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Perfluoroalkylsulfonyl fluoride in organic synthesis: a facile synthesis of 17α-hydroxy steroids

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ABSTRACT

A facile synthesis of 17α-hydroxy steroids with perfluoroalkylsulfonyl fluoride as hydroxyl activating agent was reported. The method features mild (40 °C), rapid (0.5 h), high yield, and high functional group tolerance. Notably, the method is applicable to HCOOH and CF_3COOH, unusual and synthetically useful nucleophiles in hydroxyl inversion reaction.

The important physiological properties of steroids have created a strong demand for practical preparation of these type of compounds from more abundant steroid resources.[1] Steroids bearing a 17β hydroxyl group can be easily prepared from 17-oxo steroids via a stereospecific reduction.[2] On the contrary, 17α-hydroxy steroids are much less explored due to synthetic difficulties.

Premarin, a commercial drug isolated from pregnant mare's urine for hormone replacement therapy, consists of complex mixtures of at least 10 estrogens.[3] Three active ingredients in Premarin were confirmed to be 17α-hydroxy steroidal estrogens[3a] (Fig. 1), and therefore 17α-hydroxy steroids have become important synthetic targets for the chemical synthesis of Premarin. Notably, estrogen **3** is a synthetically challenging molecule due to the instability of unconjugated double bonds toward acids, bases, and high temperature.

Generally, 17α-hydroxy steroids can be prepared from easily available 17β-epimers via a S_N2 substitution.[4,5] Conventional methods for hydroxyl inversion include Mitsunobu reaction[4] and substitution of sulfonyl ester.[5] Benzoic acid and acetic acid are common nucleophiles for the purpose. However, subsequent hydrolysis of the formed esters typically requires harsh conditions, which leads to poor functional-group compatibility. Although formate ester and trifluoroacetate esters are more labile and their deprotection is much easy under mild conditions, our attempts to achieve C-17 hydroxyl inversion with these unusual

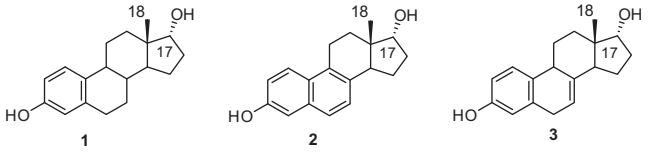

Figure 1. 17α-hydroxy steroidal estrogens in Premarin.

nucleophiles via these conventional methods[4a,5a] were unsuccessful due to the steric effect of C-18 methyl and the lower reactivity of the nucleophiles.

Therefore, developing reliable hydroxyl inversion procedures with broad nucleophile scope and functional-group compatibility is desirable. In the context of our ongoing research in the field of perfluoroalkylsulfonyl fluoride in organic synthesis,[6,9] we herein reported a facile hydroxyl inversion procedure with perfluoroalkylsulfonyl fluoride as hydroxyl activating agent. The method features mild reaction condition, short reaction time, and high functional-group compatibility. Most importantly, the method is suitable for unusual nucleophiles, such as HCOOH and CF_3COOH.

The attempts began with the preparation of highly active perfluoroalkylsulfonyl ester. Our experience indicated the ester can be stable in the absence of bases or nucleophiles. Perfluoroalkylsulfonyl fluoride was added to the mixture of substrate **4** and DBU at low temperature to provide the desired product **5** in 15 min. The base and salt were removed via a rapid

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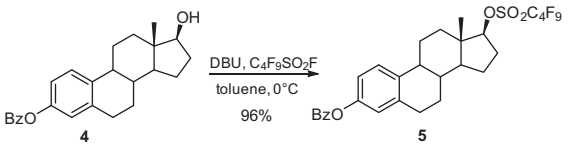


Scheme 1. Preparation of perfluoroalkylsulfonyl ester.

filtration through a short silica gel column to offer pure ester **5** in high yield (Scheme 1).[7]

With the perfluoroalkylsulfonyl ester **5** in hand, we turned our attention to the subsequent inversion reaction. Recently Shi reported the tunable complex of organic base and carboxyl acid was highly efficient nucleophiles for the S_N2 substitution of mesyl ester.[5a] As expected, the reaction rate of perfluoroalkylsulfonyl ester was dramatically faster than that of mesyl ester (0.5 h vs 9 h, Table 1, entry 1), albeit with significant amount of rearrangement and elimination byproducts. When more base was used, the byproducts were decreased at the expense of partial hydrolysis of product (entry 2). Further study indicated that the low temperature suppressed the deprotection (entries 3–6). Notably, the reaction performed well even at room temperature (entry 6). The solvent effect was then investigated, and toluene, THF, and ethyl acetate was revealed to be the best solvent of choice (entries 7–12). The amount of acid and base can be reduced without a significant decrease of yield and rate (entries 13–15). However, attempts to replace DBU with Et_3N or inorganic bases were unsuccessful (entries 16–18).

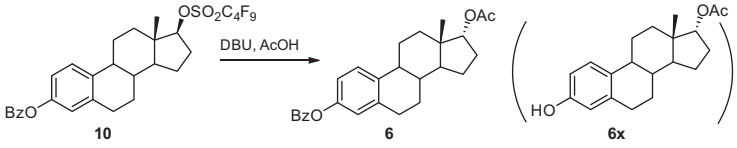
Encouraged by the initial findings, we set out to explore the nucleophile scope (Table 2). Acetic acid and benzoic acid as nucleophiles gave desired products in good yield. Formic acid, an unusual nucleophile, smoothly provided desired ester **8** in good yield (entry 3). Surprisingly, trifluoroacetic acid was tolerated in the methodology to offer trifluoroacetate ester **9** in moderate yield. The reaction with water as nucleophile took place and directly offered 17-α-hydroxyl product **10,** albeit in low yield.

We next examined the substrate scope (Table 3). The pure sulfonyl esters were separated and reacted with nucleophiles according to the procedure described above. All 17β-hydroxy steroids performed well in both the sulfonylation and substitution steps. The unstable enol ethers could be incorporated owing to the mild reaction condition (entry 3). Notably, although a stoichiometric amount of fluoride salt formed during the sulfonylation, silyl-protected substrate was insusceptible (entry 4). The non-steroid substrate derived from Hajos–Parrish ketone was tolerated, affording product **21** in high yield (entry 5). However, the sulfonic esters of Wieland–Miescher ketone, 3-hydroxy steroid, and 11-hydroxy steroid were found to be very unstable (entries 6–8), thereby resulting in deoxyfluorination and elimination side reaction[9] prior to the separation.

The method was proved to be reliable for large-scale preparation of valuable 17α-hydroxy steroids (Scheme 2). The conventional synthesis of 17β-estradiol 3-benzoate **10** from commercially available **4** was laborious because the attempts to obtain benzoate ester **10** from acetate ester **6** in one step were unsuccessful.[10] The substitution of sulfonic ester **22** with HCOOH or CF_3COOH as nucleophiles led to low yield (<30%). With perfluoroalkylsulfonyl fluoride as activating agent, alcohol **4** was converted into 17α-formate **8** on multigram scale, and subsequent selective deprotection produced 17-α-estradiol 3-benzoate **10** (3 steps, 75% yield).

In summary, our study demonstrates that perfluoroalkylsulfonyl fluoride is an efficient hydroxyl activating agent for S_N2-type substitution. Notably, the procedure is rapid and can be carried out under mild condition with broad scope of nucleophiles. Further efforts to expand this strategy to other interesting substrates are underway in our laboratory.

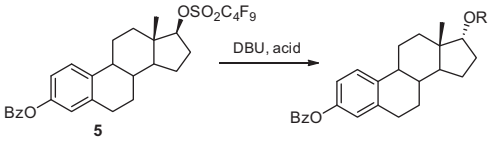
Table 1
Optimization of reaction condition

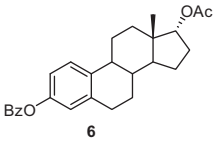
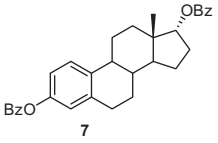
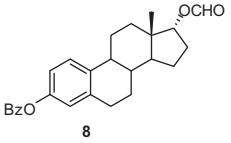
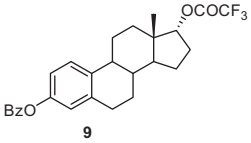
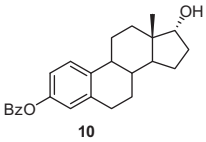


Entry[a]	Nucleophile (equiv)	Solvent	Temp (°C)	Time (h)	Yield[b,c] (%)
1	DBU–AcOH(3:6)	Toluene	100	0.5	60
2	DBU–AcOH(6:6)	Toluene	100	0.5	66(13)
3	DBU–AcOH(6:6)	Toluene	80	0.5	75(6)
4	DBU–AcOH(6:6)	Toluene	60	0.5	85
5	DBU–AcOH(6:6)	Toluene	40	0.5	84
6	DBU–AcOH(6:6)	Toluene	25	2	84
7	DBU–AcOH(6:6)	THF	40	0.5	81
8	DBU–AcOH(6:6)	EA	40	0.5	80
9	DBU–AcOH(6:6)	CH_2Cl_2	40	1	72
10	DBU–AcOH(6:6)	Acetone	40	0.5	70
11	DBU–AcOH(6:6)	MeCN	40	0.5	62
12	DBU–AcOH(6:6)	DMSO	40	5	31
13[d]	**DBU–AcOH(4:4)**	**Toluene**	**40**	**0.5**	**83**
14	DBU–AcOH(3:3)	Toluene	40	1	83
15	DBU–AcOH(2:2)	Toluene	40	2.5	79
16	Et_3N–AcOH(4:4)	Toluene	40	11	30
17	NaOAc(4)	DMSO	40	0.5	2
18	KOAc(4)	DMSO	40	0.5	9

[a] Substrate (0.05 mmol), solvent (0.5 mL).
[b] NMR yield.
[c] Yield of byproduct **6x** in brackets. EA = ethyl acetate.
[d] Optimized reaction condition.

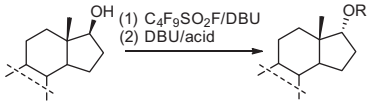
Table 2
Scope of the nucleophiles[8]



Entry[a]	Acid	Solvent	Product	Yield[b] (%)
1	AcOH	Toluene	 **6**	80
2	BzOH	THF	 **7**	77
3	HCOOH	THF	 **8**	78
4	CF_3COOH	Toluene	 **9**	54[c]
5	H_2O	THF	 **10**	20[d]

[a] Substrate (0.5 mmol), solvent (5 mL), DBU (4 equiv), acid (4 equiv) at 40 °C for 0.5 h.
[b] Isolated yield.
[c] 1.5 h DBU (6 equiv), acid (6 equiv), 2 h.
[d] NMR yield.

Table 3
Scope of substrate



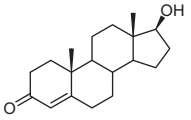
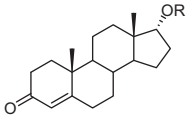
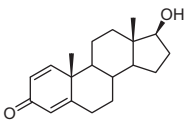
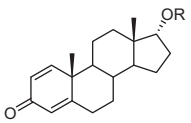
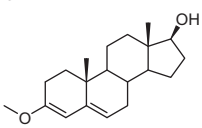
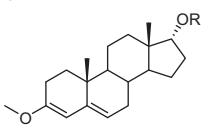
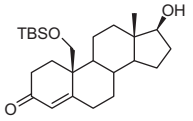
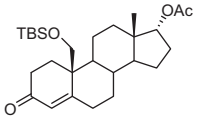
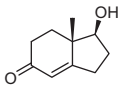
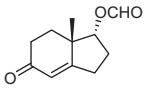
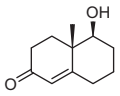
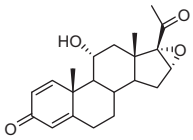
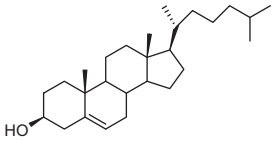
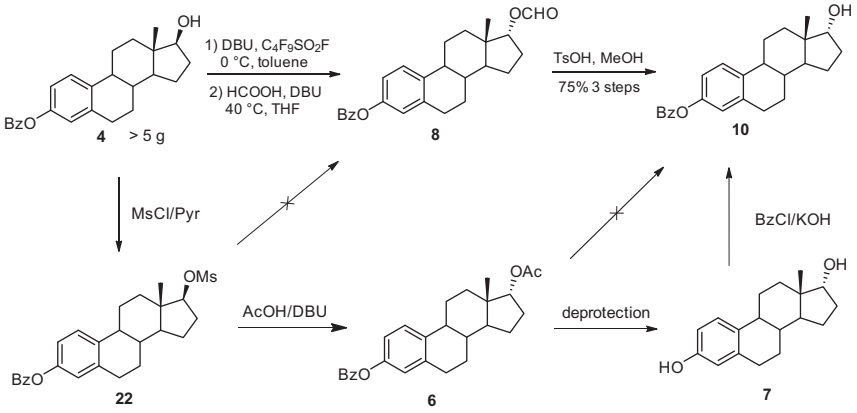
Entry[a]	Substrate	Product	Yield[b]
1			**11** R = Ac, 81% **12** R = CHO, 77% **13** R = Bz, 79%
2			**14** R = Ac, 83% **15** R = CHO, 82% **16** R = Bz, 80%
3			**17** R = Ac, 82% **18** R = CHO, 81% **19** R = Bz, 80%

Table 3 (*continued*)

Entry[a]	Substrate	Product	Yield[b]
4			**20**, 81%
5			**21,** 75%
6		—	—
7		—	—
8		—	—

[a] Substrate (0.5 mmol), toluene (5 mL), DBU (4 equiv), acid (4 equiv) at 40 °C for 0.5 h.
[b] Isolated yield (overall yield in two steps).



Scheme 2. Preparation of 17α-estradiol 3-benzoate.

Acknowledgment

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Supplementary data

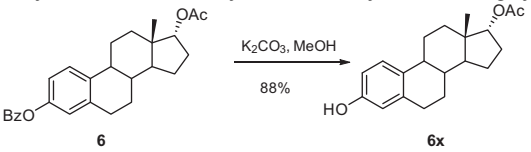
Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.026.

References and notes

1. Lednicer, D. *Steroid Chemistry at a Glance*; Wiley: Hoboken, 2011.
2. Calogeropoulou, T.; Avlonitis, N.; Minas, V.; Alexi, X.; Pantzou, A.; Charalampopoulos, I.; Zervou, M.; Vergou, V.; Katsanou, E. S.; Lazaridis, I.; Alexis, M. N.; Gravanis, A. *J. Med. Chem.* **2009**, *52*, 6569.
3. The active ingredients in Premarin are the sulfate of the estrogens. (a) Hsieh, R. W.; Rajan, S. S.; Sharma, S. K.; Greene, G. L. *Steroids* **2008**, *73*, 59; (b) Ritter, S. *Chem. Eng. News* **2005**, *83*, 100.
4. (a) Balssa, F.; Fischer, M.; Bonnaire, Y. *Steroids* **2014**, *86*, 1; (b) Dodge, J. A.; Lugar, C. W. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1.
5. (a) Shi, X. X.; Shen, C. L.; Yao, J. Z.; Nie, L. D.; Quan, N. *Tetrahedron: Asymmetry* **2010**, *21*, 277; (b) Nambara, T.; Numazawa, M.; Takahashi, H. *Chem. Pharm. Bull.* **1969**, *17*, 1725; (c) Kasal, A. *Collect. Czech. Chem. Commun.* **1993**, *58*, 2202.
6. (a) Sun, Y. S.; Ding, K.; Tian, W. S. *Chem. Commun.* **2011**, 10437; (b) Ding, K.; Sun, Y. S.; Tian, W. S. *J. Org. Chem.* **2011**, *76*, 1495; (c) Chen, L.; Ding, K.; Tian, W. S. *Chem. Commun.* **2003**, 838; (d) Liu, T.; Yan, Y. B.; Ma, H. Y.; Ding, K. *Chin. J. Org. Chem.* **2014**, *34*, 1793; (e) Yan, Z. H.; Xu, Y.; Tian, W. S. *Tetrahedron Lett.* **2014**, *55*, 7186; (f) Gui, J. H.; Wang, Y.; Tian, H. L.; Gao, Y. Q.; Tian, W. S. *Tetrahedron Lett.* **2014**, *55*, 4233; (g) Yan, Z. H.; Guan, C. B.; Yu, Z. X.; Tian, W. S. *Tetrahedron Lett.* **2013**, *54*, 5788; (h) Tian, W. S.; Ding, K.; Sun, Y. S.; Chen, L.; Lei, Z. *Synthesis* **2013**, *45*, 438; (i) Yan, Z. H.; Tian, W. S.; Zeng, F. R.; Dai, Y. F. *Tetrahedron Lett.* **2009**, *50*, 2727; (j) Yan, Z. H.; Wang, J. Q.; Tian, W. S. *Tetrahedron Lett.* **2003**, *44*, 9383; (k) Tian, W. S.; Lei, Z.; Chen, L.; Huang, Y. *J. Fluorine Chem.* **2000**, *101*, 305.
7. *Procedure for the preparation of perfluoroalkylsulfonyl ester (**5**):* To a solution of 17β-estradiol 3-benzoate **4** (947 mg, 2.52 mmol) and DBU (0.90 mL, 6.0 mmol) in 20 mL of toluene was added $C_4F_9SO_2F$ (0.54 mL, 3.0 mmol) at 0 °C. The solution was stirred for 15 min at 0 °C. At the completion of the reaction, the mixture was filtered quickly through a short silica gel column (~2 g, 200–300 mesh). The column was eluted with an elution solution (PE/EA/CH_2Cl_2 = 10:1:1). The combined solution was concentrated in vacuo to provide ester **5** as a white foam solid (1.58 g, 96%). Caution: the ester is

instable at room temperature and should be stored in the refrigerator. Mp:110 °C. $[\alpha]_D^{25}$ +7.33 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.9 Hz, 2H), 7.63 (t, *J* = 7.0 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.94 (s, 1H), 4.89 (t, *J* = 8.4 Hz, 1H), 0.95 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -80.71 (t, *J* = 9.7 Hz, 3F), −111.26 (dd, *J* = 27.0, 18.4 Hz, 2F), −121.26 (d, *J* = 9.0 Hz, 2F), −125.86 ~−126.09 (m, 2F). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 148.8, 138.0, 137.2, 133.5, 130.1, 129.6, 128.5, 126.5, 121.7, 118.9, 97.7, 48.6, 43.8, 43.7, 38.2, 35.9, 29.4, 27.8, 26.8, 25.7, 22.9, 11.8. MALDI-HRMS calcd for $C_{29}H_{27}F_9O_5S+H^+$: 659.1514, found: 659.1507.

8. *General procedure for the reaction of perfluoroalkylsulfonyl ester with nucleophiles:* Perfluoroalkylsulfonyl ester was prepared according as above procedure. The mixture of perfluoroalkylsulfonyl ester, DBU (4 equiv) and acid (4 equiv) in solvent (10 mL/mmol) was stirred for 30 min at 40 °C until the perfluoroalkylsulfonyl ester was consumed. The solution was concentrated in vacuo and the resulting residue was subsequently purified by flash chromatography.
9. (a) Bennuaskalmowski, B.; Vorbruggen, H. *Tetrahedron Lett.* **1995**, *36*, 2611; (b) Yin, J. J.; Zarkowsky, D. S.; Thomas, D. W.; Zhao, M. M.; Huffman, M. A. *Org. Lett.* **2004**, *6*, 1465; (c) Vorbruggen, H. *Synthesis* **2008**, 1165.
10. The hydrolysis of ester **6** selectively offered 17-acetyl ester **6x** in high yield.



6 **6x**