Review of Chemical Syntheses of 7-Keto-Δ^5-sterols

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ABSTRACT: Steroids bearing ketone functionality at carbon-7 are found commonly in nature, and the most prevalent of these are the 7-keto-Δ^5-sterols. These substances have diverse biological properties and are present in biological samples and food products. For the purpose of studying this class of oxysterols, many chemical methods, involving the chemical oxidation of Δ^5-sterols to the corresponding 7-keto-Δ^5-sterol derivatives have been developed to produce these compounds. We have undertaken a review and evaluation of chemical methods for the synthesis of these compounds and have endeavored to enhance one of these procedures to yield products for chemical and biological investigations.

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Some of the most frequently encountered oxysterols are those with a ketone function at carbon-7. The major portion of these is the 7-keto-Δ^5-sterols, which originate from the oxidation of Δ^5-sterols. These compounds, which are found in animal tissues, food products (1,2), and certain folk medicines (3–6), are significant inhibitors of HMG-CoA reductase (7,8), sterol synthesis (7,9), and cell replication (10–12).

The chemical synthesis of 7-keto-Δ^5-sterols relies on the allylic oxidation of carbon-7 of Δ^5-sterols. We have studied a number of different synthetic methods and procedures and review our findings here.

In many chemical and biological studies, 7-keto-Δ^5-sterols containing the 3β-hydroxyl group are the desired compounds. During the chemical (allylic) oxidation of the corresponding Δ^5-sterols, the 3β-hydroxyl group must be protected, usually as the acetate or benzoate ester (13,14), to avoid oxidation of the C-3 hydroxyl group to a ketone. The benzoate derivative is usually preferred owing to its superior crystallinity (i.e., ease of crystal formation leading to higher yields) when purified by recrystallization. Figure 1A demonstrates the reaction paths of oxidation that occur when the 3β-hydroxyl is not protected (15–19).

The most common methods of allylic oxidation of Δ^5-sterols are those that rely on the use of chromium(VI) reagents. Early or "classical" methods of oxidation used chromium trioxide (CrO_3) (20–23) or sodium chromate (24–26) and *t*-butyl chromate (27,28) in acetic acid; these afforded only limited success and produced the 7-keto compounds in modest yields. For example, the allylic oxidation of cholesteryl benzoate with sodium chromate in acetic acid/acetic anhydride gave 7-ketocholesteryl benzoate in an optimal yield of 38% (29). Figure 1B demonstrates the reaction that occurs when the 3β-hydroxyl group is protected.

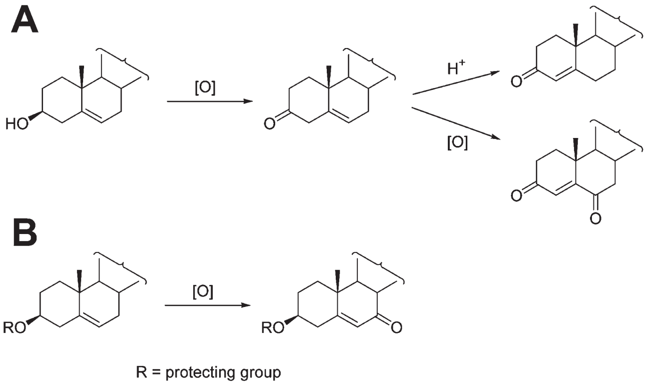

FIG. 1. Chemical oxidation of 3β-hydroxy-Δ^5-sterols (A) in the absence of a protection for the β-hydroxyl group and (B) in the presence of a protective group.

Synthetically useful changes in the properties and reactivity of chromium(VI) reagents have been brought about by the formation of amine complexes. The Collins reagent is formed by the complexation of chromium trioxide with pyridine (30,31). With this reagent, the allylic oxidation of cholesteryl benzoate gave a 68% yield of 7-ketocholesteryl benzoate (32), and in a related study, using anhydrous conditions, cholesteryl acetate was oxidized to 7-ketocholesteryl acetate in 72% yield (33). Similar complexes have been formed using chromium trioxide and pyrazole (34), 3,5-dimethylpyrazole (29), and benzotriazole (35) and have been shown to oxidize cholesteryl benzoate to 7-ketocholesteryl benzoate in 70–76% yields. These reactions require the preparation of the reagent complex before each reaction.

Commercially available pyridinium chlorochromate (PCC) has been widely used in organic synthesis for the oxidation of primary and secondary alcohols to carbonyl compounds (36). This reagent, in methylene chloride containing pyridine (37), other aromatic amines (38), pyrazole (39), 3,5-dimethylpyrazole (40), and benzotriazole (35), was reported to effect the selective oxidation of the allylic hydroxyl function of a number of steroidal alcohols. At room temperature, PCC in methylene chloride was an ineffective reagent for allylic oxidation (29). In contrast to these results, we have achieved moderate success by using PCC in refluxing methylene chloride for allylic and benzylic oxidations (41). PCC in DMSO also has been used for the oxidation of β-ionone to the corresponding diketone (42).

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Abbreviations: PCC, pyridinium chlorochromate; PFC, pyridinium fluorochromate; TBHP, *t*-butyl hydroperoxide.

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In a related study, we found that benzene was a superior solvent for allylic oxidations using PCC (43). PCC in refluxing benzene could effect a high-yield (87%) oxidation of cholesteryl benzoate to 7-ketocholesteryl benzoate. This conversion was accomplished with a 1:30 ratio of reagent (PCC) when 1–10 g of cholesteryl benzoate was oxidized. Oxidation of quantities of less than 1 g cholesteryl benzoate was successfully performed by using smaller quantities of reagent (1:25) with similar yields, thus demonstrating the usefulness of the described method for both large- and small-scale preparations. This efficient (i.e., high-yielding) procedure represents a significant improvement in both yield and convenience compared with other reported methods for the allylic oxidation of cholesteryl benzoate to 7-ketocholesteryl benzoate.

With the reaction conditions described (43), we conducted additional studies using other solvents with cholesteryl benzoate and PCC. Under these conditions, refluxing acetone, pyridine, *N,N*-dimethylformamide, and DMSO at 100°C yielded 7-ketocholesteryl benzoate in 2, 0, 18, and 77% yield, respectively. In an earlier study, we found that using refluxing methylene chloride as solvent yielded 54% of 7-ketocholesteryl benzoate from cholesteryl benzoate (41).

In another additional study, we showed that pyridinium fluorochromate (PFC), in refluxing benzene, was also an effective and convenient reagent for the efficient allylic oxidation of Δ^5-sterols to the corresponding C-7 unsaturated ketones in high yields (44). With this reagent, the allylic oxidation of cholesteryl benzoate resulted in an 88% yield of 7-ketocholesteryl benzoate. In the same study, cholesteryl acetate was oxidized to its 7-keto derivative in an 87% yield.

Other oxidation studies have used hydroperoxides [e.g., *t*-butyl hydroperoxide (TBHP)] with different types of catalysts. Chromium trioxide (45) and bis(tributyltin oxide)dioxochromium (46) have been used as catalysts to obtain 7-keto-Δ^5-sterols. However, epoxidation of the double bond was also observed. Good yields of these products were also reported when the reaction with the oxidizing agent TBHP was catalyzed by hexacarbonyl chromium (47,48) and ruthenium trichloride (49). However, the high toxicity of hexacarbonyl chromium, the high cost of the ruthenium catalyst, and potential safety risks have led researchers to explore other methods (50). The use of TBHP with catalysts such as Cu(I), Cu(II), or Cu metal (51) gave good yields in the allylic oxidation of Δ^5-sterols and required small amounts of reagents and solvents, and the copper catalysts were inexpensive and less toxic than the chromium reagents.

More environmentally friendly oxidations by molecular oxygen and *N*-hydroxyphthalimide as catalyst (52,53) give good yields of 7-keto-Δ^5-sterols. These methods are readily applicable and inexpensive, and the catalyst can be recovered. However, the required use of an oxygen atmosphere makes them inconvenient (50). In a related procedure, allylic oxidation at the C-7 position was accomplished using *N*-hydroxyphthalimide-catalyzed oxidation in air with benzoyl peroxide as a free radical initiator (54,55). The resulting C-7 hydroperoxide was dehydrated with copper(II) chloride in pyridine to produce the corresponding C-7 ketone of stigmasterol in 81–82% yield. In addition to being environmentally friendly, this procedure had an added advantage in that no protecting group was required for the 3β-hydroxyl group, since it was not oxidized under these reaction conditions.

Recently, TBHP has been used in the presence of copper(I) iodide, and tetra-*n*-butylammonium bromide was used as a phase-transfer catalyst in a two-phase system of water and methylene chloride (56,57). The allylic oxidation was found to proceed more efficiently when TBHP was added to the reaction mixture in portions. The high-yield conversion (>70%) of Δ^5-sterols into the corresponding C-7 unsaturated ketones in short reaction times was reported.

We have continued our studies on the allylic oxidation of Δ^5-sterols using PCC to produce the C-7 ketones. The use of both PCC and PFC in refluxing benzene represents one of the most convenient methods for the allylic oxidation of these substrates (43,44,58). However, long reaction times, large volumes of solvent, and high molar ratios of the oxidant are required.

To improve on these procedures, we tested the use of diphenyl diselenide as a catalyst to reduce reaction times and amounts of reagent required for oxidation and observed that lower quantities of the required reagent (PCC) were needed. That selenium reagents introduce a hydroxyl group at allylic positions in a substrate has long been known (59–61). In our case these substrates would be oxidized to a ketone. The involvement of the catalyst in this reaction would alter the mechanism and would be similar to that already described for the enhanced allylic chlorination of β-pinene using diphenyl diselenide as a catalyst (62).

When we modified our established procedure (43), PCC (1:5 molar ratio of steroid substrate/PCC) and catalytic amounts of diphenyl diselenide (1:0.1 molar ratio of steroid substrate/diphenyl diselenide) were heated together in refluxing benzene with cholesteryl benzoate; allylic oxidation at the

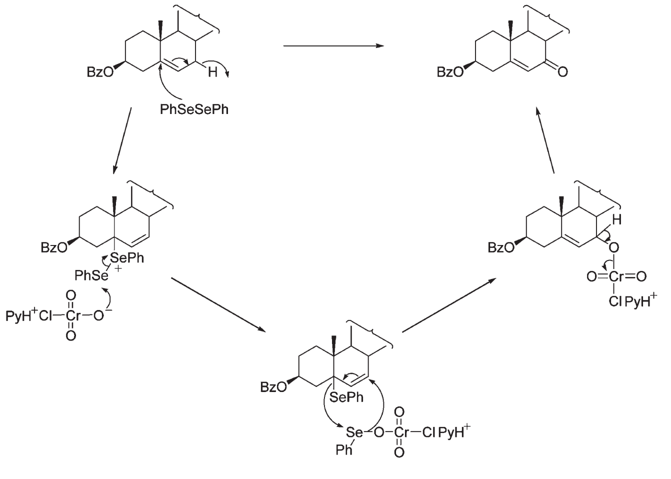

FIG. 2. Mechanism of allylic oxidation of cholesteryl benzoate by pyridinium chlorochromate and a diphenyl diselenide catalyst.

C-7 position occurred in 5 h, and 7-ketocholesteryl benzoate was obtained in 50% yield. Continued heating for a total of 24 h produced a 76% yield. When this reaction was conducted in the absence of a diphenyl diselenide catalyst, an 11% yield of the C-7 ketone was obtained after 24 h of reaction. Without the catalyst, a molar ratio of 1:30 of PCC was required for optimal product yield (87%). A proposed mechanism for the allylic oxidation of cholesteryl benzoate using PCC and diphenyl diselenide is shown in Figure 2. The ionic mechanism shown is supported by the addition of 2,2′-azobisisobutyronitrile, a radical initiator (63), which produced no observed enhancement of the reaction rate (monitored by TLC) or final yield of the reaction product.

In conclusion, we believe the results presented herein provide useful information concerning the chemical synthesis of 7-keto-Δ^5-sterols resulting from the allylic oxidation of Δ^5-sterols. The major methods of synthesis have been reviewed and the advantages of certain procedures have been indicated. In addition, we have attempted to develop novel and efficient approaches to the synthesis of these products.

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