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A Facile Conversion of Primary or Secondary Alcohols with n-Perfluorobutanesulfonyl Fluoride/1,8-Diazabicyclo[5.4.0]undec-7-ene into their Corresponding Fluorides

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Abstract: The combination of n-perfluorobutanesulfonyl fluoride (**2**) with 1,8-diazabicyclo-[5.4.0]undec-7-ene efficiently converts primary and secondary alcohols in unpolar solvents into their corresponding fluorides.

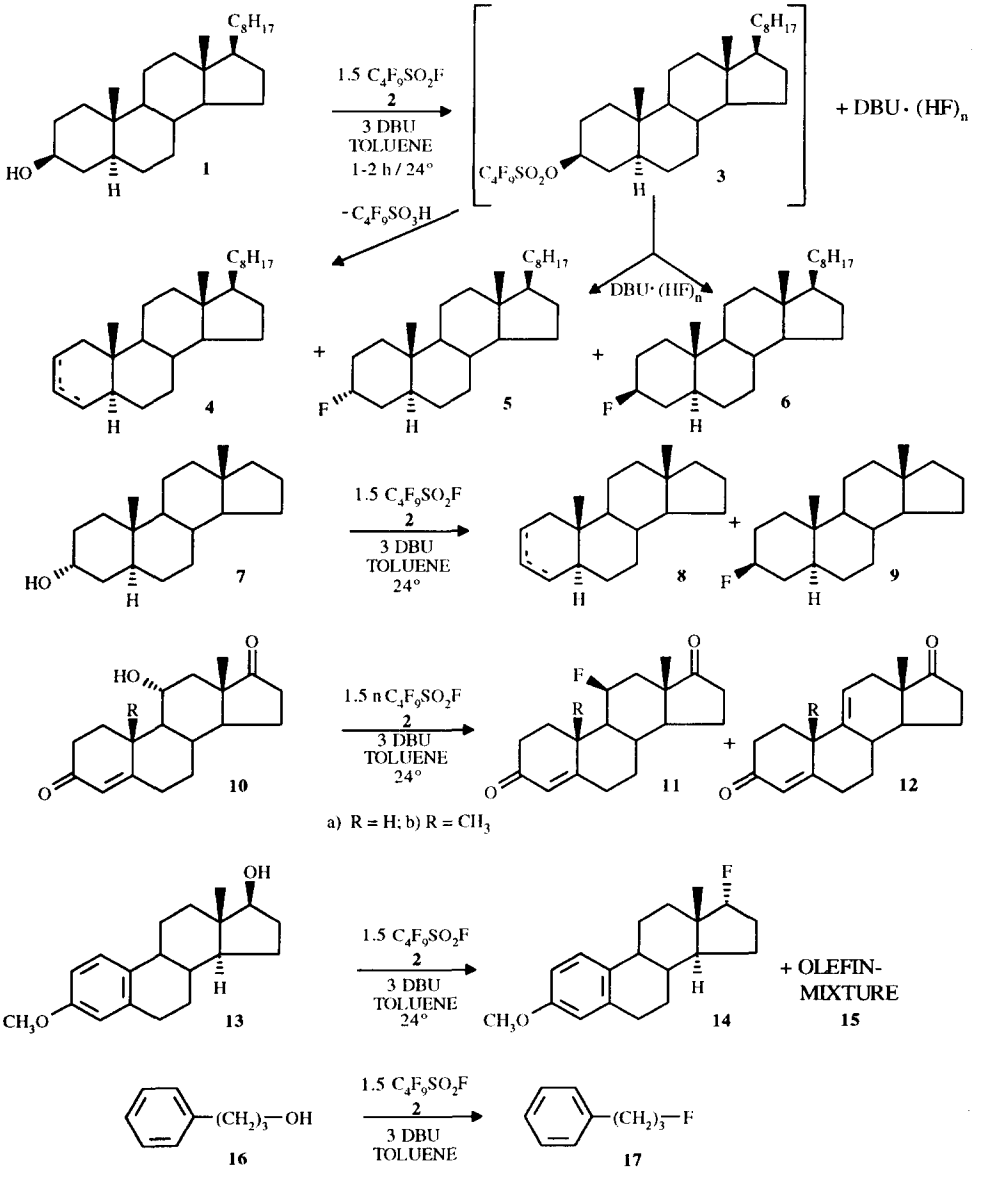
One-step conversions of primary or secondary alcohols with diethylaminosulfur trifluoride (DAST)[1)2)] or the Yarovenko reagent, N-(2-chloro-1,1,2-trifluoroethyl)diethylamine,[2)-4)] into their corresponding fluorides have become standard reactions in preparative organic chemistry. Unfortunately, these reagents are rather expensive and have to be stored in the refrigerator. Furthermore, on using DAST or N-(2-chloro-1,1,2-trifluoroethyl)diethylamine[2)-4)] the yields of the resulting fluorides are often only moderate.[1)-4)] Alternatively, alcohols can be converted in a two-step procedure via their O-triflates on reaction with CsF in DMF[5)] or Bu_4NF in acetone[6)] into their corresponding fluorides.

Since the stable and readily available n-perfluorobutanesulfonyl fluoride $C_4F_9SO_2F$ (**2**) (bp. 64-65°C), which is produced in ton-quantities by anodic fluorination of sulfolene,[7-10)] may be viewed as a mixed anhydride between n-perfluorobutanesulfonic acid (nonaflic acid) and HF, we wondered whether the O-nonaflates, which can be expected to form on reaction of alcohols with n-perfluorobutanesulfonyl fluoride (**2**) in the presence of triethylamine[11)], would not be transformed *in situ* by the generated anhydrous ammonium fluorides into the desired inverted fluorides. When we reacted secondary alcohols such as 5α-cholestane-3β-ol (**1**) with n-perfluorobutanesulfonyl fluoride (**2**) and an excess of the nucleophilic base 4-dimethylaminopyridine (DMAP)[12)] in abs. toluene, we obtained via the presumed intermediate **3** a complex mixture of 5α-cholest-2-ene/3-ene (**4**), 3α-fluoro-5-α-cholestane (**5**), some 3β-fluoro-5α-cholestane (**6**) as well as 5α-cholestan-3α-yl-N-(4-dimethylaminopyridinium) nonaflate as the main product.[13)]

To avoid the participation of the nucleophilic base DMAP, we reacted 5α-cholestane-3β-ol (**1**) with 1.5 equiv. of n-perfluorbutanesulfonyl fluoride (**2**) in the presence of 3 equiv. of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in abs. toluene for 1-2 h at 0° or 24° and obtained after careful chromatography in hexane on silica gel 25% of 5α-cholest-2-ene/3-ene (**4**), 61% of 3α-fluoro-5α-cholestane (**5**) and circa 4% of 3β-fluoro-5α-cholestane (**6**)[14)], whereas the reaction of **1** with DAST affords only 43% of **5**[15)16)]. Repeating the reaction of **1** with **2** and DBU for 1-2 h at -30° in toluene resulted in the same yields of **4**, **5** and **6**. Likewise, the much more basic commercial phosphazene base P_4-t-Bu[17)18)], instead of DBU, afforded at 24° in toluene 29% of **4**, 57% of 3α-fluoro-5α-cholestane (**5**), but practically no 3β-fluoro-5α-cholestane (**6**)[14)]. When we substituted DBU by anhydrous triethylamine, the reaction took more than a week at 24° resulting in 58% of 5α-cholest-2-ene and 3-ene (**4**), 10% of 3α-fluoro-5α-cholestane (**5**), but 20% of 3β-fluoro-5α-cholestane (**6**) as well as 5% of unreacted starting material **1**.

To exclude any nucleophilic displacement of the axial fluorine atom in **5** by fluoride ion to give **6**, we treated a solution of 3α-fluoro-5α-cholestane (**5**) in toluene for 4 days at 24° with DBU•$(HF)_n$, prepared by introducing HF gas into a cooled solution of DBU in toluene, as well as with commer-

cial $Et_3N\bullet(HF)_3$[19] but recovered, in both cases, unchanged 3α-fluoro-5α-cholestane (**5**). We furthermore excluded any potential addition of HF to 5α-cholest-2-ene/3-ene (**4**) by treating **4** with $DBU\bullet(HF)_n$ as well as with $NEt_3\bullet(HF)_3$ in toluene for several days without observing any formation of **5** or **6**. Thus, the presumed intermediate 5α-cholestan-3β-yl-nonaflate (**3**) reacts with $DBU\bullet(HF)_n$ to give preferentially 61% of the desired 3α-fluoro-5α-cholestane (**5**). In addition, some of the labile intermediate **3** apparently dissociates to an intimate ion pair, which will either loose a proton to give the olefins **4** or react with $DBU\bullet(HF)_n$ to afford **5** and **6**. The much stronger phosphazene base[17][18] apparently favors elimination of a proton from the intimate ion pair to **4**, so that only very small amounts of **6** are formed.



The reaction of the axial hydroxyl group in 5α-androstane-3α-ol (**7**) with 1.5 equiv. of n-perfluorobutanesulfonyl fluoride (**2**) and 3 equiv. of DBU in toluene was somewhat slower and gave after 4 h 44% of 5α-androst-2-ene and 3-ene (**8**) and 48% of 3β-fluoro-5α-androstane (**9**)[20] as well as 4% of recovered starting material **7**. The equatorial hydroxyl group in 11α-hydroxy-estr-4-ene-3,17-dione (**10a**) reacts analogously with **2** and DBU in toluene to afford after ca. 2 h at 24° 66% of the known[21)22)] 11β-fluoro-estr-4-ene-3,17-dione (**11a**) besides some olefins mainly containing **12a**[23)], whereas the reaction of **10a** with N-(2-chloro-1,1,2-trifluoroethyl)diethylamine gave less than 45% of **11a**[21)22)]. The equatorial hydroxyl group in 11α-hydroxy-androst-4-ene-3,17-dione (**10b**), whose O-nonaflate is much more hindered towards nucleophilic attack from the β-side, however, reacted after 2 h with **2** and DBU in toluene at 24° to afford only 12% of **11b** as well as 82% of a 7 : 3 olefin-mixture containing the $\Delta^{9,11}$-olefin **12b** as the major reaction product[24)]. **11b** had hitherto only be prepared via the 9α-bromo-11β-fluoro-androst-4-ene-3,17-dione[25)]. Likewise, 3-methoxy-estra-1,3,5(10)-trien-17β-ol (**13**) with a cyclopentanol moiety is converted by **2** and DBU in 43% yield into 17α-fluoro-3-methoxy-estra-1,3,5(10)-triene (**14**) and a mixture of 4 olefins **15**[26)], whereas the reaction of **13** with N-(2-chloro-1,1,2-trifluoroethyl)diethylamine has been reported to afford **14** in only 26% yield[27)]. Analogously, a primary alcohol such as 1-hydroxy-3-phenylpropanol (**16**) afforded in toluene the corresponding 1-fluoro-3-phenyl-propane (**17**) in 70% yield according to GC/MS analysis. To facilitate the isolation of **17**, the reaction was repeated in methyl-t-butyl ether for 1 h at 24° to give after workup and chromatography 79% of **17**[28)]. For different recent preparations of **17**, compare refs. 29)-32).

All these reactions are exothermic. Thus, on converting larger amounts of primary or secondary alcohols into their corresponding fluorides, the n-perfluorobutanesulfonyl fluoride (**2**) should be added gradually to a stirred and cooled solution or suspension of the alcohol and DBU (or a phosphazene base) in abs. toluene, methyl-t-butyl ether, or any other unpolar solvent. Replacing DBU or the phosphazene base by DBN, pentaisopropylguanidine or triethylamine as well as employing more polar solvents such as acetonitrile resulted in lower yields of the desired fluoro derivatives. The less basic 1,8-bisdimethylaminonaphthaline (proton sponge), which has been described to give a reactive, soluble hydrofluoride[33)], did not react with **1** and **2** in toluene at 24° within 4 h.

DBU•$(HF)_n$ is apparently in unpolar solvents a salt with a pronounced nucleophilic and less basic fluoride anion. DBU•$(HF)_n$ has hitherto only been mentioned as a side product obtained on treatment of fluorinated polymers with DBU[34-35)], and has as yet not been further characterized or used as a reagent. The reactive phosphazene-HF salts have recently[36)] been demonstrated, however, to cause E2 eliminations of O-benzenesulfonates and iodides.

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References and Notes

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14. **3α-Fluoro-5α-cholestane (5)**: To a cooled solution of 5α-cholestan-3β-ol (**1**) (0.97 g, 2.5 mmol) and DBU (1.12 mL, 7.5 mmol) in toluene (20 mmol), $C_4F_9SO_2F$ (**2**) (1.13 g, 3.75 mmol) was added with stirring at +2°C, whereupon the reaction temperature rose to +10°C. After 1 h at +2°C, the reaction mixture was evaporated in vacuo and the residue chromatographed in hexane on a column of 50 g silica gel. The first 150 mL hexane eluted a mixture of 5α-cholest-2-ene/3-ene (**4**) (0.23 g = 25%), identified by ^{1}H-NMR and by comparison with an authentic sample, whereas the subsequent 100 mL hexane afforded pure 3α-fluoro-5α-cholestane (**5**) (0.37 g = 38%) mp 107-108°C (hexane) (lit.[15][16] mp 103-104°C), identified with an authentic sample and by ^{1}HNMR. Further elution with 250 mL hexane furnished a mixture (0.27 g = 28%) containing acc to t.l.c. (SiO_2, hexane) mostly **5** as well as circa 4% of 3β-fluoro-5α-cholestane (**6**), which could be isolated in a pure state, mp 82-84°C (hexane) (lit.[15] mp 82°C (acetone)), after repeated chromatography on a silica gel column or by preparative t.l.c. on SiO_2 plates with hexane. Analogous reaction of **1** (1 mmol) with **2** (1.5 mmol) in the presence of 3 equiv. of phosphazene-base P_4-tert.-Bu (Fluka) in toluene (10 mL) at 24°-30°C, evaporation after 2 h and chromatography afforded 5α-cholest-2-ene/3-ene (**4**) (0.107 g = 29%) as well as of 3α-fluoro-5α-cholestane (**5**) (0.223 g = 57%) containing only traces of 3β-fluoro-5α-cholestane (**6**).
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20. **3β-fluoro-5α-androstane (9)**: mp 93-95°C (hexane). MS (EI) m/z = 278 (M^+), 263 (M-15), 235, 221, 203, 189, 167, 149, 135, 121, 107, 95, 81, 67, 65. ^{1}HNMR ($CDCl_3$) 0.64 (s, 3 H, C-18), 0.83 (s, 3 H, C-19), 4.48 (m, J = 50 Hz, 3α-H).
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24. **11β-Fluoro-androst-4-ene-3,17-dione (11b)**: Analogous reaction of **10b** (cf. Ref. 14, 23) at +24°→30°C afforded after workup and chromatography 82% of a 7 : 3 mixture of olefins containing androst-4,5,9,11-diene-3,17-dione (**12b**) as the major compound followed by 12% of **11b**, mp 168-170°C (acetone - hexane) (lit.[25] mp = 165-166°C (acetone-hexane)). ^{1}HNMR ($CDCl_3$) 1.08 (s, 3 H, C-18), 1.39 (d, 3 H, J = 4 Hz, C-19), 5.17 (d, q, J = 50 Hz, J = 2 Hz, 11α-H), 5.74 (s, 4-H).
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26. **17α-Fluoro-3-methoxy-estra-1,3,5(10)-triene (14)**: 3-Methoxy-estra-1,3,5(10)-trien-17β-ol (**13**) gave analogously with $C_4F_9SO_2F$ (**2**)/DBU after 2 h in toluene at 24-30°C, workup and chromatography 32% of a mixture of 4 olefins, determined by GC/MS and 43% of **14**, mp 94-96°C (hexane) (lit.[27] 96-98°C (methanol)). MS (EI) m/z = 288 (M^+), 268 (M-HF), 225, 199, 173, 147, 128, 115, 103, 91, 77, 67, 53. ^{1}HNMR ($CDCl_3$) 3.78 (s, 3H, OCH_3), 5.83 (dd, J = 50 Hz, 4 Hz, 17β-H).
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