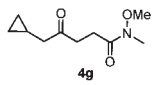
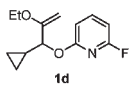
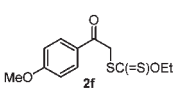
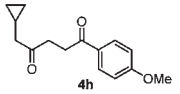
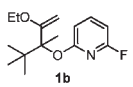
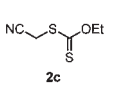
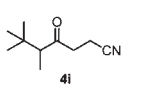
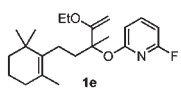
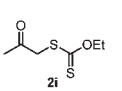
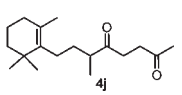
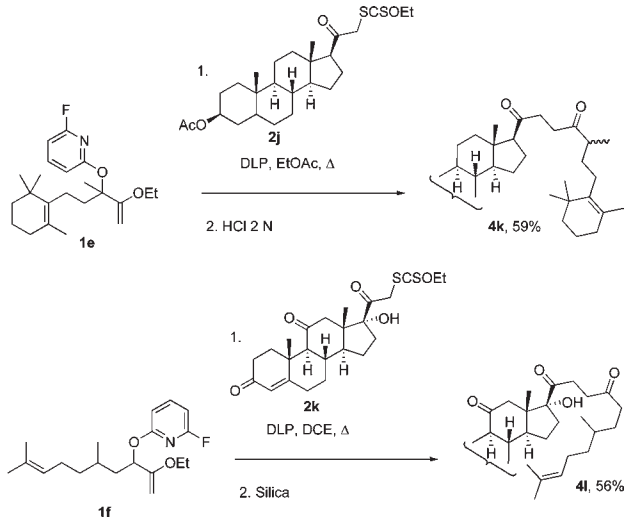
1	 1a	 2c	 4b	64%
2	 1a	 2d	 4c	69%
3	 1a	 2e	 4d	47%
4	 1a	 2f	 4e	46%
5	 1c	 2g	 4f	50%
6	 1d	 2h	 4g	35%
7	 1d	 2f	 4h	36%
8	 1b	 2c	 4i	61%
9	 1e	 2i	 4j	70%

Scheme 3. Access to Complex 1,4-Diketones



containing 1,4-dicarbonyl groups are particularly easy to obtain (Table 2), but numerous other combinations may also be envisaged.

The potential of this approach for the construction or modification of complex structures is further highlighted by the transformations involving steroid derived xanthates **2j**[14] and **2k**. The side chain in these substrates are readily extended through the addition−fragmentation/hydrolysis procedure to give 1,4-diketones **4k** and **4l**. Construction of various steroid side-chains remains an important undertaking, especially in the context of vitamin D-related studies (Scheme 3).[15]

As previously stated, 1,4-diketones are key intermediates for the synthesis of five-membered carbo- and heterocycles.[3−6] Following literature procedures, pyrroles **5a,b**,[16,17] furan **6**[18] and cyclopentenone **7**,[11] not readily accessible by other routes, were swiftly prepared in good yield as pictured in Scheme 4.

Another important feature of this approach derives from the possibility of a prior addition of the xanthate to vinyl acetate,[13] followed by the addition−fragmentation to the activated enol ether radical trap **1**, as pictured in Scheme 5. Upon hydrolysis, a β-acetoxy ketone is produced, which undergoes base-induced β-elimination on exposure to DBU to give an unsaturated ketone. This variant is illustrated by the synthesis of enones **8a**−**c**.

(14) (a) Leanza, W. J.; Conbere, J. P.; Rogers, E. F.; Pfister, K. *J. Am. Chem. Soc.* **1954**, *76*, 1691. (b) Bergstrom, C. G.; Sollman, P. B.; Nicfiolson, R. T.; Dodson, R. M. *J. Am. Chem. Soc.* **1960**, *82*, 2323.

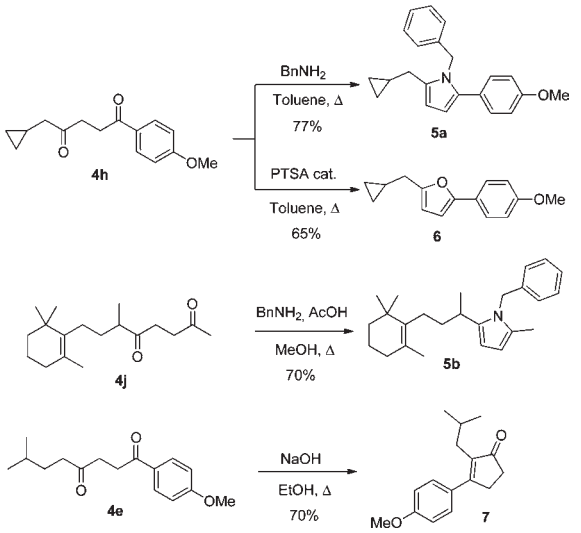
(15) Review: (a) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. For some recent references, see:(b) Michalak, K.; Wicha, J. *J. Org. Chem.* **2011**, *76*, 6906. (c) Xu, W. -M.; He, J.; Yu, M. -Q.; Shen, G. -X. *Org. Lett.* **2010**, *12*, 4431. (d) Maehr, H.; Lee, H. J.; Perry, B.; Suh, N.; Uskokovic, M. R. *J. Med. Chem.* **2009**, *52*, 5505.

(16) Amarnath, V.; Amarnath, K. *J. Org. Chem.* **1995**, *60*, 301.

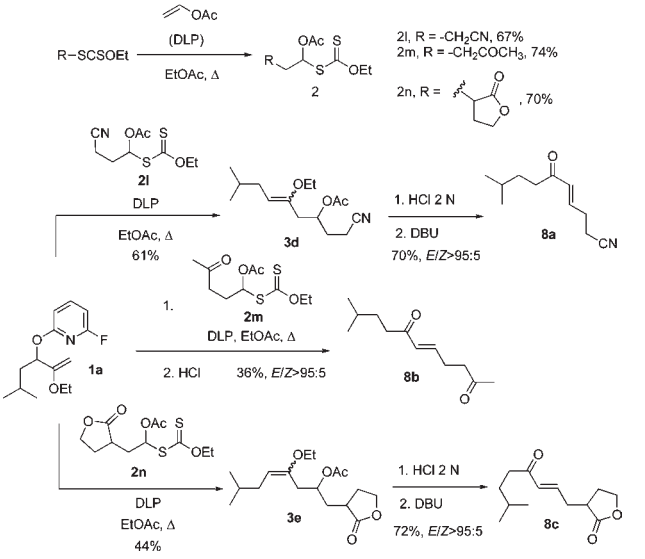
(17) Brummond, K. M.; Curran, D. P.; Mitasev, B.; Fische, S. *J. Org. Chem.* **2005**, *70*, 1745.

(18) Yuguchi, M.; Tokuda, M.; Orito, K. *J. Org. Chem.* **2004**, *69*, 908.

Scheme 4. Transformation of Various 1,4-Diketones into Five Membered Ring Carbo- and Hetero-cycles



Scheme 5. Synthesis of Enones



In summary, we have developed a simple, flexible and modular approach to ketones, 1,4-diketones and α, β-unsaturated ketones. These are indeed the cornerstones of organic synthesis. The mildness of the experimental conditions and broad tolerance for most of the common functional groups open up numerous synthetic opportunities not otherwise available through more traditional routes. It is worth emphasizing the fact that the intermediate enol ethers **3** may be isolated and eventually used for further *regioselective* functionalization.

Acknowledgment. We dedicate this paper with respect and affection to the memory of Prof. Costas H. Issidorides (American University of Beirut), a wonderful teacher of organic chemistry. L.D. thanks the ANR for a scholarship.

Supporting Information Available. Experimental procedures, full spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.