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New Methodology toward α,β-Unsaturated Carboxylic Acids from Saturated Acids

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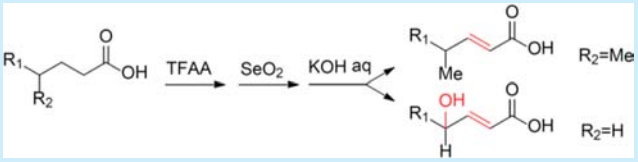
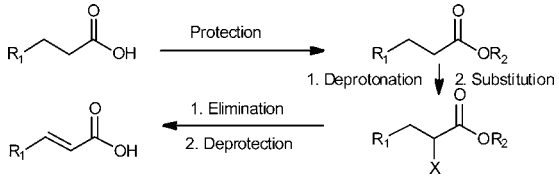
Supporting Information

ABSTRACT: A carefully designed three-step unsaturation of carboxylic acids is described. Briefly, carboxylic acids were converted to the trifluoromethyl ketone. Subsequent treatment with selenium dioxide followed by hydrolysis afforded α,β-unsaturated carboxylic acids. The mechanism of the reported transformation was investigated, which led us to propose a novel explanation featuring selenium dioxide assisted enolizaion of a trifluoromethyl ketone followed by β-deprotonation.



A wide variety of synthetic methodologies targeting either the construction or utilization of α,β-unsaturated carbonyl compounds have been developed due to their ubiquitous nature in organic chemistry. Two major approaches have been utilized in constructing such functional groups: (1) concomitant formation during synthetic construction of a molecule (for example via aldol condensation or Wittig-type reactions[1]) or (2) dehydrogenation of a previously established carbonyl compound.[2,3] Although the first approach is usually more efficient, the second approach is more important, as it provides the only option for regioselective introduction of unsaturation to previously established carbonyl compounds. Typically, the second approach involves deprotonation α to the carbonyl group to generate an enolate, which is then condensed with a variety of functional groups that can act as a leaving group in a subsequent elimination reaction. This generalized method, affording α,β-unsaturated carbonyl compounds is shown in Scheme 1. Relatively recent work from Nicolaou et al.

Scheme 1. A General Strategy for α,β-Unsaturation



represents an important step forward for the α,β-unsaturation of aldehydes and ketones using *o*-iodoxybenzoic acid (IBX), but this work also highlights the lack of progress and the underdeveloped nature of the unsaturation of acids.[3]

As evidenced by the work with IBX, dehydrogenation approaches are generally more tractable with ketone- or aldehyde-containing substrates as compared to carboxylic acids. This fact is primarily derived from the low propensity of acids to undergo enolization, a required step in almost any approach. As a result, satisfactory reports on the α,β unsaturation of carboxylic acids are rare.

During the course of our work on bile acids, we found that traditional methods (Scheme 1; examples include α-selenation and halogenation)[2b,4] to produce α,β-unsaturated carboxylic acids proved unreliable on these highly functionalized molecules. This served as the impetus to further investigate the transformation and identify new approaches with the goal of identifying an efficient route with s broad scope.

A three-step unsaturation strategy was proposed (Table 1) whereby the carboxylic acid is converted to trifluoromethyl ketone **2**, which is followed by dehydrogenation (in this case with selenium dioxide). Subsequent treatment of the enone under basic conditions provides the unsaturated acid **4** as the final product. Conversion to the trifluoromethyl ketone was chosen as the surrogate group for carboxylic acid for three reasons. First, it can be easily generated from a parent acid[5] and readily removed under relatively mild conditions. Second, the strong electron-withdrawing effect of trifluoromethyl groups favors the enol form of ketone−enol equilibrium and, therefore, facilitates dehydrogenation. Third, protection of hydroxyl groups can be concurrently accomplished during the conversion of acid to trifluoromethyl ketone.

The use of selenium dioxide to generate a carbon−carbon double bond adjacent to carbonyl functionalities[6] possesses clear advantages when compared to the traditional approaches. First, it is more efficient stepwise, as it circumvents the deprotonation−substitution−elimination process and gives the final enone in a single step. Second, it can avoid the use of a strong base, which is required for α-deprotonation and elimination. This, of course, improves the functional group tolerance. The use of selenium dioxide proved ideal for our approach, as its neutral nature was compatible with the acid and base sensitive trifluoromethyl ketone, which proved to be

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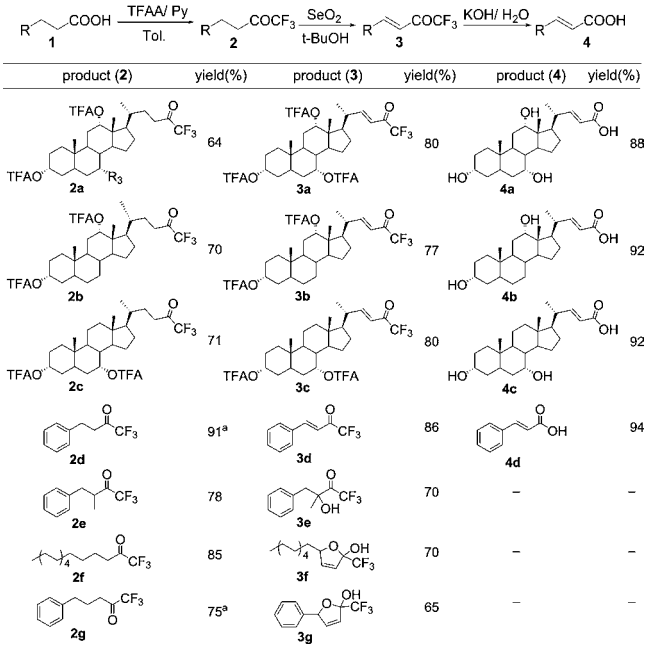
Table 1. Yields for the Three-Step α,β-Unsaturation of Carboxylic Acids



[a]An alternate method was used for a better yield.[5b]

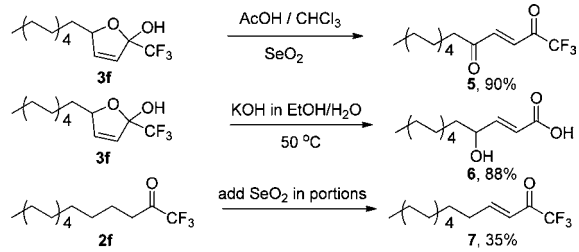
incompatible with the IBX methodology mentioned above.[3] Further, the strong electron-withdrawing effect of trifluoromethyl ketone dictates the selenium reactivity we report here. This is critical, as the dehydrogenation of linear carbonyl compounds by selenium dioxide has been repeatedly proven intractable.[7] A careful literature search identified the proposed mechanisms for selenium unsaturation as proceeding via the enol of a carbonyl equilibrium.[8] By activating the carbonyl group with an electron-withdrawing group, the equilibrium shifted toward the enol form, which we hypothesized would drive the reaction pathway toward unsaturation. Based on this assumption, we predicted that, with increased reactivity, the yield of the dehydrogenation product on an acyclic monoketone could be improved to the point of being a viable and efficient route for the α, β-unsaturation of acids.

Bile acids are a diverse class of natural product amphiphiles with multiple hydroxyl groups of various regio- and stereochemistry. As shown in Table 1, when treated with trifluoroacetic anhydride using Reeves' method,[5a] all of the hydroxyl groups were effectively protected with concomitant conversion of acid to trifluoromethyl ketone. As we postulated, introduction of the electron-withdrawing group made the dehydrogenation step tractable and the reaction of trifluoromethyl ketones (**3a**–**c**) with 2 equiv of selenium dioxide proceeded smoothly to provide enones with good yields. Less selenium dioxide resulted in the incomplete conversion of trifluoromethyl ketone. Several solvent combinations, including various permutations of dioxane, water, ethanol, and isopropanol, were tried but only *tert*-butanol afforded the desired products. Inconsistent with previous reports[9] on selenium reactivity, the addition of acids had no significant accelerating effect on the reaction rate. Ultimately, α,β-unsaturated bile acids were obtained in good yields after being hydrolyzed in a 10% solution of KOH in EtOH/H_2O at room temperature.

With all three bile acids successfully synthesized, we studied the scope of this methodology. As shown in Table 1, trifluoromethyl ketone containing aryl substitution at the γ-position (**2d**) was proven to be an ideal substrate, affording high yields and facile conversion to the unsaturated acid. We then studied the steric effect by introducing methyl groups on different positions close to carbonyl groups starting with an β-substituted ketone (**2e**). In this case, only α-hydroxylated product **3e** was isolated instead of enone. Dehydrogenation of compounds without γ-substitution (**2f**–**g**) by selenium dioxide did occur, but did not stop at the enone stage. Further oxidation at the γ-position introduced a hydroxyl group, which rapidly reacted with the trifluoromethyl ketone to afford a stable hemiketal (**3f**–**g**). This result is noteworthy, as several biologically relevant lipid peroxidation products contain this γ-hydroxy, α,β-unsaturated functionality including 4-hydroxy-2-(*E*)-nonenal (4-HNE),[10] the corresponding acid (4-HNA),[11] and the entire family of $OxPC_{CD36}$ molecules.[12] The methodology reported here is easily the most efficient route to their synthesis.

To this point, the hemiketal products (**3f**–**g**) are sufficiently stable that ring-opening reactions must be combined with further conversion of the enone to avoid recyclization during the workup process. Two conditions were tried: (1) strong acidic conditions in the presence of selenium dioxide resulted in 1,4-diketone **5**, which can be isolated in excellent yield (Scheme 2); (2) saturated KOH EtOH in the presence of water, which

Scheme 2. Dehydrogenation of Substrate with γ-Hydrogen and Subsequent Conversions



afforded the hydrolyzed 4-HNA derivative **6**. Attempts to stop the cascade at the enone stage by adding selenium dioxide in portions were also conducted and successful, but low yielding.

The versatility of selenium dioxide in terms of accomplishing multiple oxidative conversions also makes its mechanistic studies more difficult. From one substrate to multiple products, it is hard to decipher where reaction pathways diverge from uniformity and, consequently, whether intermediates are shared between pathways. To date, three mechanisms have been proposed for the dehydrogenation process by selenium dioxide: direct β-deprotonation proposed by Speyer,[13] elimination of an α-selenated species **10** proposed by Sharpless,[8] and elimination of selenous ester **12** proposed by Corey and Schaefer[9] (Scheme 3). In the first two proposed mechanisms, the enol form **8** of the carbonyl is the active species that directly reacts with selenium dioxide, while Corey et al. proposed enolization as assisted by selenium dioxide, which served as a Lewis acid.

Since no proposed mechanism could sufficiently explain our results, we decided to test them individually. Starting with the direct β-hydrogen transfer mechanism, we designed an isotope labeling experiment. Based on the logic of the proposed mechanism, we reasoned that replacement of β-hydrogens of the substrate with deuterium would result in a first-order

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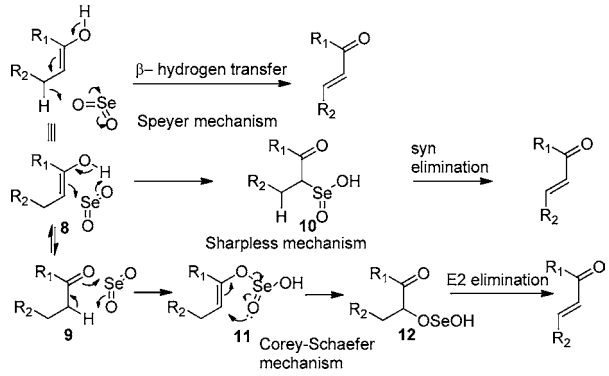
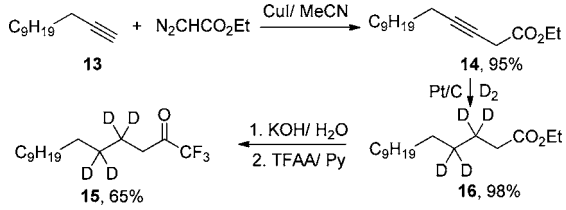
Scheme 3. Mechanistic Studies of Dehydrogenation by Selenium Dioxide



isotope effect in the reaction rate. Consequently, a β-deuterated fatty acid was prepared in the synthesis described below and converted to trifluoromethyl ketone to react with selenium dioxide. The reaction rate was monitored by NMR and compared with that of the analogous fatty acid without deuterium.

As shown in Scheme 4, 1-dodecyne **13** was cross-coupled with ethyl diazoacetate catalyzed by copper(I) iodide[14] in

Scheme 4. Synthesis of Deuterated Trifluoromethyl Myristyl Ketone



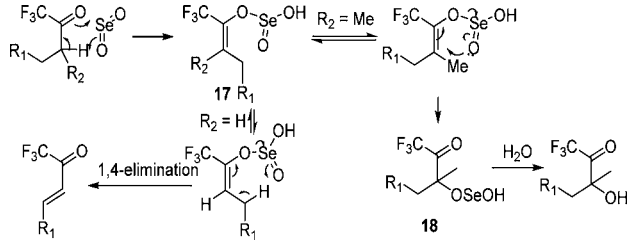
excellent yield. Subsequent deuteration in the presence of 5% platinum on carbon, hydrolysis, and conversion to the trifluoromethyl ketone **16** was achieved in excellent overall yield.

The deuterated ketone was refluxed in *tert*-butanol with selenium dioxide, and the reaction rate was monitored by NMR at 24 h intervals to compare with that of the undeuterated compound. The reaction rate was calculated by the integral of the peaks of starting materials vs that of the product (Supporting Figure 1). No significant difference in reaction rates was observed, which suggested that the removal of β-hydrogen to form a carbon−carbon double bond is not likely to be the rate-limiting step, and we therefore excluded the β-hydrogen transfer mechanism.

We then analyzed our results in the context of both the Sharpless and Corey−Schaefer mechanisms. The main disagreement between these models pertains to the reactive species that initiates the reaction with selenium dioxide. The Sharpless mechanism proposes a direct electrophilic attack of selenium dioxide to the enol form based on the indirect observation of carbon−selenium species, while Corey and Schaefer proposed that the enolization of the ketone was assisted by selenium dioxide as a Lewis acid (Scheme 3). When the two mechanisms are compared, adding acid should accelerate the Sharpless mechanism by accelerating the enol−ketone tautomerization, as the rate limiting step is electrophilic attack of selenium dioxide to the enol. Since no significant increase of the reaction rate was observed when adding acetic acid to the reaction mixture, the Corey−Schaefer mechanism seemed more reasonable. To further verify this observation, 1.2 equiv of $Ti(O^iPr)_4$, a strong Lewis acid to coordinate with the carbonyl group, was added to the trifluoromethyl ketone for 1 h prior to selenium dioxide addition. This experiment resulted in no reaction, which subsequently served as further evidence that the reaction initiates with the ketone instead of the enol. Additionally, the Sharpless mechanism cannot explain the formation of the α-hydroxylation product (**3e**, Table 1)

The major defficiency of the Corey mechanism, as pointed out by Sharpless et al.,[8] is the involvement of selenous ester **12**, which is unstable and undergoes rapid hydrolysis before elimination can occur. After considering these arguments, we propose a new mechanism by combining the selenium dioxide assisted enolization with a β-deprotonation process. As shown in Scheme 5, we propose that high valence selenium reacts with

Scheme 5. Proposed Mechanisms of Dehydrogenation by Selenium Dioxide



trifluoromethyl ketone to form the enol ester **17**. The enol ester undergoes 1,4-elimination directly instead of nucleophilic attack of the carbon−carbon double bond to form selenium ester. In the case of an α-substituted substrate, such as compound **2e** in Table 1, 1,4-elimination is prohibited in the most energetically stable conformation since the selenium ester is trans to the β-hydrogens. When 1,4-elimination is restricted, nucleophilic attack at the α-position occurs and the subsequent hydrolysis of selenium(II) ester **18** affords alcohol as the product instead of enone. This explains the formation of the observed α-hydroxylation product(s).

In summary, a three-step method for the α,β-unsaturation of carboxylic acids that features the shortest synthetic route and most versatile substrate scope was developed. Careful thought was given to the introduction of a trifluoromethyl ketone, which made the utilization of this reaction possible. The intermediates, trifluoromethyl enone and γ-hydroxyl enone, as versatile substrates to multiple conversions,[15] are potentially important as the final products, especially in the context of medicinal chemistry as precursors of potent enzyme inhibitors.[16] Furthermore, a very important class of lipid peroxidation products can be easily prepared from a saturated fatty acid in three steps utilizing this methodology featuring a tandem γ-oxidation by selenium dioxide.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectral data. 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.

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