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Novel Method For The Preparation Of Monofluoroacetyl And Difluoroacetylfuran Derivatives

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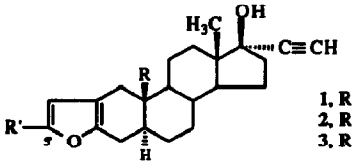
Abstract: Monofluoroacetyl and difluoroacetylsteroidal furans were prepared by selective reductive dehalogenation of chlorofluoro and chlorodifluoroacetyl intermediates with sodium formaldehyde sulfoxylate.

We have recently reported[1] the synthesis of 5'-methylsulfonyl[3,2-b]steroidal furan (1) and the androgen receptor activity of this compound. In order to explore the structure-activity relationship of this series of compounds, we have introduced a number of other electron withdrawing substituents at 5' position of the furanosteroids.[2] Among these, our interest was to prepare 5'- fluorinated ketones. The trifluoromethyl ketones could be readily synthesized using the literature procedures.[3,4] However there are not many straight forward methods reported in the literature[3,4,5] to prepare either monofluoromethylketones or difluoromethylketones (2 and 3). Fluorinated ketones are the subject of renewed interest not only for use as intermediates to prepare other fluorinated compounds but also as inhibitors of a variety of esterases and proteases.[3] We describe here a novel two step procedure to prepare the title ketones from 17-unsubstituted furanosteroids and sodium formaldehyde sulfoxylate, an inexpensive selective reducing agent. Although this methodology was only applied to the preparation of 5'-substituted monofluoro (11) and difluoromethyl (12 and 13) steroidal ketones, it may have a more general application.

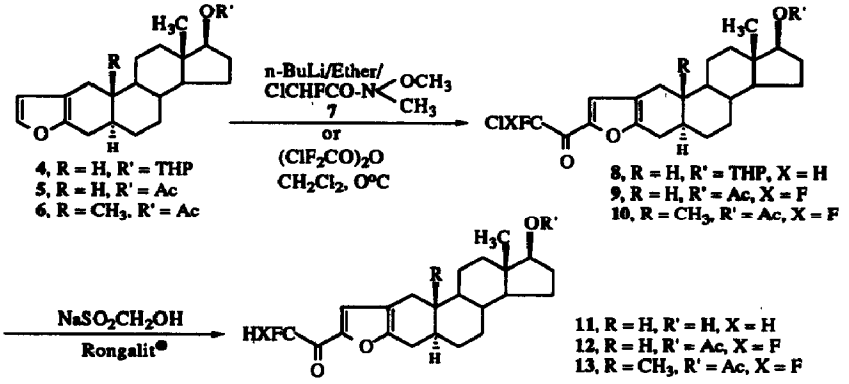


1, R = CH_3, R' = SO_2CH_3
2, R = H, R' = $COCH_2F$
3, R = H, CH_3, R' = $COCHF_2$

The requisite starting materials, steroidal[3,2-b]furans, were prepared by the procedure reported earlier.[1] The mono-fluoroacetyl derivative was obtained following the reaction pathways as depicted below. Early attempts to react the 5'-lithio derivative (n-BuLi/TMEDA/ether, 0°C→20°C) of 4 with methyl chlorofluoroacetate to give chlorofluoroacetyl derivative 8 resulted only in a minor amount of the desired compound along with other products. Alternative bases such as sec-BuLi, LDA, LiHMDS or KHMDS similarly did not improve the yield of 8 and in all cases a mixture of products was obtained. The ^{1}H-NMR of the crude mixture revealed that the ester as well as the chloro group reacted with the anion.

To circumvent these problems the amide 7 [bp 125-130°C (18mm), yield 80%] was prepared following Weinreb's procedure[6] from methyl chlorofluoroacetate. The 5'-lithio derivative of 4 reacted smoothly with amide 7 to give 8 (yield 84%). The ^{1}H-NMR of the crude material indicated only minor amounts of side products and the desired product 8 was easily purified by recrystallization. Reductive dehalogenation of 8 with

sodium formaldehyde sulfoxylate (Rongalit®),utility of this reagent for dehalogenation and the mechanism is first described by Harris[7], in boiling ethanol or THF/ethanol (1:1) gave the monofluoroketone 11[8] (R' = H) after the hydrolysis of the THP in 80% yield. Besides being inexpensive, the selectivity of the reagent was remarkable since most other reducing agents (LAH, DIBAL-H, 10%Pd/C) led to the desired compound but also gave considerable amounts (>25%) of over reduced products.



Difluoroketones were prepared following a similar reaction pathway. However, we opted to utilize the commercially available chlorodifluoroacetic anhydride. If desired, the amide similar to 7 could be easily prepared from commercially available methyl chlorodifluoroacetate and the remaining reaction sequence follows as above. Thus, to a solution of 17-O-acetylated derivatives 5 and 6 at 0°C was added chlorodifluoroacetic anhydride dropwise. After stirring for 16 h at room temperature followed by basic workup (10% aq $NaHCO_3$) 9 and 10 were obtained in 84% and 80% yields, respectively. Reductive dehalogenation with sodium formaldehyde sulfoxylate gave the difluoroketones 12 (yield 83%)[9] and 13 (yield 86%).[10]

In summary we have developed a novel two step procedure to prepare monofluoroacetyl and difluoroacetyl furanosteroidal derivatives which uses an inexpensive and selective reducing agent and avoids the use of toxic fluorine containing reagents. This methodology should be readily adapted to prepare mono- or difluorinated ketones from other heterocyclic or non-heterocyclic compounds. Applications of this methodology to prepare such ketones are in progress.

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8. 11, mp 133-135°C, MS (CI) MH^+ 361, ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.74 (s, 3H), 0.89-2.80 (m, 21H), 3.67 (t, J = 10 Hz, 1H), 5.22 (d, J_{HF} = 47 Hz, 2H), 7.16 (s , 1H).
9. 12, mp 183-185°C, MS (CI) MH^+ 423, ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.79 (s, 3H), 1.12-2.75 (m, 22H), 2.01 (s, 3H), 4.56 (t, J = 9 Hz, 1H), 6.12 (t, J_{HF} = 54 Hz), 7.27 (s, 1H).
10. 13, mp 189-191°C, MS (CI) MH^+ 435, ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.73 (s, 3H), 0.78 (s, 3H), 0.81-2.67 (m, 22H), 2.01 (s, 3H), 4.57 (t, J = 8 Hz, 1H), 6.12 (t, J_{HF} = 54 Hz, 1H), 7.28 (s, 1H).

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