Synthesis of Silyl Enol and Silyl Dienol Ethers of 20-Oxosteroids: The Effect of β-Substituents

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An efficient method to obtain regioselectively the title compounds is described. Experimental studies concerning the effect of β-substituents on the generation of β-substituted silyl enol ethers made feasible for the first time the isolation and identification of the products resulting from the unstable thermodynamic silyl enol ether.

Silyl enol and silyl dienol ethers are important synthetic intermediates with broad applications for electrophilic α-substitution.[1] On the basis of our interest in the development of new methods for the C-21 functionalization of 20-oxosteroids,[2] these potential enolate ions could represent useful intermediates. Although some isolated studies on the silylation of 20-oxosteroids have been reported,[3] to the best of our knowledge β-substituted (-OH or -OSiR$_3$) and α,β-unsaturated derivatives have not been investigated.

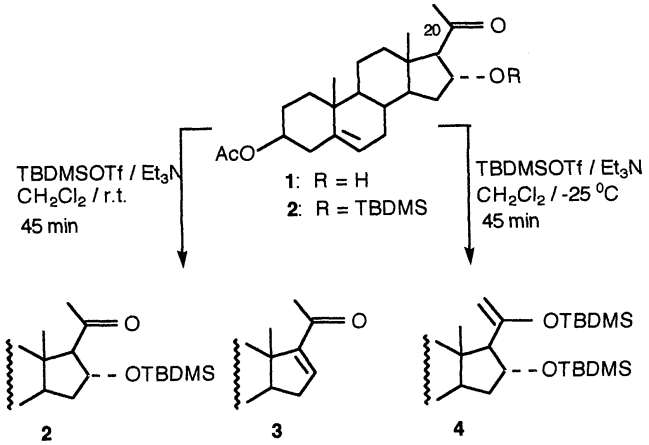
The exceptional reactivity of trialkylsilyl triflates,[4] namely the t-butyldimethylsilyl triflate (TBDMSOTf), as well as the possibility to obtain good yields of both silyl enol and dienol ethers using identical reaction conditions,[3c, 5] led us to explore the potentialities of these reagents. Studies concerning the effect of β-substituents on the generation of β-substituted silyl enol ethers and their thermodynamic equilibrium are also included.

Reactions of the β-hydroxy- and β-siloxy-20-oxosteroids **1**[6a,b] (1.0 mmol) and **2**[6c] (1.0 mmol) with TBDMSOTf (2 mmol for compound **1** and 1 mmol for compound **2**) in the presence of triethylamine (0.50 mL for compound **1** and 0.25 mL for compound **2**) as an auxiliary base have provided unexpected results (Scheme 1).

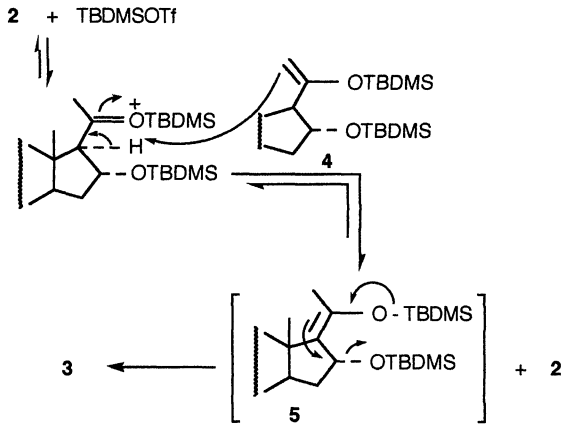
The reactions performed at -25 °C produced exclusively the silyl enol ether **4** in very good yields (88-90%).[7] This is in agreement with the account that alkyl groups present at any of the α-positions interfere with the transition state and unstabilize the more substituted enol.[8] Reported studies for acyclic methyl ketones have also shown the influence of α-alkyl groups on reactions with trimethylsilyl triflate performed at room temperature,[5b] the proton abstraction ocurring preferentially at the less substituted α-position. However, for the reactions performed at room temperature (Scheme 1), the α,β-unsaturated ketone **3**[9] was the single isolated product from the β-siloxy ketone **2** and was the minor product along with the silyl ether **2** from the β-hydroxy ketone **1**, rather than the enol **4** or a more substituted regioisomer, as observed by ^{1}H-NMR. The formation of the silyl ether **2** from compound **1** was expected on the basis of a β-hydroxy group silylation, but the presence of compound **3** in these reactions is not so easily explained.

In order to gain a further understanding of these results, a closer examination of the equilibrium process between the silyl enol ether **4** and the more substituted regioisomer **5** was undertaken. Reflux of **4** in dichloromethane for 4 h afforded compound **2** as the main product and the same result was achieved after 90 min using an excess of ketone **2** and TBDMSOTf[5b] (Scheme 2). When this reaction time was extended for a further period of 18 h, complete conversion of the silyl enol ether **4** yielded almost exclusively the α,β-unsaturated ketone **3**.

From this set of experiments we propose the formation of the unstable intermediate **5** (Scheme 2). In fact the decomposition of enol **5** with elimination of the β-siloxy group is consistent with the formation of the unsaturated ketone **3** in all reactions performed under thermodynamic conditions. Furthermore, the different results obtained during the enolization at room temperature of compounds **1** and **2** reveal, indirectly, that the β-siloxy group favours the formation of the more substituted silyl enol ether **5**. And, as a consequence, the unsaturated compound



Scheme 1.



Scheme 2.

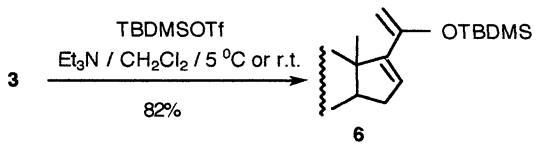
3 was the only isolated product.

For the β-hydroxyketone **1**, the -OH silylation which may precede or be concomitant with the enolization, makes difficult the interpretation of the product distribution. As aforementioned, the reaction carried out at room temperature afforded a result similar to those obtained in the equilibration reaction with the less substituted enol **4** by warming or after the first 90 min at room temperature with excess of ketone. Therefore, this suggests that the β-hydroxy group plays a different role from the β-siloxy one, but at this point it is impossible to establish the preferential generation of the enol **4**.

Under kinetic conditions the steric factors overcome the electronic effects of the β-substituents (-OH and -$OSiR_3$) resulting exclusively in the less substituted silyl enol ether **4**.

Our results are not only in agreement but also complement the elegant study on the chemistry of aldolate dianions reported by Martin *et al.*[10] Moreover, the β-substituted ketones we have studied by reaction with TBDMSOTf, a process identical to the classical internal quench, made feasible for the first time the isolation and identification of the products resulting from the unstable thermodynamic silyl enol ether **5**.

The scope of this study was broaden to the enolization of the α,β-unsaturated ketone **3**. The same outcome was observed for reactions conducted either at 5 °C or at room temperature, producing both the spectroscopically pure silyl dienol ether **6**[2] (Scheme 3).



Scheme 3.

The most significant features of this methodology are the regioselectivity observed under the mild reaction conditions used and the high yields of isolated products. Studies to evaluate the potentialities of these silyl enol and silyl dienol ethers for the synthesis of 21-hydroxy- and 21-acetoxy-20-oxosteroids are now in progress.

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References and Notes

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6 a) The β-designation refers to the position of the substituents relatively to the carbonyl group. For both substrates the stereochemistry is α. b) For preparation of **1**: M. J. S. M Moreno, M. L. Sá e Melo, and A. S. Campos Neves, *Tetrahedron Lett.*, **34**, 353 (1993) and references cited therein; IR 3380 (16-OH), 1720 (3-OAc), 1685 (20-CO), 1240, 1035, 900, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73 (s, 18-H_3), 1.01 (s, 19-H_3), 2.02 (s, 3-OCOCH_3), 2.17 (s, 21-H_3), 2.60 (d, J=7.5 Hz, 4-H_2), 2.90 (d, J=5.9 Hz, 17α-H), 4.62 (m, 3α-H), 4.85 (m, 16β-H), 5.38 (m, 6-H); ^{13}C NMR δ 72.46 (C-17), 74.26 (C-16), 74.35 (C-3), 122.29 (C-6), 139.80 (C-5), 170.57 (MeOCO), 208.69 (C-20). c) For preparation of **2**: silylation of **1** according to E. J. Corey, and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972); IR 1730 (3-OAc), 1700 (20-CO), 1240, 1080, 1065, 1030, 910, 835, 780 cm^{-1}; ^1H NMR ($CDCl_3$) δ -0.04 [s, $Si(CH_3)_2{}^tBu$], 0.0 [s, $Si(CH_3)_2{}^tBu$], 0.6 (s, 18-H_3), 0.82 [s, $SiMe_2C(CH_3)_3$], 1.00 (s, 19-H_3), 2.02 (s, 3-OCOCH_3), 2.12 (s, 21-H_3), 2.30 (d, J=7.5 Hz, 4-H_2), 2.59 (d, J=5.9 Hz, 17α-H), 4.60 (m, 3α-H), 4.75 (m, 16β-H), 5.35 (m, 6-H); ^{13}C NMR δ -5.35 ($SiCH_3$),-5.25 ($SiCH_3$), 25.56 [$SiC(CH_3)_3$], 72.98 (C-17), 73.75 (C-16), 74.22 (C-3), 122.85 (C-6), 140.00 (C-5), 173.00 (MeOCO), 209.30 (C-20).

7 Aliquots were withdrawn at intervals of 10 min and, without any treatment, analysed by ^1H NMR recording the spectra between 1.5 and 2.5 ppm. The reaction was completed when the absence of the 21-H_3 singlet[6b,c] has occurred. The yields refer to isolated, chromatographically and spectrally homogeneous product **4**: ^1H NMR ($CDCl_3$) δ 0.020 and 0.027 [2s, 16-$OSi(CH_3)_2{}^tBu$], 0.18 and 0.19 [2s, 20-$OSi(CH_3)_2{}^tBu$], 0.66 (s, 18-H_3), 0.88 [s, 16-$OSiMe_2C(CH_3)_3$], 0.92 [s, 20-$OSiMe_2C(CH_3)_3$], 1.00 (s, 19-H_3), 2.02 (s, 3-OCOCH_3), 4.02 and 4.09 (2s, 21-H_2), 4.47 (m, 16β-H), 4.60 (m, 3α-H), 5.37 (m, 6-H).

8 H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).

9 Product **3**: IR 1725 (3-OAc), 1655 (20-CO), 1580 (16-ene), 1245, 1035, 975, 905, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (s, 18-H_3), 1.05 (s, 19-H_3), 2.03 (s, 3-OCOCH_3), 2.26 (s, 21-H_3), 4.60 (m, 3α-H), 5.38 (m, 6-H), 6.71 (m, 16-H); ^{13}C NMR δ 73.86 (C-3), 121.94 (C-6), 140.15 (C-5), 144.65 (C-16), 155.21 (C-17), 170.59 (MeCOO), 196.97 (C-20).

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