α-Xanthyl Cyclopentenones and Cyclohexenones: New, Highly Versatile Building Blocks

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Abstract

A versatile strategy to synthesize *α,β*-functionalized cyclopentanones and cyclohexanones is described. It takes advantage of new reagents, *α*-xanthyl enones, which can be prepared from the reaction of xanthate salts with epoxides under acidic conditions. *β*-Functionalization of these compounds can be performed by conjugate additions without affecting the xanthate moitety. This significantly expands the pool of xanthate substrates, allowing the synthesis of open chain and fused bicyclic building blocks useful in the synthesis of natural products.

Introduction

Cyclopentanones and cyclohexanones are ubiquitous among natural products and active pharmaceutical ingredients.[1] Despite the significant progress in synthetic methodologies in recent decades,[2] construction of highly substituted or polycyclic structures of this type by vicinal dialkylation still represents a major challenge.

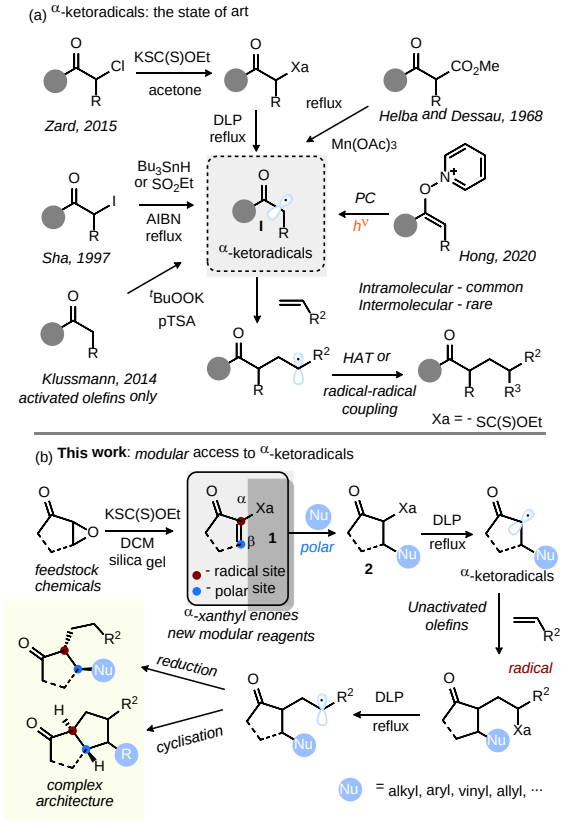


Figure 1. (a) Generation and reactivity of *α*-ketoradicals **I** from various precursors: xanthates, ketones, halides and ketoesters. Intermolecular additions of **I** to unactivated olefins are rare and lack modularity, except with xanthates. (b) This work – readily available *α*-xanthyl enones, highly modular new reagents with 2 sites of functionalization – polar (*α*) and open-shell (*β*). Sequential conjugate addition followed by radical addition to olefins allows facile access to complex molecular architectures.

In order to fill this gap in synthetic methodology we wondered if the chemistry of *α*-ketoradicals **I** could be used to construct such scaffolds (Figure 1a). These weakly nucleophilic, semi-stabilized radicals are known to engage in addition reactions with olefins. Since the seminal reports of Kharasch[3] and Nikishin,[4] they have been widely employed for intramolecular reactions,[5] while examples of intermolecular C-C bond

formations are scarce.[6] Traditionally, they have been accessed *via* oxidation of enolates,[7] tin-mediated atom transfer[8] and hydrogen atom abstraction. Harsh conditions, narrow scope, difficulty to control and the necessity of using pre-functionalized substrates limits their application, especially in intermolecular reactions with unactivated olefins. A solution for the latter can be provided by generating *α*-ketoradicals from xanthates which are convenient and easy-to prepare radical precursors.[9]

Xanthates are a well-established, versatile source of stabilized and semi-stabilized radicals widely used in the creation of C-C bonds, particularly through intermolecular radical addition to electronically unbiased alkenes. In particular, we envisaged that cyclic *α*-xanthyl ketones could play a strategic role as key reagents for establishing new synthetic pathways leading to substituted and polycyclic cyclopentanones and cyclohexanones.

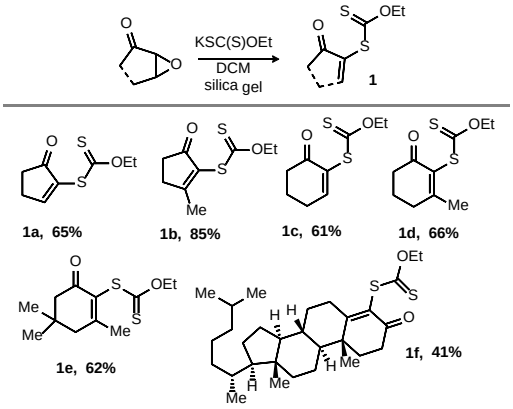
Cyclic *α*-xanthyl ketones are underexplored in organic synthesis, with only a handful of reports describing their synthesis and applications up to date.[10] Up until now they have been prepared *via* S_N2 reaction of *α*-bromo or chloro ketones with potassium xanthate or by reaction of enolates with bis-xanthates (Figure 1a).[11] However, this method lacks modularity and each substrate needs to be prepared separately.

Here we propose an alternative, *modular* approach to cyclic *α*-xanthyl ketones **2**, starting from readily available epoxides (Figure 1b). We surmised that the reaction between epoxides and potassium ethyl xanthate will produce *α*-xanthyl enones **1**: new and versatile reagents, which could be further functionalized by means of polar conjugate addition. This plan would allow access to a large number of *α*- and *β*-functionalized cyclic ketones from a single *α*-xanthyl enone, significantly expanding the pool of substrates and providing a synthetic tool to produce highly desirable building blocks.

Results and Discussion

Our laboratory started explorations by studying ring opening of 2,3-epoxycyclopentanone. Knowing that *α*,*β*-epoxyketones undergo nucleophilic thiolysis

with sulfur nucleophiles, potassium ethyl xanthate was employed as both nucleophile and base, in the hope of producing *α*-xanthyl enones in a single step. In our initial experiments we were pleased to find that the desired compound **1a** was indeed formed in 65% yield, where DCM was used as a solvent and silica gel as an additive. The method was found to be general for a variety of cyclopentanones and cyclohexanones (Scheme 1). However, in the case of larger rings and highly hindered substrates, *α*-xanthyl enones were not formed and, in a non-cyclic example, only the retro-aldol product was detected. In a separate study, we found that the *α*-xanthyl-*β*-hydroxy ketones can be isolated when the reaction is performed in lower temperature (-10 ^{o}C) and quenched *in situ*.[12]

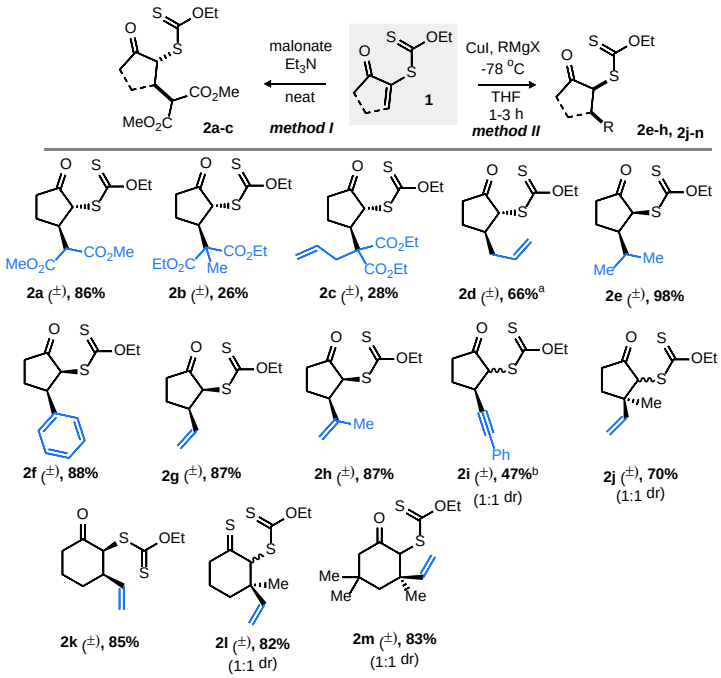


Scheme 1. Preparation of *α*-xanthyl enones **1**.

Having synthesized the small library *α*-xanthyl enones **1** (Scheme1) we proceeded to study their reactivity and properties. We found that reagents **1** undergo Michael addition with malonates in the presence of Et_3N to produce *β*-substituted ketones **2a-c** in good to moderate yields. The reaction was carried out neat and required long reaction times for hindered substrates. Encouraged by these initial results, we found that the *α*-xanthyl enones can act as precursors to *β*-allyl ketones **2d** by triflimide catalyzed Sukarai type reaction.

More importantly, we discovered that *α*-xanthyl enones undergo clean 1,4-cuprate additions at -78 ^{o}C in THF without affecting the xanthate moiety. This observation allowed us to prepare a range of *β*-substituted *α*-xanthyl ketones **2** in high yields. The reaction was found to be general and allowed facile installation of isopropyl **2e**, phenyl **2f** and vinyl groups **2g-h**, **2j**. Quaternary stereocentres can also be constructed as a 1:1

mixture of diastereoisomers, as in **2j** and **2l**. We were also pleased to find that an alkyne moiety can be introduced into the *β*-position of enone **2i**. In this case, the organolithium reagent is formed *in situ* from phenylacetylene before its transmetallation to copper. In all the above cases the xanthate moiety remained untouched. The reactions were particularly clean and regioselective. The starting material and small amounts of thiocarbonate, a product of the xanthate oxidation, were the only undesired side products. However, when it came to the addition of methyl cuprate, we detected considerable (40%) amounts of 1,2-addition products. Despite this minor limitation, the present conjugate addition to *α*-xanthyl cyclopentenones and cyclohexenones constitutes a major breakthrough in xanthate chemistry, opening numerous synthetic opportunities.

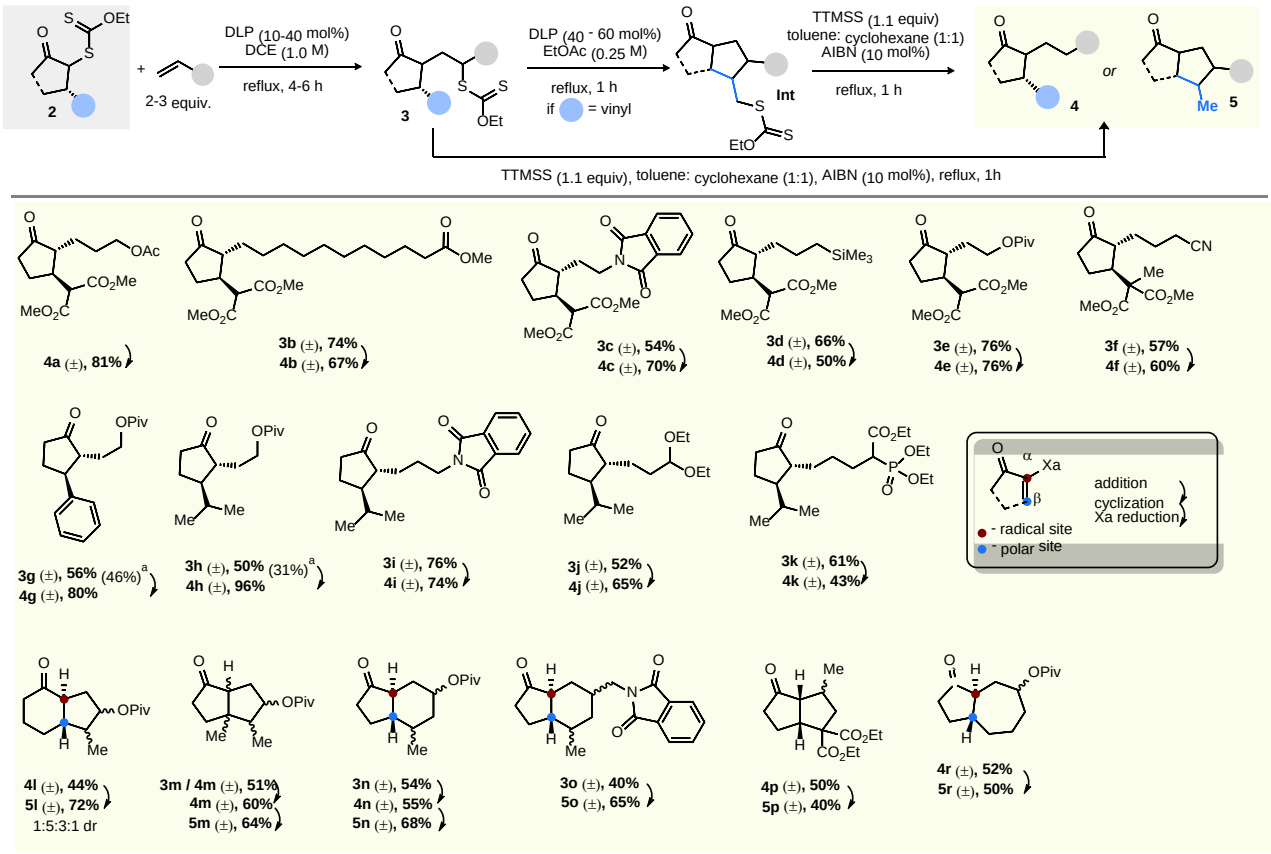


Scheme 2. Derivatization of *α*-xanthyl enones **1** by conjugate addition. Substrates **2a-2c** were prepared using method I and **2e-2h** and **2j-2n** using method II. (a) Compound **2d** was prepared using Sakurai reaction with allyl-TMS and triflimide at -20 °C;[13] (b) Adduct **2i** was prepared using conditions developed by Olsson et al. starting from phenylacetylene and *n*-BuLi.[14]

We then evaluated the synthetic potential of these new reagents in intramolecular xanthate transfer reactions to unactivated olefins (Scheme 2). *β*-Malonate xanthates **2a-c** reacted cleanly with alkenes in DLP-initiated chain process to yield *α*,*β*-substituted

xanthate adducts **3**, which were then reduced to furnish the final compounds **4** in high to moderate yields (Scheme 3). The reaction tolerated a variety of functional groups, such as ester **4b**, amide **4c**, silane **4d** and nitrile **4f**. Both *β*-aryl **4g** and alkyl **4h** substituted *α*-xanthyl ketones furnished difunctionalized cyclopentanones in 50% / 80% and 50 / 96% (addition / reduction) yields. When vinyl pivalate was used as the olefin, some oligomerization took place as the side reaction. We also found that the activation of xanthates **2e** and **2f** can be performed photochemically with direct irradiation using high power Hg lamp. In this case, yields were similar to the thermal activation route.

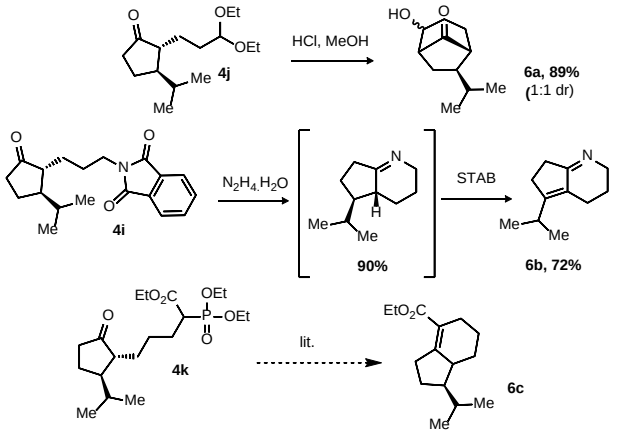
When vinyl or allyl group was introduced in the *β*-position, after addition of *α*-keto radical to olefin, intramolecular cyclization took place as expected.[15] This allowed us to prepare a series of fused ring systems. The reaction of xanthate **2k** with vinyl pivalate furnished the 6-*exo*-*trig trans*-[6,5] product in 44% yield. In the case of the methyl-vinyl group **2h**, a 6-*endo*-*trig* ring closure took place and *trans*-[5,6] product was isolated. The method also allowed formation of fused [5,5] systems bearing a quaternary stereocenter in the *β*-position **5m**. Employing *N*-allylphthalimide as the olefin furnished *trans*-[5,6] product **5o**, which could, if desired, be further transformed into tricyclic structures by exploiting the presence of the protected amine, for example through application of the Mannich reaction. Finally, cyclization of allyl xanthate **2d** yielded the *cis*-[5,5] compound and reaction of allyl xanthate **2d** with vinyl pivalate furnished the 7-*trig*-*endo trans*-[5,7] product **5t**.



For non-cyclic cases only a single *trans* stereoisomer was formed and we did not observe any stereochemical scrambling. This is consistent with the known mechanism of xanthate transfer reactions whereby the *α*-ketoradical adds from the least hindered site of the substrate. Therefore, we conclude that the radical addition to olefin, which is the first step of the reaction, is stereoselective and gives rise to the *trans* configuration in all cases, apart from compound **5m**, where there is little discrimination between methyl and vinyl group. Indeed, compound **5m** was formed as a complex mixture of diastereoisomers. For compound **5l**, the diastereoselectivity in the cyclization step was minor, giving rise to four *trans* diastereoisomers formed in a ratio of 1:5:4:1.

In order to further exploit the synthetic utility of our methodology, we carried out further transformations of our adducts (Scheme 4). Reaction of compound **4j** with HCl in MeOH gave rise to almost quantitative amounts of bicyclic aldol product **6a** in 1:1 diastereoisomeric ratio. Deprotection of the phthalimide **4i** with hydrazine released a primary amine, which immediately underwent intramolecular condensation with the carbonyl to form an imine (single, yellow spot on TLC). Since isolation of the latter was problematic, we subjected it to reduction with excess sodium triacetoxyborohydride in

MeOH, hoping to drive the reaction towards amine formation. However, we were surprised to find that the unsaturated imine **6b** was formed instead, presumably the result of aerial oxidation. Finally, we prepared Horner-Wadsworth-Emmons adduct in 61% yield **4k.** This compound is a convenient precursor to the bicyclic *α*,*β*-unsaturated ester **6c** which can be reached in a single step.[16]



Scheme 4. Derivatization of products.

Conclusions

In summary, we have developed a new synthetic strategy to access various substituted and polycyclic cyclopentanones and cylcohexanones via a combination of ionic and radical pathways. Starting from readily available epoxides we have prepared a new class of reagents, *α*-xanthyl enones, which can serve as versatile building blocks in organic synthesis. Upon derivatization they were transformed into radical precursors which add stereoselectively in most cases to unactivated olefins, followed by cyclizations, leading to a variety of new synthetic opportunities. We also demonstrated that the method can be used to construct fused ring systems as well as other useful molecular architectures.

Conflict of interests

The authors declare no competing interests.

Acknowledgements

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