Preliminary Note

Trifluoromethylation of steroidal ketones

Zhongqi Wang* and Benfang Ruan
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032 (China)

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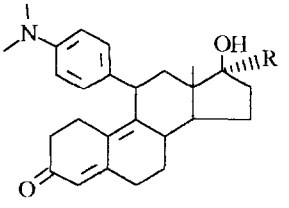
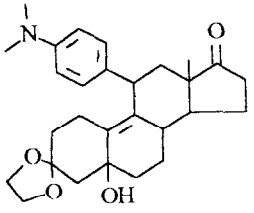
Abstract

An improved procedure for the efficient trifluoromethylation of steroidal ketones using CF_3SiMe_3 has been developed. One of the steroidal compounds with a trifluoromethylated carbinol unit has been shown to exhibit high contraceptive activity in biotests.



R = C≡CCH$_3$ (1)

CF$_3$ (2)



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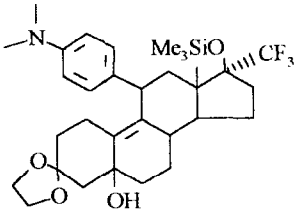

(4)

Trifluoromethyl-substituted compounds have been examined for their potential as biologically active drugs and agrochemicals [1]. Consequently, much effort has been paid to developing efficient methods for the construction of these fluorine-containing compounds [2]. Trifluoromethylation of carbonyl compounds with CF_3SiMe_3 promoted by Nu_4NF followed by HCl-catalysed hydrolysis is a well-recognized procedure for constructing compounds with a trifluoromethylated carbinol unit [3]. However, we found this procedure could not be applied satisfactorily to hindered ketones such as Δ^5-pregene-3β-ol-20-one-3-acetate (**5a**). Herein, we report an improvement to this procedure for hindered ketones which can be trifluoromethylated effectively to yield trifluoromethyl-substituted carbinols in almost quantitative yield.

During the course of our studies directed at improving the biological activity of the contraceptive drug 11β-(*p*-*N*,*N*-dimethylaminophenyl)-17α-propynyl-estra-4,9 diene-17β-ol-3-one (**1**) [4], we became interested in its trifluoromethyl-substituted analogue (**2**) and envisaged that such a substitution of a CF_3 group might modify the biological activity of the original molecule in some respects. To obtain this CF_3-containing compound, we proposed direct trifluoromethylation of the ketone **3** using Prakash's method [3]. Although Prakash et al. reported that their procedure could also be used for the trifluoromethylation of hindered ketones, we found that **3** reacted with great difficulty. There were two problems associated with this procedure: (a) treatment of **3** with CF_3SiMe_3 in the presence of Bu_4NF only resulted in a very low conversion (about 20%) to the silyl ether **4**; (b) the corresponding silyl ether **4** did not readily undergo desilylation with HCl. To solve these two problems, we tried various conditions. We found that efficient trifluoromethylation of **3** could be effected by using the more effective catalyst Me_4NF and that the difficult hydrolysis of the corresponding silyl ether could be solved by using 40% aqueous HF solution in CH_3CN. Thus, when treated with CF_3SiMe_3 in the presence of Me_4NF, followed by hydrolysis with 40% aqueous HF, compound **3** could be converted quantitatively to the desired CF_3-containing compound **2**.

This improved procedure can be widely used for the trifluoromethylation of hindered ketones as shown by the results listed in Table 1. The desired CF_3-substituted carbinols were all obtained in high yield. Thus, we have developed an improved procedure for the trifluoromethylation of ketones with CF_3SiMe_3.

*Author to whom correspondence should be addressed.

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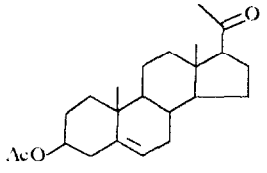
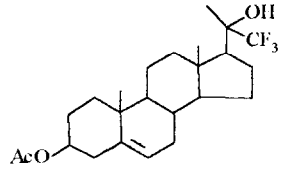
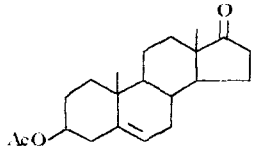
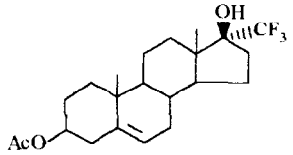
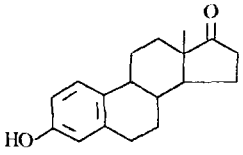
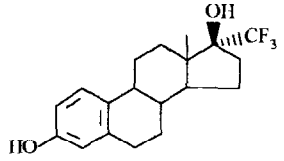
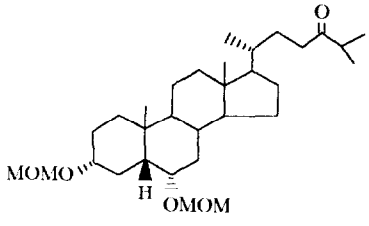
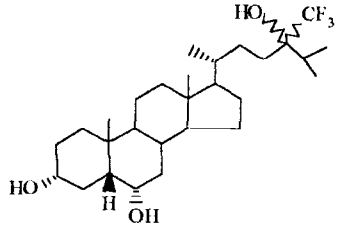
TABLE 1. Trifluoromethylation of ketones with CF_3SiMe_3

Entry	Ketone	Product[a]	Yield(%)[b]
1	 **5a**	 **6a**	88[c]
2	 **5b**	 **6b**	83[c]
3	 **5c**	 **6c**	88
4	 **5d**	 **6d**	96

[a]All the products were fully characterised by IR, ^{19}F NMR, ^1H NMR, MS and elemental analyses or HRMS.
[b]Isolated yield based on the ketone.
[c]The slightly low yield was caused by partial deacetylation of the product.

As a potential biologically active material, compound **2** exhibited increased bioactivity in biotests, as we had envisaged. The detailed bioactivity will be reported elsewhere.

A typical experiment was conducted as follows. To an ice-cooled solution of **3** (200 mg) in 1.5 ml of THF was added CF_3SiMe_3 (0.3 ml) and Me_4NF (10 mg), and the mixture stirred at 0 °C for 0.5 h and then at room temperature for 4 h. After evaporation of THF under reduced pressure, the residue was dissolved in 2 ml of CH_3CN followed by the addition of 1 ml of a 40% aqueous HF solution. The resulting solution was stirred at room temperature for 0.5 h. Usual work-up followed by chromatography on silica gel using a 20:1 mixture of petroleum ether and acetone as eluent afforded **2** (196 mg, 96%) as a solid, m.p. 128–129 °C. IR (KBr) (cm^{-1}) 3400; 1730; 1650; 1600; 1440; 1370; 1340; 1100; 800. ^1H NMR ($CDCl_3$) δ: 0.580 (s, 3H); 3.06 (s, 6H); 5.82 (s, 1H); 7.03 (m, 4H) ppm. ^{19}F NMR ($CDCl_3$) (TFA) δ: 2.06 (s) ppm. MS *m/z* (relative intensity): 460 (M+1, 5.06); 389 (12.4); 121 (100). HRMS: Calc. for $C_{27}H_{32}NO_2F_3$: 459.2385. Found: 459.2357.

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