CHEMISTRY LETTERS, pp. 1963-1966, 1990.

Synthesis of α-Keto-steroidal Spiro-thiazolidines

Tomoyoshi TAKAHASHI,* Miki TAKAHASHI, † Akira HASHIMOTO, † and Yasuo SATOH†

Department of Chemistry, The Jikei University School of Medicine,

Kokuryo-cho, Chofu, Tokyo 182

†Department of Chemistry, Faculty of Science, Rikkyo (St . Poul`s) University,

Nishi-Ikebukuro, Toshima-ku, Tokyo 171

α-Bromo-steroidal ketones were converted into α-keto spiro-thiazolidine derivatives with β-aminothiols ($H_2N(CH_2)_2SH$, *o*-$H_2NC_6H_4SH$), in pyridine solution at room temperature.

As a part of our study [1] towards the development of new azasteroids with biological interest, we studied the reaction of α-bromo-steroidal ketones with β-aminothiols. A literature survey revealed the precedent of the analogous reaction. Treatment of α-halo ketones with β-aminothiols afforded dihydro-1,4-thiazines.[2]

We now report a new type of condensation between α-bromo-steroidal ketones **1a-e** and β-aminothiols which leads to α-keto spiro-thiazolidine derivatives (**2a-e** and **3a**). In this condensation, the carbonyl group apparently rearranged to the carbon atom that was in possession of bromine atom in starting bromo ketone **1**.

The reaction and spectral characteristics of these products are discussed. In a typical experiment, to a solution of 2α-bromo-5α-cholestan-3-one **1a** (5 g) in pyridine (50 ml) was added 2- aminoethanethiol (5 g) with stirring for 120 h at room temperature. After work-up, the resulting oil was chromatographed on a silica-gel column. Elution with benzene gave 5α-cholestan-3-one (0.451 g, 11%). Further elution with benzene-AcOEt (19:1) gave thiazolidine derivative **2a**, which crystallized from acetone as needles (2.123 g, 43%). Thiazolidines **2a,b** are acetylated to give the N-acetyl derivatives **4a,b** in 65-69% yield in the usual way.

All new compounds had satisfactory analytical and spectroscopic data.[3] The mass spectra of **2a,b** and **4a,b** had characteristic peaks at m/z 140 (a,33%; b,35%) and m/z 182 (a,47%; b,45%), respectively (see Scheme 2). The presence of the spiro-thiazolidine ring at C-3 was indicated by these fragment ions (i). Djerassi et al.[4] mentioned that the mass spectrum of 5α–androstan-3-one ethylene thioketals had the characteristic peaks at m/z 157 (ii, fission at the C-2,3; C-5,10; C-7,8) and m/z 131 (iii, fission at the C-3,4; C-

1,10). The fragment ions (i) of the thiazolidine derivatives are analogous to that of the corresponding ethylene thioketals. The presence of the carbonyl group at C-2 was indicated indirectly by lack of the fragment ion that correspond to fragment ion (iii) in the case of ethylene thioketals.

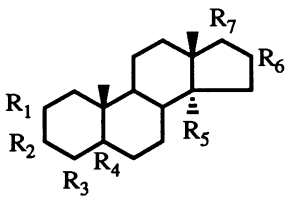
The configurations of the spirane carbon atoms in compounds **2a,b** were assigned, as shown in Scheme 3, on the basis of the values of the acetylation shifts in ^{1}H NMR spectrum. The positions of characteristic signals in the 500 MHz ^{1}H NMR spectra of spiro-thiazolidines **2a,b** and N-acetyl derivatives **4a,b** are shown in Table 1. Paryzek et al.[5] evaluated the effect of N-acetylated thiazolidinone ring present in C-3 position of 5α-steroid molecule on the chemical shift of C-19 methyl group protons. The effect of acetyl groups on the signal of angular C-19 methyl groups depends on the distance between the acetyl group and the C-19 methyl group. Paryzek et al. discribed that acetylation shifts $\Delta\delta_{19\text{-Me}}$ (δ_{NAc}-δ_{NH}) are +0.12 ppm for **6a** and +0.03 ppm for **8a** (sign + means deshielding) on the basis of $\delta_{19\text{-Me}}$ of free thiazolidinone derivatives **5a** and **7a** respectively. Such a large deshielding effect for **6a** is due to the *cis* position of the C(3)-N bond with respect to the C-19 methyl group. In our cases, 5α-cholestane derivatives **4a** cause the large deshielding by 0.2567 ppm, whereas 5β-cholestane derivative **4b** have the small shielding effect equal to -0.0473 ppm (Table 1). These results lead to conclusions regarding the configuration of the spirane carbon atom. In 5α-cholestane

Table 1. 500 MHz NMR spectrum of spiro-thiazolidine derivatives and acetylation shifts[a]

	19-Me	4β-H	4α-H	1α-H	1β-H
2a	0.7664 (s)	2.0025 (t, J=12.82)	_____	2.4110 (d, J=13.89)	2.5254 (d,J=13.89)
4a	1.0231 (s)	3.2279 (t, J=13.46)	1.7627 (dd, J= 13.74,3.57)	2.4907 (2H, s, 1-H$_2$)	
Δ Value	0.2567	1.2254			
	19-Me	4α-H	4β-H	1α-H	1β-H
2b	1.0714 (s)	2.6304 (t, J=14.35)	_____	2.6002 (d, J=14.35)	2.4952 (d, J=14.35)
4b	1.0241 (s)	3.2270 (t, J=13.31)	1.7636 (dd, J= 13.68,3.41)	2.4934 (2H, s , 1-H$_2$)	
Δ Value	-0.0473[b]	0.5966			

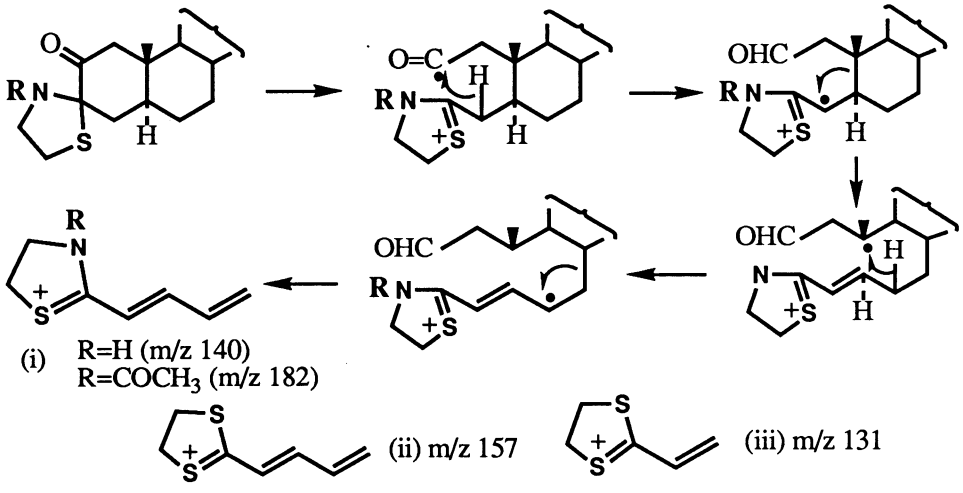
a) δ units, TMS standard. b) Sign - means shielding.

derivative **4a** the C(3)-N bond is in position *cis* (3β-bond) with respect to the C-19 methyl group, while in 5β-cholestane derivative **4b** it is in position *trans* (3α-bond). The C-4 axial protons of compounds **4** are also deshielded by the acetyl group (Table 1). Such a large deshielding effect of axial protons is probably due to

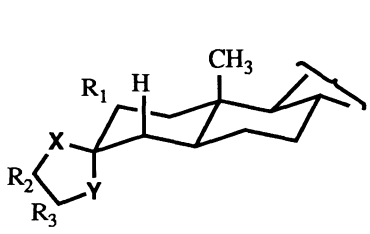


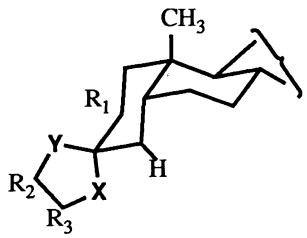
	R1	R2	R3	R4	R5	R6	R7	Yield (%) from **1** and reaction time (h)
1a	α-Br	=O	H_2	α-H	H	H_2	$-C_8H_{17}$	
1b	β-Br	=O	H_2	β-H	H	H_2	$-C_8H_{17}$	
1c	α-Br	=O	Me_2	α–H	Me	H_2	$-C_8H_{17}$ (Δ^8)	
1d	H_2	=O	β-Br	β-H	H	H_2	$-C_8H_{17}$	
1e	H_2	α-OH	H_2	α-H	H	α-Br	=O	
2a	=O	S(α), NH(β)	H_2	α-H	H	H_2	$-C_8H_{17}$	43% (120 h)
2b	=O	NH(α), S(β)	H_2	β-H	H	H_2	$-C_8H_{17}$	49% (24 h)
2c	=O	NH, S	Me_2	α–H	Me	H_2	$-C_8H_{17}$(Δ^8)	64% (48 h)
2d	H_2	NH, S	=O	~H	H	H_2	$-C_8H_{17}$	5% (72 h)
2e	H_2	α-OH	H_2	α-H	H	=O	NH, S	19% (120 h)
3a	=O	S(α), NH(β)	H_2	α-H	H	H_2	$-C_8H_{17}$	61% (48 h)
4a	=O	S(α), NAc(β)	H_2	α-H	H	H_2	$-C_8H_{17}$	
4b	=O	NAc(α), S(β)	H_2	β-H	H	H_2	$-C_8H_{17}$	

Scheme 1.



Scheme 2.





	X	Y	R_1	R_2	R_3
2a	NH	S	=O	H_2	H_2
4a	NAc	S	=O	H_2	H_2
5a	NH	S	H_2	=O	H_2
6a	NAc	S	H_2	=O	H_2
7a	S	NH	H_2	H_2	=O
8a	S	NAc	H_2	H_2	=O

	X	Y	R_1	R_2	R_3
2b	NH	S	=O	H_2	H_2
4b	NAc	S	=O	H_2	H_2

Scheme 3.

the closeness of the acetyl group to the axial proton (Scheme 3). From these results, the configurations and positions of spirane carbon atoms were assigned as shown in Scheme 3. The α-bromo-steroidal ketones react with β-aminothiols regio- and stereoselectively to produce the spiro-thiazolidines **2**. The isomers having different configuration of the spirane carbon atom was not detected. If the condensation were not stereospecific, the ^{13}C-NMR spectrum would show two absorption for the C-3 absorption.[6]

The present reaction is the first case of the synthesis of α-keto-steroidal spiro-thiazolidines, including 1,2-shifts of the carbonyl group. It affords a promising method for the synthesis of various steroidal heterocycles. The reaction mechanism and structures of **2c,d** are being investigated.

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3) All new compounds cited herein were fully characterized on the basis of spectral and analytical data. Selected spectroscopic data are as follows; **2a**: IR (KBr) 3300, 1700, and 792 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 205.37 and 82.92; m/z 459.3536 (M^+). **2b**: IR (KBr) 3300, 1714, and 788 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 205.64 and 82.79; m/z 459.3544 (M^+). **2c**: IR (KBr) 3304, 1706, and 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.3132 (2H, m), 3.0421 (1H, d, J=12.91 Hz), 2.7855 (2H, t, J=5.50 Hz), and 2.4805 (1H, d, J=12.91 Hz); ^{13}C NMR ($CDCl_3$) δ 207.40, 135.40, 132.91, and 90.72; m/z 499.3395 (M^+). **3a**: IR (KBr) 3290, 1708, and 735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.9946–6.7554 (4H, m); 2.5403 (1H, d, J=13.18 Hz), 2.3523 (1H, dd, J=3.02 and 13.16 Hz), and 1.9489 (1H, t, J=13.60 Hz); m/z 507.3549 (M^+).

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(Received August 6, 1990)