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A Practical Procedure for Chemo- and Regioselective Conversion of Steroid 3-ketones into the Corresponding Enol Sulfonates Using 3-oxa-octafluoropentanosulfonyl fluoride

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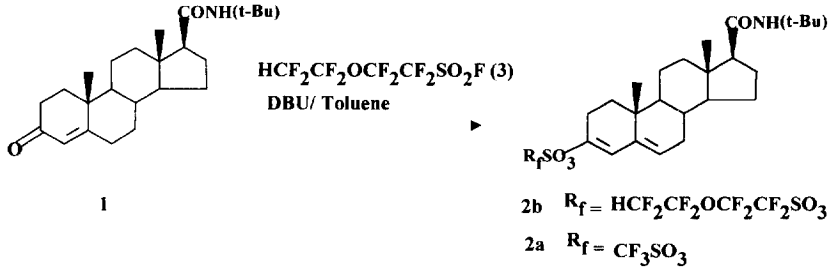
Abstract: In the presence of 3 equiv. of 5H-3-oxa-octafluoropentanosulfonyl fluoride and 3 equiv. of DBU in toluene at 90°C, steroid 3-ketones were chemo- and regioselectively converted in 56-91% yields to the corresponding 3-enol sulfonates, which could be easily transformed into the 3-carboxyl unsaturated steroids, a group of compounds of significant pharmacological importance.

Enol triflates are excellent precursors to vinyl cations and alkylidene carbenes. For this reason, they have become increasingly popular in organic synthesis (especially in the synthesis of natural products and bioactive molecules)[1]. One of the important applications of enol triflates is their easy conversion to corresponding carboxylic acids via palladium-catalyzed carbon monoxide insertion. In this way steroid 3-ketones can be converted to the corresponding 3-carboxyl unsaturated steroids[2], which have proven to be a new type of human 5α-reductase inhibitor[3] with great potency. However, for practical applications, this method suffers from the involvement of expensive and moisture-sensitive triflic anhydride. In addition, in a direct conversion of α,β-unsaturated steroid-3-one-17β-carboxamide **1** into the corresponding dienol triflate **2a** with triflic anhydride[3a], a 2:1 mixture of **2a** and its 17-nitrile byproduct was obtained. Therefore, it is highly desirable to seek more practical and economical alternative procedures for chemo- and regioselective conversion of steroid 3-ketones into their corresponding enol sulfonates[4].

Per- and polyfluoroalkanesulfonyl fluorides are structurally similar to the triflating agents. However, they are much easier to handle and much less expensive. It has been known that nonfluorobutanesulfonyl fluoride can be reacted with the sodium enolates of some simple ketones to produce the corresponding

enol nonfluorobutanosulfonates in 15-50% yields[5]. Reaction[6] of polyfluoroalkanesulfonyl fluoride with phenols or per(or poly)fluoroalkanyl alcohols is also known to take place easily. This inspired us to examine if per- or polyfluoroalkanesulfonyl fluoride could react with enolizable ketones in the presence of a proper base.

When we treated steroidal ketone **1** with 3 equiv. of 5H-3-oxa-octafluoropentanosulfonyl fluoride (**3**) in the presence of **DBU** (1, 8-diazabicyclo-[5,4, 0]undec-7-ene) at 90°C , the steroid 3-enol 5H-3-oxaoctafluoro-pentano sulfonate **2b**[7] was produced as the sole product (Scheme 1). Several other per- or polyfluoro-alkanesulfonylfluorides were also tested and the results are summarized in Table 1.



Scheme 1

Table 1 The results of the reaction of compound **1** with sulfonyl fluoride

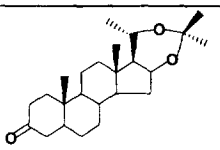
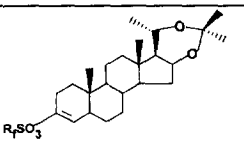
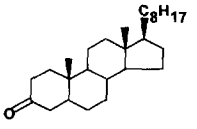
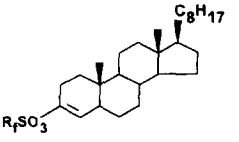
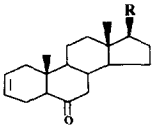
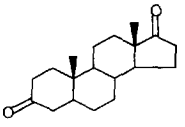
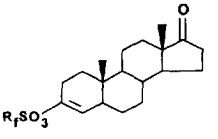
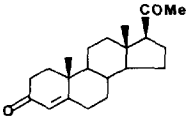
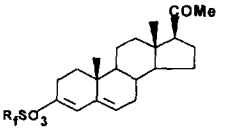
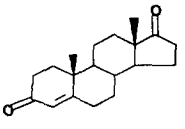
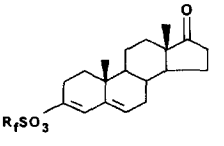
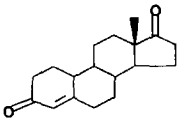
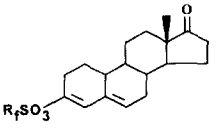
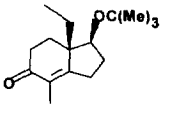
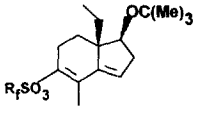
Entry	Reagent	Time (hrs)	Yield (Conversion ratio %)[a]
1	$HCF_2CF_2OCF_2CF_2SO_2F$	6	**2b** 77(100)
2	$C_8F_{17}SO_2F$	18	**2c** 44(60)
3	$ICF_2CF_2OCF_2CF_2SO_2F$	11	**2d** 28(70)
4	$MeOOCCF_2SO_2F$	8	no reactions

a. Isolated yields based on the conversion of **1**

The most satisfactactory solvent for this reaction seems to be anhydrous toluene. In other solvents such as dichloromethane, chloroform, tetrachloromethane, tetrahydrofuran , no reaction was observed. We have also tested a series of other organic bases, but these were no better than **DBU** .

To explore the scope and limitations of this reaction, we further examined other ketones (part of the results shown in Table 2). Interestingly, it was found that the 5H-3-oxa-octafluoropentanosulfonylation reaction of steroid-3-one occurred only at the C-3 position, other functional groups such as amide and ketal (entry **1**) were not affected. When steroidal diketones were subjected to this reaction, no reactions occurred to the C-6 (entry **3**), the C-17 (entry **4, 6, 7**) and the C-20 carbonyls (entry **5**) while the C-3 ones were readily transformed to the corresponding enol sulfonate. Such high chemo- and regioselectivity is obviously of great

Table 2 The outcomes of the reaction of 5H-3-oxooctafluoropentanosulfonyl fluoride with some ketones

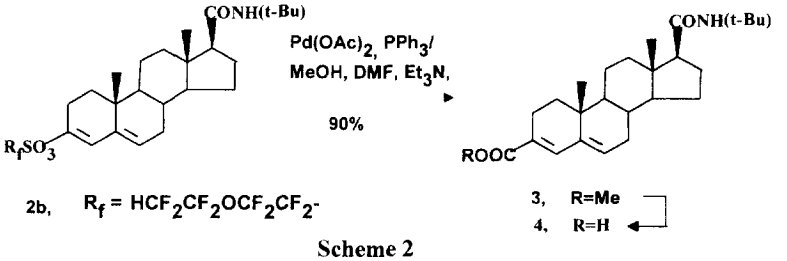
Entry	Substrate	Time (hr)	Product[a,b]	Yield (%)
1		12		76
2		11		80
3		12	No reaction	0
4		9		91
5		11		60
6		12		50
7		11		64
8		8.5		56

a. $R_f = HCF_2CF_2OCF_2CF_2$-

b. R = -$(CH_3)CHCH{=}CHCH(CH_3)CH(CH_3)_2$

value in steroid chemistry. This reaction was also applicable to other easily enolizable ketones (entry **8**).

With 5H-3-oxa-octafluoropentanosulfonates in our hands, we further examined their reactivity. Similar to enol triflates, the palladium catalyzed carbonylation of 5H-3-oxa-octafluoropentanosulfonate **2b** produced 3-carboxyl steroid **3** in 90% yield (Scheme 2), which could be converted to a new type of steroidal 5α-reductase inhibitor---Epristeride (**4**) by hydrolysis.



Scheme 2

In conclusion, we have found that 5H-3-oxaoctafluoropentanosulfonyl fluoride can react directly with steroid-3-one in exellent chemo- and regoselectivity to produce the corresponding steroid 3-enol sulfonates, which possess similar reactivities to enol triflates in the palladium-catalyzed carbonylation. Therefore, the present procedure provides a new practical and economical route to 3-carboxyl steroids.

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7. Typical procedure: To a solution of **1** (1mmol) and **DBU** (1-5mmol) in dry toluene was added dropwise 5H-3-oxaoctafluoropentanosulnyl fluoride (1-5mmol) at 90°C over 3 hours. The reaction then was continued until the spot of **1** on TLC disappeared. Removal of the solvent under reduced pressure gave the crude product, which was purified by column flash chromatography on silica gel to give **2b**, m.p. 78.5-80.7°C. $[\alpha]^{20}_D$ - 7. 33° (c 1. 05, $CHCl_3$). ^{1}**HNMR**(300MHz, $CDCl_3$, TMS) : 0.73 (s, 3H, 18-CH_3), 0.97 (s, 3H, 19-CH_3), 1.36 (s, 9H, C(CH_3)$_3$), 5.09 (br, 1H, NH), 5.57 (d, 1H, J=3.3 Hz, C_6-H), 5.86 (tt, 1H, J=3.0, 52.4Hz, HCF_2), 6.0 (s, 1H, C_4-H) ppm. **MS** m/z: 652
(M^+ +1), 651 (M^+), 587, 372, 371, 370, 314, 57. **IR** (film)v: 3400, 2900, 1660, 1500, 1450, 1410, 880 cm^{-1}; satisfactory elemental analysis was obtained.

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