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Some new reactions of poly(per)fluoroalkanesulfonyl fluorides with steroidal molecules

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Abstract

The reactions of poly(per)fluoroalkanesulfonyl fluorides with steroidal ketones and alkenyl halides as well as 19-hydroxyl steroids were studied in detail. Utilizing these reactions, some steroidal molecules with the biological activity or structurally unique properties have been synthesized.

Keywords: Steroid; Enol poly(per)fluoroalkanesulfonates; Trifluoromethylation

1. Introduction

The unique chemical reactivity and the potential biological activity of fluorine-containing molecules attract us to come to this field of organic fluorine chemistry [1–4]. Several years ago, we have studied the reaction of trifluoromethyloxazolones with C=C or C=X or X=Y bond and utilized such reaction to synthesize some (trifluoromethyl) heterocycles [5–7].[1] After feeling the fascination of fluorinated compounds, we pay more attention on the reaction of poly(per)fluoroalkanesulfonyl fluorides and their application in organic synthesis, because many poly(per)fluoroalkanesulfonyl fluorides have been manufactured for the demand of industrial product. In general, these fluorides are commercially available. For instance, we can easily get the required polyfluoroalkanesulfonyl fluorides from our attached factory. The reaction of poly(per)fluoroalkanesulfonyl fluorides, such as nucleophilic reaction on the sulfur atom, has been reported [9–11]. And some polyfluoroalkanesulfonyl fluorides, such as methyl fluorosulfonyldifluoroacetate, iododifluoromethanesulfonyl fluoride, have been also used as good precursors of difluorocarbene and trifluoromethyl carbanion [12]. We wish to present some new results of the reaction of poly(per)fluoroalkanesulfonyl fluorides with steroids as well as their application to the synthesis of steroidal molecules with biological activity or unique structure.

2. The reaction of per(poly)fluoroalkanesulfonyl fluorides with steroidal ketones and their application to the synthesis of steroidal 5α-reductase inhibitors

Enol triflates are the important intermediates for carbon–carbon bond formation and they are applied to the synthesis of natural products and bioactive molecules [13]. In general, enol triflates can be prepared via the direct reaction of carbonyl compounds with triflic anhydride or the reaction of the enolate with other triflating agent, such as trifluoromethanesulfonimide. However, there are some disadvantages due to the moisture-sensitive nature of these rather expensive triflating agents. In order to seek new reagent suitable for the practical application (similar efforts refer to [14]), we tested the reaction of poly(per)fluoroalkanesulfonyl fluorides with steroidal ketones **1** and found that poly(-per)fluoroalkanesulfonyl fluoride reacted with 3-ketosteroids to produce the corresponding enol sulfonates **2** (Scheme 1) [15].

Yields of the enol sufonates **2** were dependent upon not only the poly(per) fluoroalkanesulfonyl fluoride, base as well as solvent, but also related to the ability of enolization of the carbonyl group. Table 1 shows the effect of the structure of poly(per)fluoroalkanesulfonyl fluoride on the yield of the enol sufonates **2** in the reaction of 3-ketosteroid **1a**. Table 2 shows the effect of base and solvent in the reaction of **1a** with sulfonyl fluoride leading to **2a**.

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[1]Synthesis of trifluomethylated heterocycleos have been also reported at Hong Kong International Symposium on Heterocyclic Chemistry (see [8]).

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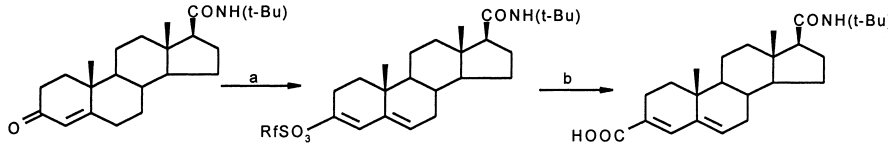


1a **2a** **3a**

Scheme 1. Reagents: (a) 5H-3-oxa-octafluoropentanesulfonyl fluoride/DBU/toluene; (b) $Pd(OAc)_2$, CO/DMF.

Table 1
The effect of poly(per)fluoroalkanesulfonyl fluorides[a]

Entry	Reagent	Time (h)	Product	Yield (conversion)
1	$HCF_2CF_2OCF_2CF_2SO_2F$	6	**2a**	77% (100)
2	$C_8F_{17}SO_2F$	18	**2b**	44% (60)
3	$ICF_2CF_2OCF_2CF_2SO_2F$	11	**2c**	28% (70)
4	$MeOOCCF_2SO_2F$	8	**2d**	No reaction

[a]The reaction of compound **1a** and the indicated sulfonyl fluoride was carried out in toluene at 90–100°C in the presence of DBU.

Table 2
The effect of base and solvent[a]

Entry	Base	Solvent	Temperature (°C)	Time (h)	Yield (conversion)
1	Et_3N	CH_2Cl_2	r.t	24	No reaction
2	Et_3N	CH_2Cl_2	Reflux	7	No reaction
3	DBU	CH_2Cl_2	Reflux	8	Nearly no reaction
4	DBU	THF	Reflux	4	Nearly no reaction
5	DBU	CCl_4	Reflux	8	(50%)
6	DBU	Toluene	90–100	10	77%

[a]In the reaction of compound **1a** and 5H-3-oxa-octafluoropentanesulfonyl fluoride.

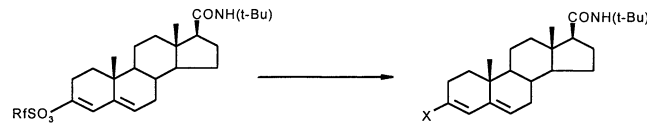
Table 3
Pd catalyzed coupling reaction of **2a**

Entry	Reagents	Product	Yield (%)
1	CO/DMF	**3a**, R = COOH	70
2	CO/DMF–MeOH	**3b**, R = COOMe	90
3	HCOOH/DMF	**3c**, R = H	85
4	$CO/DMF/Et_2NH$	**3d**, $R = CONEt_2$	82
5	$EtOCH{=}CH_2$	**3e**, $R = COCH_3$	74
6	$HPO(OEt)_2$	**3f**, $R = PO(OEt)_2$	92
7	PhC≡CH	**3g**, R = C≡CPh	85

Enol sulfonation reaction described here was found to be specific for the conversion of carbonyl group at C-3. Under the present condition, poly(per)fluoroalkanesulfonyl fluorides shown in Table 1 did not react with amides, ketals as well as the carbonyl group at other than C-3 position. Therefore, poly(per)fluoroalkanesulfonyl fluorides can serve as an efficient chemo- and regioselective reagents in the preparation of steroid 3-enol fluorinated sulfonates.

The reactivity of the enol poly(per)fluoroalkanesulfonates is comparable to enol triflates. For instance, palladium catalyzed coupling reaction of the enol poly(per)fluoroalkanesulfonates proceeded very well. For example, we utilized this reaction to achieve a practical synthesis of epristeride **3a**, a new steroidal 5α-reductase inhibitors [15].

We also synthesized some new 3-substituted steroids through the coupling reaction of the steroid 3-enol 5H-3-oxaoctafluoropentanesulfonate as shown in Table 3. Interestingly, the synthesized 3-substituted steroids **3f** and **3g** showed inhibitory activity against steroidal 5α-reductase in preliminary bioactivity assay [16].



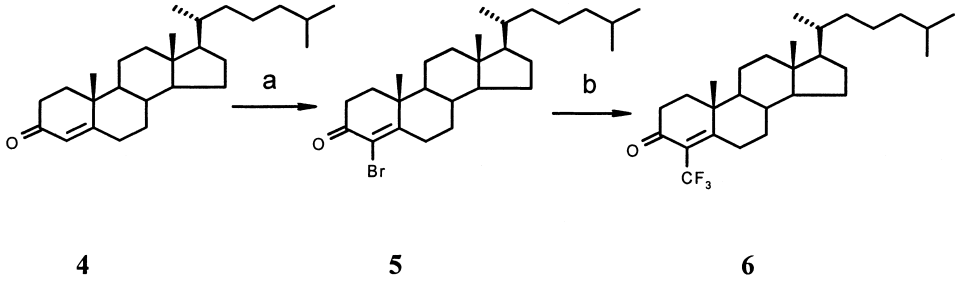
2a **3**

3. Trifluoromethylation of steroidal alkenyl halides with fluorosulfonyldifluoroacetate and the design, synthesis and bioactivity of 4-(trifluoromethyl)-steroid Δ^4-3-ones

Trifluoromethylated compounds have received much attention because of their potential application value in the materials, medicines and agrochemicals [1–4]. Numerous methods for synthesis of trifluoromethylated compounds, the building block strategy or trifluoromethylation, have been reported [17]. As previously reported, methyl fluorosulfonyldifluoroacetate (MFSDA) with CuI served as inexpensive trifluoromethylating agent, in particular for the preparation of (trifluoromethyl)alkenes and (trifluoromethyl)arenes [12]. We found that this reagent system works well with steroidal alkenyl bromides or iodides to produce the corresponding trifluoromethyl steroids in moderate to good yield [18] (Scheme 2).

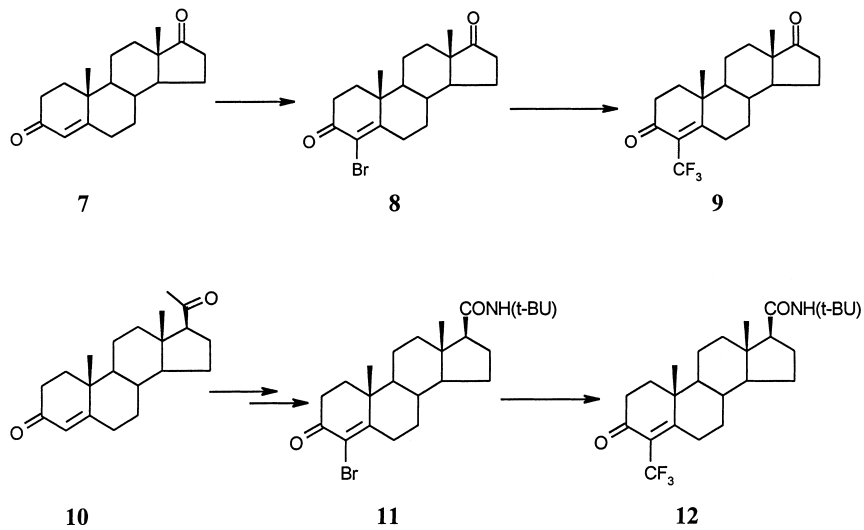
This procedure is also suitable for the introduction of trifluoromethyl group at C-3, C-6, C-12, C-17 and other position in steroidal skeleton using the corresponding alkenyl halide [18]. The alkenyl halide adjacent to carbonyl group is more reactive than the one without adjacent carbonyl group.

Using this method, we synthesized 4-(trifluoromethyl)-testesterone **9** and 4-(trifluoro methyl)-*N*-(*t*-butyl)-4-androsten-17-carboxamide **12** from testosterone **7**and progesterone **10,** respectively (Scheme 3). Both compounds **9, 12** exhibited highly inhibitory activity against 5α-reductase in the preliminary bioactivity assay [19].



4 5 6

Scheme 2. Reagents and conditions: (a) Br_2/HOAc, collidine/ether; (b) $FO_2SCF_2CO_2CH_3$, CuI, DMF, 75°C.



7 8 9

10 11 12

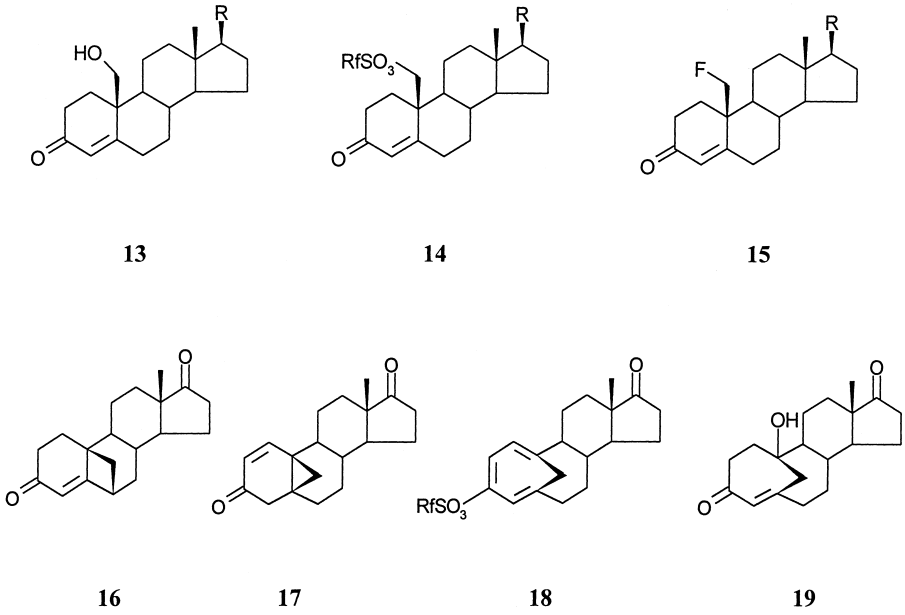
Scheme 3

4. The reaction of poly(per)fluoroalkanesulfonyl fluorides with 19-hydroxymethyl steroids

19-Hydroxymethyl testosterone is an important intermediate both in the biological transformation of androstenone into estrogen and the preparation of estrogen starting from andronstenone. In order to prepare new fluorine-containing steroid for screening of enzyme inhibitor, the reaction of 19-hydroxymethyl testosterone with DAST reagent as well as Yarovenko reagent ($Et_2NCFCHClF$) have been reported [20,21]. The reaction of androst-4-ena-3,17,19-triol 3,17-diacetate with DAST reagent followed by Oppennauer oxidation afforded 19-fluorinated steroid **15** only in lower than 1% yield [20]. The reaction of 19-hydroxymethyl testosterone with Yarovenko reagent formed 10-fluorosteroid in 38% yield. During the course of our study on the reaction of poly(per)fluoroalkanesulfonyl fluorides with 19-(hydroxymethyl)testosterone, we obtained several new steroids **16**, **18** and **19** together with the known 19-fluorinated steroid **15** [20] and rearrangement product **17** [21] (Scheme 4). The reaction of poly(per)fluoroalkanesulfonyl fluorides with 19-(hydroxymethyl) testosterone **13** at 0°C firstly produced the thermally unstable poly(per)fluoroalkanesulfonates **14**, which then decomposed to corresponding products.

The products and their yields can be controlled by the choice of reaction conditions. 19-(Hydroxymethyl)testosterone **13** reacted with 2 equivalent of 5H-3-oxaoctafluoropentanesulfonyl fluoride in toluene at 30°C in the presence of 1,8-diazabicyclo[5.3.0]undec-7-ene (DBU) to afford compound **15** (9.2%), **16** (24.7%) and **18** (40.8%). When 4 equivalent of sulfonyl fluoride was used, the yield of compound **15**, **16** and **18** is 35%, 20% and 40%, respectively. On using triethylamine instead of DBU, only **17** was obtained in 95% yield. A successive treatment of **13** with the sulfonyl fluoride and triethylamine followed by DBU gave the product with the A/B ring of 6,7,8,9-tetrahydro-5,10-methano-[10]-annulen **18** ($Rf = HCF_2CF_2OCF_2CF_2$) in 83% yield. Compound **14** without isolation reacted with tetrabutylammonium fluoride to give **16** in 90% yield. When **13** reacted with sulfonyl fluoride under the moisture reaction condition, another rearrangement product **19** was obtained. Both of **17** and **19** can be transformed into **18** further by the reaction with sulfonyl fluoride. A plausible reaction mechanism for the direct conversion of **13** to **18** is considered to be related to a tandem homoallylic alcohol–norcaradien–cycloheptatiene rearrangement.

The new steroid compounds described above can be considered as analogs of androgen or estrogen. They are suitable to serve as the inhibitors of 5α-reductase and/or



Scheme 4

aromatase. The study on the biological evaluation of synthesized steroids and the scope of this reaction are in progress.

In summary, we studied the reactions of steroidal ketones, alkenyl halides and 19-hydroxyl steroids with poly(per)-fluoroalkanesulfonyl fluorides, particularly with the poly-fluoroalkanesulfonyl fluorides easily available in China. The usefulness of such reactions have been demonstrated by applying them to the synthesis of some biologically active or structurally unique molecules.

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