A Mild One-Pot Method for Conversion of Various Steroidal Secondary Alcohols into the Corresponding Olefins

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Dedicated to Professor Carmen Nájera on her 60th birthday

Abstract: The addition of Tf_2O to some hydroxy steroids in the presence of excess base directly leads to steroidal olefins. This methodology is useful for the one-pot synthesis of Δ^2- or Δ^3-steroids under mild conditions from the corresponding alcohols.

Key words: alcohols, biliary acid, elimination, steroids, triflic anhydride

Steroids are important compounds in biological systems due to their vital role in hormonal cycles.[1] Among them steroid epoxides belong to the class of oxysterols (derivatives of cholesterol) that regulate cell proliferation and cholesterol homeostasis in organism.[2a] They are also versatile intermediates for organic synthesis as they can be transformed to various steroidal derivatives.[2b–d] The precursors for such epoxides may be the corresponding olefins. There are various direct and indirect established methods for the synthesis of such olefins. Usual procedures involve transformation of keto-steroids to α-halo ketones subsequently converted into the corresponding hydrazone followed by a Kishner reduction to obtain the olefins[3a] or reduction of α-haloketones to halohydrins followed by Zn-mediated reductive elimination.[3b,c] An alternative approach is the conversion of steroidal secondary alcohols into the corresponding tosylates,[4] halides,[5] or propargyl xanthates[6] followed by the base-mediated elimination.

There are few reports of direct conversion of steroid secondary alcohols into the corresponding olefins. For example, TsOH on silica gel[7] or methyl(carboxysulfamoyl)triethylammonium hydroxide inner salt[8] can act as dehydrating agents, but these methods require harsh conditions or a special reagent.

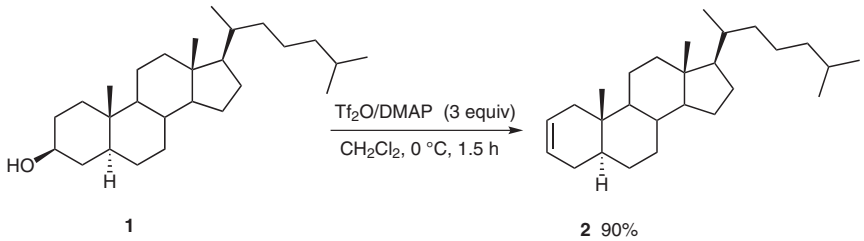
Herein we report the use of Tf_2O (triflic anhydride)/DMAP (dimethylaminopyridine) or Tf_2O/pyridine as an efficient system for the direct synthesis of various steroid olefins from the corresponding secondary alcohols.

In our ongoing research on steroid systems we treated 5α-cholestan-3β-ol **1** with 1 equivalent of Tf_2O and 3 equivalents of DMAP in dichloromethane (CH_2Cl_2) at 0 °C. Instead of the expected triflate, the corresponding olefin **2** was isolated in excellent yield (Scheme 1).

Since the scope of this reaction has not been explored, we decided to apply it to various steroids.[10] Thus, compounds **3a** and **3b** under Tf_2O/DMAP conditions were transformed to the corresponding olefins **4a**[11] and **4b**[12] in good yields (Table 1). 5α-cholestan-3α-ol (**3c**) also gave Δ^2-cholestene (**2**) under similar reaction conditions, but longer reaction time was needed.

Homoallylic alcohols, such as cholesterol **3d** and pregnenolone **3e**, were transformed to the corresponding *i*-steroid olefins **4d**[13] (46%) and **4e**[14] (58%). Testosterone (**3f**) provided a mixture of unsaturated olefins **4f**[15] in 70% yield. In this case the dehydration was accompanied by a methyl migration as is often observed in the case of a carbocation generated at C17.[10]

The DMAP/Tf_2O methodology was also applied to several biliary acid derivatives (Table 2). Methyl cholate (**3g**) gave a mixture of olefins **4g** in 76% yield (Δ^2/Δ^3 = 1:4). Methyl deoxycholate (**3h**) gave the corresponding olefin **4h**[16] (74%); whereas methyl lithocholate (**3i**) led to an inseparable mixture of Δ^2/Δ^3-olefins **4i**[17] (78%).



1 **2** 90%

Scheme 1 Synthesis of Δ^2-cholestene

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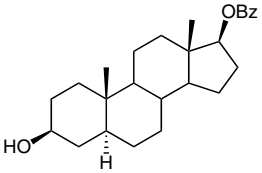
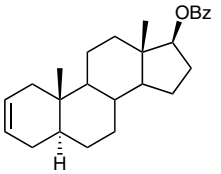
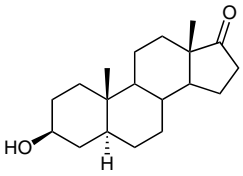
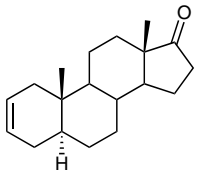
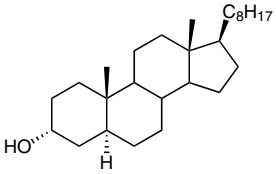
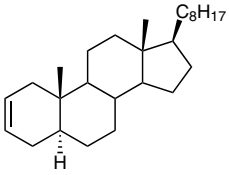
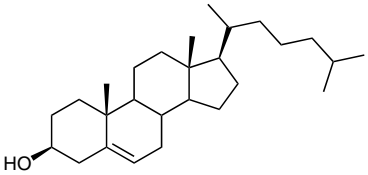
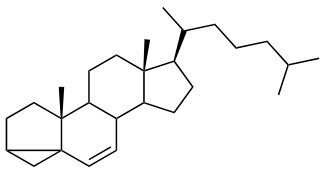
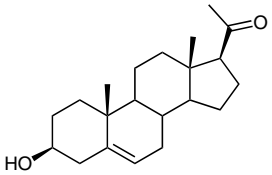
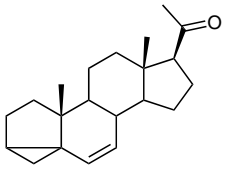
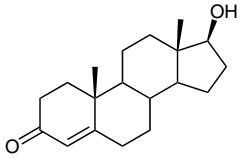
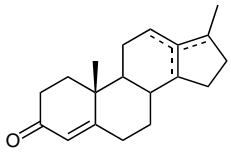
Table 1 Synthesis of Steroidal Olefins Using Tf_2O/DMAP System

Alcohol	Product	Yield (%)[a,b]
 **3a**	 **4a**	92
 **3b**	 **4b**	70[c]
 **3c**	 **2**	70[d]
 **3d**	 **4d**	46
 **3e**	 **4e**	58
 **3f**	 **4f** $\Delta^{17}/\Delta^{13}/\Delta^{12}$ = 1.2:1.1:0.4	70

[a] Reaction conditions: steroid (1 mmol), Tf_2O (1 equiv), DMAP (3 equiv), CH_2Cl_2 (5 mL), 0 °C, 2 h. Isolated yield after flash chromatography on silica gel.

[b] Structure established by comparison of ^1H NMR spectra with reported compounds.

[c] Reaction was quenched over cold solution of sat. $NaHCO_3$ solution to destroy some enol triflate at C17.

[d] Reaction was quenched after 5 h.

The influence of the base on the elimination reaction was checked with cholestanol **1** (Table 3). DMAP, pyridine, and DIPEA (diisopropylethylamine) gave excellent yields while triethylamine provided moderate yields.

In order to make the procedure synthetically useful we developed an approach for the multigram-scale synthesis of Δ^2-cholestene (**2**) from commercially available cholestanol (**1**) using pyridine as a base. The reaction was scaled up to 10 g scale with 75% yield after crystallization.

In conclusion, we have developed conditions where the use of Tf_2O in the presence of excess base leads directly to steroidal olefins. This methodology is particularly useful for the one-pot synthesis of certain Δ^2- or Δ^3-steroids from the corresponding alcohols. We have also developed a multigram-scale approach for the synthesis of Δ^2-cho-

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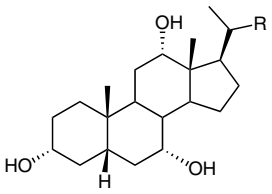
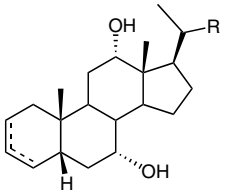
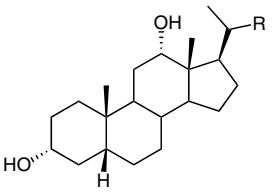
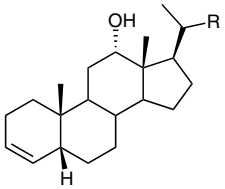
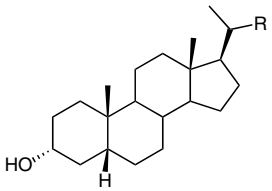
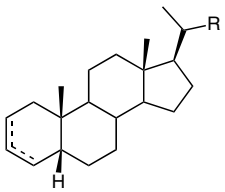
Table 2 Treatment of Various Biliary Acid Derivatives with Tf_2O/DMAP System

Alcohol	Product	Yield (%)[a,b]
 **3g** R = CH_2CH_2COOMe	 **4g** Δ^2/Δ^3 = 1:4	76
 **3h** R = CH_2CH_2COOMe	 **4h**	74
 **3i** R = CH_2CH_2COOMe	 **4i** Δ^2/Δ^3 = 3:7	78

[a] Reaction conditions: steroid (1 mmol), Tf_2O (1 equiv), DMAP (3 equiv), CH_2Cl_2 (5 mL), 0 °C, 2 h. Isolated yield after flash chromatography on silica gel.
[b] Structure established by comparison of proton NMR spectra with reported compounds.

Table 3 Effect of Base on Elimination Reaction with Cholestanol (**1**)

Base	Yield of olefin **2** (%)[a,b]
DMAP	90
pyridine	85
DIPEA	89
Et_3N	72

[a] Isolated yield after chromatography on silica gel.
[b] Reaction conditions: cholestanol (**1**, 1 mmol), Tf_2O (1 equiv), DMAP (3 equiv), CH_2Cl_2 (5 mL), 0 °C, 2 h.

lestene. Details on the scope and the mechanism of the reaction are under investigation.[18]

General Procedure

Triflic anhydride (1.5 mmol) was slowly added to a solution of alcohol (1 mmol) and DMAP (3 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After completion of addition the reaction was stirred for 2 h. The reaction was quenched in ice-cold H_2O and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were separated and dried over anhyd Na_2SO_4. After evaporation of solvent, the crude solid was purified by flash chromatography on silica gel to furnish the corresponding alkene.

Multigram Scale Synthesis of Δ^2-Cholestene (2)

Triflic anhydride (6.52 mL, 38 mmol) was slowly added to a solution of cholestanol **1** (10 g, 25 mmol) and pyridine (6 mL, 150 mmol) in CH_2Cl_2 (60 mL) at 0 °C. After completion of addition, the reaction was stirred for 2 h. The reaction was quenched in ice-cold H_2O and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was separated and dried over anhyd Na_2SO_4. After evaporation of solvent, the crude solid was purified by crystallization using CH_2Cl_2–MeOH to obtain Δ^2-cholestene **2** (7.28 g, 75%).

Δ^2-Cholestene[9]

Mp 68 °C; $[\alpha]_D$ +63.5 (*c* 1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 0.70 (s, 3 H), 0.79 (s, 3 H), 0.88 (d, *J* = 6.8 Hz, 6 H), 0.91 (d, *J* = 7.8 Hz, 3 H), 1.01–2.00 (m, 29 H), 5.61–5.63 (m, 2 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 125.9, 128.8, 54.1, 56.5, 56.3, 42.5, 41.4, 40.0, 39.8, 39.5, 36.2, 35.8, 35.6, 34.6, 31.8, 30.3, 28.8, 28.3, 28.0, 24.2, 23.9, 22.8, 22.6, 22.9, 18.7, 12.0, 11.7.

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