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Etherification of Hydroxysteroids *via* Triflates[1]

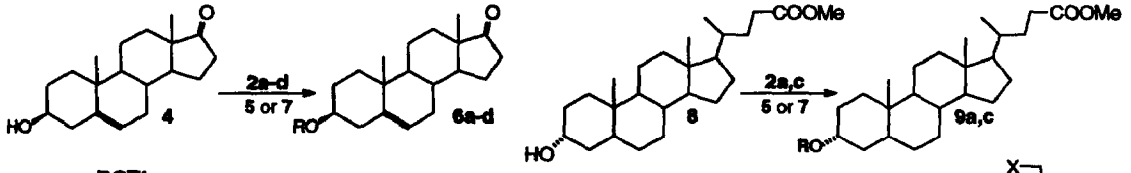
Anatoly M. Belostotskii and Alfred Hassner*
Chemistry Department, Bar-Ilan University, Ramat-Gan 52900, Israel

Abstract: *Triflates of saturated alcohols are useful in the alkylation of 3- and 17-hydroxysteroids in the presence of hindered amines. The etherification is successful even in those cases where other alkylating agents are noneffective.*

Steroidal or fatty acid esters of biologically active compounds[2,3] including anti-AIDS agents[4] have shown in many cases enhanced activity. Since esters are too easily degradable *in vivo*, steroidal ethers containing additional functions are desirable. Yet, the known methods of etherification are limited in the steroidal field, e.g., Williamson ether synthesis is often unsuccessful even for unhindered 3-hydroxysteroids[5]. Reactions via tosylates[6,7] are not always effective (see below) and diazo compounds are useful only if the simplest diazo alkanes are employed[5]. Oxidative displacement of iodo compounds[5] cannot be applied to steroids containing isolated double bonds and oxidative displacement of 3-tosylhydrazinosteroids[8] is not stereoselective. Only benzyl ethers are available by the use of sodium hydrogen telluride and phenyl imidinium salts[9].

We now report that triflates of aliphatic alcohols can serve as convenient reagents for etherification of hydroxysteroids. Both 3-hydroxysteroids and more hindered 17-hydroxysteroids can be etherified in moderate yield, and the use of bifunctional triflates was effective also in cases where the above mentioned alkylating agents were inferior.

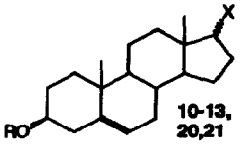
For instance, among the 2',3',4',5'-diisopropylidene galactose derivatives (DIG-X) neither the iodide **1a**[10] nor the tosylate **1b**[10] reacted with the sodium salt of 3β-hydroxy-5-androstene-17-one **4** (nitromethane, reflux). By contrast, reaction of steroid **4** with 1.5-2 equiv. of triflate **2a**[11] in the presence of 2,6-di-*tert*-butylpyridine **5** (nitromethane, reflux 3 h) led to ether **6a** in 61% yield[12]. Similarly, formation of ethers **6b,c** was achieved by heating of **4** with triflates **2b,c**[13] in nitromethane in the presence of **5** or of 1,2,2,6,6-pentamethylpiperidine **7** (60-65°, 1.5 h). The unstable triflate **2d** was generated *in situ* in the presence of 1.1 equiv. of **7** and when treated with 0.5 equiv. of steroid alcohol **4** in the presence of 1 equiv. of **7** (nitromethane, 60-65°, 1 h) followed by hydrolysis of the product, ether **6d** was obtained in 67% yield.



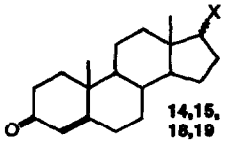
The choice of amine as proton acceptor is important: the yield decreases as the steric hindrance of the amine group diminishes. Thus, the yields of **6b** were 90, 32, or 2% when the amine was **7**, lutidine and pyridine, respectively. The yields of **6c** were 63, 47 and 3% when amine **5**, lutidine and pyridine, respectively, were used. Obviously, in the case of less hindered amines, quaternization of the amine function competes effectively (e.g., lutidine is methylated by methyl fluorosulfate at room temperature[13]).

In the case of 3α-hydroxy steroids the yield of the etherification product is lower: the methyl ester of lithocholic acid **8** gives in the reaction with triflates **2a** or **2c** under the above conditions the products **9a** or **9c** in 36 and 39% yield, respectively.

Etherification of 17β-hydroxysteroids **10** and **14** by 2-4 equiv. of haloalkanol triflates **2b** and **2e**, respectively, was also carried out in the presence of **7** under the above described conditions and led to the products **12** and **15**. Similarly, when *in situ* generated triflate **2d** was treated with 0.5 equiv. of steroid alcohol **11** in the presence of 1 equiv. of **7** followed by hydrolysis of the product ether **13** was obtained.



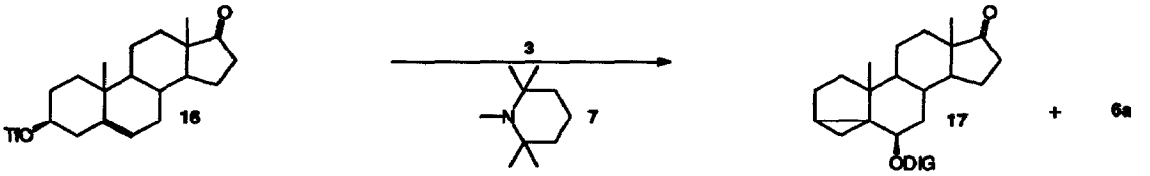
10: R = TBS, X = OH (β)
11: R = $(CH_2)_3Br$, X = OH (β)
12: R = TBS, X = $O(CH_2)_4Cl$ (β)
13: R = $(CH_2)_3Br$, X = $O(CH_2)_6OH$ (β)
20: R = Ac, X = OTf (β)
21: R = Ac, X = I (α)



14: X = OH (β)
15: X = $O(CH_2)_6Br$ (β)
18: X = OTf (β)
19: X = Br (α)

The yields of the products **12**, **13** and **15** were 35, 37 and 27%, respectively. The lower yields of the more hindered 17β-alkoxy derivatives in comparison to those of 3β-alkoxy steroids is consistent with the assumption that triflate decomposition competes with etherification.

Attempts to obtain α-ethers from triflates of β-hydroxysteroids and **3** were unsuccessful. Cholestanol triflate led to cholest-2-ene, while the triflate **16** gave an *i*-steroid rearrangement product **17** (42%) and ether **6a** (21%) or a 3β,3β'-bis steroidal ether (40%) and **4** (60%) in the reaction with water. Testosterone triflate **18** in reaction with alcohols gave a mixture of products instead of an expected ether. On the other hand, softer nucleophiles like $Bu_4N^+Br^-$ or $Bu_4N^+I^-$ converted **18** to 17α-bromide **19** (64%) or **20** to α-iodide **21** (100%).



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