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Reaction of α-halo ketone with 2-aminothiol: a new synthesis of thiazolidines with the oxo group migrated to the original position occupied by halogen atom

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Abstract—The reaction of 2-bromo-3-oxo steroids with 2-aminoethanethiol led to the stereoselective formation of spiro[steroid-3,2′-thiazolidin]-2-ones as the major product. With both cyclic and acyclic α-halo alkanones, the reaction gave the thiazolidines with the oxo group migrated to the original position occupied by the halogen atom. In addition, it was found that the use of microwaves affords improvement of yields and shortening the reaction time in comparison with usual conditions.

1. Introduction

The chemistry[1–6] and pharmacology[7–9] of thiazolidines have been widely investigated. Some thiazolidines possess radioprotective[7] and antihypertensive effects.[8] Our interests in new synthetic approaches to biologically active steroids possessing functional nitrogen and sulfur groups led us to investigate spiro[steroid-3,2′-thiazolidine]s. Recently considerable attention has been focused on the reactions of carbonyl compounds with 2-aminoethanethiols to form thiazolidines.[10,11]

In the previous paper,[12] we reported that condensation of 2α-bromo-3-oxo steroids with 2-amino thiols (2-aminoethanethiol or 2-aminobenzenethiol) gives spiro[steroid-3,2′-thiazolidin]-2-ones. In the resulting product, the oxo group migrated to the original position occupied by the bromine atom. Moreover, in order to clarify the generality of migration for oxo group, the reaction of cyclic and acyclic α-halo alkanones with aminothiol gave the corresponding thiazolidine derivatives. Herein, we report the details concerning these reactions.

2. Results and discussion

The condensation of 2-bromo-3-oxo steroids **1, 2, 4** with 2-amino thiols led to the stereoselective formation of spiro-[steroid-3,2′-thiazolidin]-2-ones **1a, 2a, 4a** (Table 1). As can be seen from Table 1, it was found that the reaction gives preferentially the corresponding spiro[steroid-3,2′-thiazolidin]-2-ones as the major product. Thus in order to discuss the reactivity for low solubility of α-bromo steroidal ketone, it was compared with that of benzene (entry 2). The use of benzene as the reaction solvent was found to improve the reaction yield significantly. So, we employed benzene as the reaction solvent for the reaction of α-halo cycloalkanone and α-halo acyclic ketone. Reaction of **1** for 1.5 h gave the intermediate **1b** (entry 3). Compound **1b** is converted into the spiro[steroid-3,2′-thiazolidin]-2-one **1a** under the same conditions (entry 5). In the case of 4β-bromo 3-oxo 5β-steroid **3**, spiro[steroid-3,2′-thiazolidin]-4-one **3a** and spiro[5β-cholestan-3,2′-thiazolidine] (**3d**) were obtained (entry 7). From these results, it is considered that in the case of 4β-bromo derivative **3**, the unstable properties are based on 1:3-interaction between the C-6,7 bond and C-4α bond.

If the condensation did not proceed stereospecifically, the ^{13}C NMR spectrum would show two absorptions for the spiro carbon.[13] The ^{13}C NMR spectral data supported the consideration that only one of two possible C-3 isomers was obtained during thiazolidine formation under these conditions. Therefore, it is considered that in this condensation, the ring

Keywords: α-Bromo ketone; 2-Aminoethanethiol; Spiro[steroid-3,2′-thiazolidine]s; Condensation; 1-Thia-4-azaspiro[4.5]decan-6-one; Microwave.
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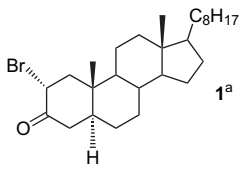
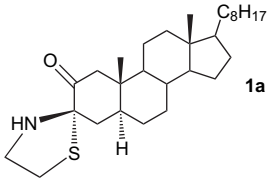
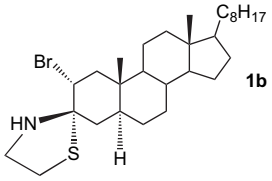
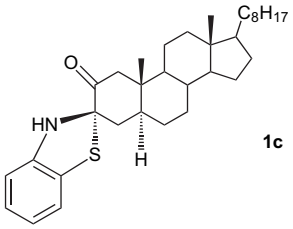
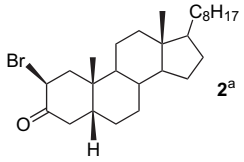
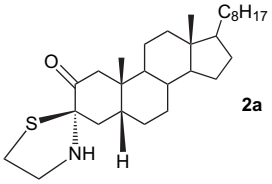
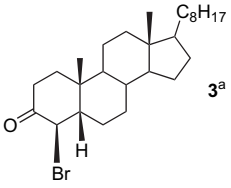
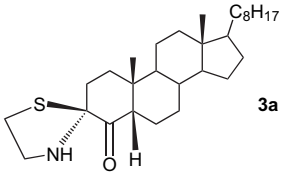
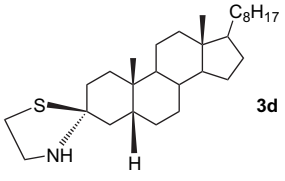
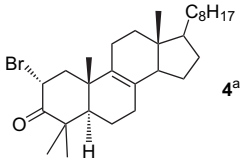
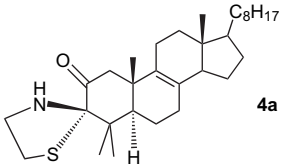
Table 1. Reaction of α-halo steroidal ketone with 2-aminoethanethiol or 2-aminobenzenethiol at room temperature

Entry	Substrate	Time (h)	Solvent	Product	Yield[c] (%)
1	 **1**[a]	120	Pyridine	 **1a**	43
2	**1**[a]	168	Benzene	**1a**	66
3	**1**[a]	1.5	Pyridine	 **1b**	22
4	**1**[b]	100	Pyridine	 **1c**	61
5	**1b**	100	Pyridine	**1a**	48
6	 **2**[a]	120	Pyridine	 **2a**	49
7	 **3**[a]	120	Pyridine	 **3a**	8
				 **3d**	11
8	 **4**[a]	120	Pyridine	 **4a**	64

[a] Reaction condition: substrate (10 mmol), 2-aminoethanethiol (60 mmol), and solvent (50 ml) were employed.
[b] Reaction condition: substrate (1 mmol), 2-aminobenzenethiol (6 mmol), and solvent (10 ml) were employed.
[c] Isolated yield.

opening–ring closing equilibrium between the two isomers did not occur. It was found that the thiazolidines **1a**–**4a** existed in the reaction mixtures as single isomers from the NMR spectrum. In this condensation, the carbonyl group apparently rearranged to the carbon atom possessing bromine atom in the starting bromo ketones **1**–**4**. This condensation led to the first isolation of pure spiro[steroid-3,2′-thiazolidine]s by a simple procedure.

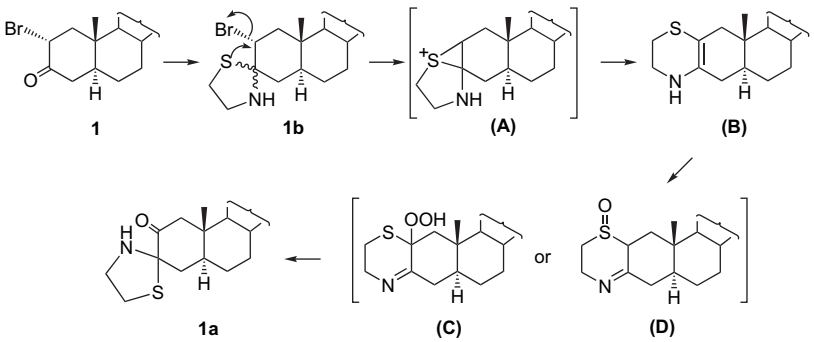
The probable mechanism for the condensation is shown in Scheme 1. The conversion of α-bromo ketone **1** into spiro-[steroid-3,2′-thiazolidin]-2-one **1a** presumably involves the autoxidation of 1,4-thiazine intermediate **B**. ^{13}C NMR measurement was applied to the 2α-bromo-3-oxo steroid **1**–2-aminoethanethiol system in order to clarify the spectroscopic evidence for dihydro-1,4-thiazine intermediate **B**. The bromo ketone **1** was allowed to react with 2-aminoethanethiol under an argon atmosphere in the NMR tube. If the intermediate **B** is present at high concentrations, the two sp^2 carbon atoms' (–S–C═C–NH–) resonance should be identified easily. The initial NMR spectrum (2 h, 25 °C) showed two sp^2 carbon absorptions at 93.81 ppm and 129.28 ppm due to the dihydro-1,4-thiazine intermediate **B**. However, the reactions under argon atmosphere did not proceed.

After the NMR spin tube reaction for 2 h, dry oxygen was bubbled into the reaction mixtures for 1 h. The ^{13}C NMR spectrum showed the peak at 205.37 ppm, due to the carbonyl group. The final ^{13}C NMR spectrum (24 h, 25 °C) showed the signals for compound **1a** at 205.37 ppm for the C-2 carbonyl carbon and at 82.92 ppm for the C-3 spiro carbon. The absorptions of –S–C═C–NH– due to the intermediate **B** disappeared almost completely after 24 h. In general, it is known that the alkyl-substituted dihydro-1,4-thiazines are readily converted into the corresponding *S*-monoxides.[14] Dihydro-1,4-thiazine **B** converts into the *S*-monoxide **D** or the hydroperoxide intermediate **C** by oxygen.[5] And then the spiro compound **1a** was probably generated by the ring contraction of **C** or **D**. Attempts to secure the desired intermediate **C** or **D** were unsuccessful. However, the intermediate **1b** could be isolated from the reaction mixtures. The compound **1b** is converted into the spiro[steroid-3,2′-thiazolidin]-2-one **1a** under the same conditions.

Moreover, in order to clarify the generality of migration of the oxo group (Table 2, entries 6–8, 14), the reactions of α-halo cycloalkanones with 2-aminoethanethiol were conducted and in all cases the corresponding thiazolidine derivatives were obtained. In the cases of 2-bromo-4-*tert*-butylcyclohexanone (**9**), 2-bromo-4-methylcyclohexanone (**10**), or 2-bromo-1-tetralone (**15**), the product of migration of the oxo group, 1-thia-4-aza-8-*tert*-butylspiro[4.5]decan-6-one (**9a**), 1-thia-4-aza-8-methylspiro[4.5]decan-6-one (**10a**) or spiro[naphthalene-1(2*H*),2′-[1,3]thiazolidine]-3′,4′-dihydro-2′-one (**15a**) was obtained. Also, it was found that in the case of α-halo acyclic ketones **16**–**21**, the oxo group migrated to the position occupied by the halogen atom (Table 3).

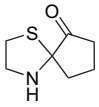
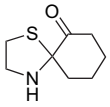
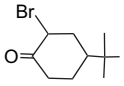
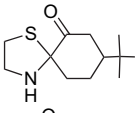
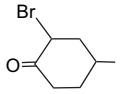
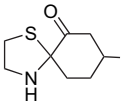
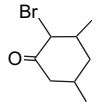
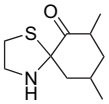
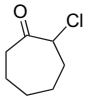
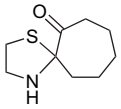
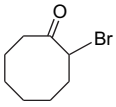
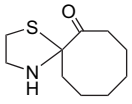
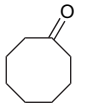
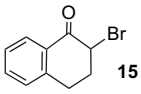
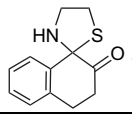
However, for the synthesis of simple thiazolidine, the method mentioned above requires long reaction times. It is known that the microwave irradiation method has become a powerful tool for preparation of various organic compounds. So we conducted the present reactions under microwave conditions in water from the viewpoint of green chemistry. The reaction of 2-bromocyclohexanone (**7**) with 2-aminoethanethiol in water under microwave irradiation gave the corresponding 1-thia-4-azaspiro[4.5]decan-6-one (**6a**) within 10 min at 40 °C. The reaction under heating conditions in water with no microwave irradiation proceeded gradually in low yield (<5%). Several examples are shown in Table 4. From these results, it was found that the microwave irradiation has the power to shorten the reaction time of the key step reactions using water in comparison with heating conditions.

The mass spectra of thiazolidines **1a** and **2a** had characteristic fragment ions at *m*/*z* 140 (**1a**, 33%; **2a**, 35%) (Scheme 2). The existence of the spiro-thiazolidine ring at C-3 was indicated by these fragment ions (i). Similarly, the presence of the benzothiazoline ring at C-3 for **1c** was also indicated by the fragment ion (iii). Djerassi et al. mentioned that the mass spectrum of 5α-androstan-3-one ethylene thioketals had characteristic peaks at *m*/*z* 157 (iv, fission at the C-2,3, C-5,10, C-7,8) and *m*/*z* 131 (vi, X=S, fission at the C-3,4, C-1,10).[15] The fragment ions (i) of the thiazolidine derivatives are analogous to those of the corresponding ethylene thioketals. The existence of the carbonyl group at C-2 was indicated indirectly by lack of the fragment ion (v) (X=NH) that corresponds to the fragment ion (vi) (X=S) in the case of ethylene thioketals. In the case of 4-oxo derivative **3a**, the mass spectrum showed a peak at *m*/*z* 114 (23%) due to the fragment (v) (X=NH) arising from fission of the C-1,10 and C-3,4 bonds. The presence of the thiazolidine ring at C-3 and the carbonyl group at C-4 was indicated by the fragment. The ^1H NMR spectrum showed a singlet at δ 1.109 which was assigned to the C-19 methyl group and



Scheme 1. The mechanism for the condensation reaction of 2α-bromo steroidal 3-ones.

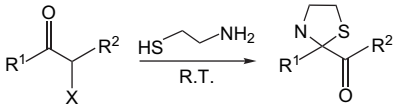
Table 2. Reaction of α-halo cycloalkanone with 2-aminoethanethiol at room temperature

Entry	Substrate[a]	Time (h)	Solvent	Product	Yield[b] (%)
1	 **5**	1	Benzene	 **5a**	88
2	**5**	1	MeOH	**5a**	83
3	 **6**	6	Benzene	 **6a**	100
4	 **7**	3.5	Benzene	**6a**	98
5	 **8**	6	Benzene	 **6d**	93
6	 **9**	10	Benzene	 **9a**	100
7	 **10**	6	Benzene	 **10a**	94
8	 **11**	6	Benzene	 **11a**	65
9	 **12**	46	Benzene	 **12a**	83
10	 **13**	24	Benzene	**12a**	93
11	**13**	4	MeOH	**12a**	96
12	 **14**	62	Benzene	 **14a**	80
13	**14**	4	MeOH	**14a**	14
				 **14d**	86
14	 **15**	1	Benzene	 **15a**	100

[a] Reaction condition: substrate (1 mmol), 2-aminoethanethiol (6 mmol), and solvent were employed.
[b] Determined by GLC analysis using *n*-dodecane as internal hydrocarbon standard.

a one proton double doublet at δ 2.602 (J=1.91 and 4.55 Hz) due to 5β-H that agrees with the 5β-structure of compound **3a**. The inversion of the stereochemistry at C-5, from the less common 4-oxo 5β-steroids to more frequently encountered 4-oxo 5α-steroids, occurred readily in the course of the reaction. For the 4-oxocholestane system, optical rotatory dispersion measurement has indicated the presence of 99% 5α-isomer at equilibrium.[16] In our case, the corresponding 5α-derivative was not detected. The ^{13}C NMR spectrum indicated that the thiazolidine derivative **3a** existed as very stable isomer in solution. Because of the high stability of α-keto spiro-thiazolidine systems, equilibrium did not occur.

Table 3. Reaction of α-halo acyclic ketone with 2-aminoethanethiol[a]



16-21 **16a-21a**

Entry	Compound	R^1	R^2	X	Solvent	Time (h)	Product[b] (%)
1	**16**	CH_3	CH_3	Cl	Benzene	1	**16a** (71)
2					MeOH	1	**16a** (60)
3	**17**	C_3H_7	C_2H_5	Br	Benzene	82	**17a** (94)
4					MeOH	7	**17a** (86)
5	**18**	C_4H_9	C_3H_7	Br	Benzene	82	**18a** (94)
6					MeOH	5	**18a** (86)
7	**19**	C_5H_{11}	C_4H_9	Br	Benzene	55	**19a** (100)
8					MeOH	4	**19a** (96)
9	**20**	Ph	CH_3	Br	Benzene	24	**20a** (100)
10					MeOH	1	**20a** (95)
11	**21**	Ph	C_3H_7	Br	Benzene	2	**21a** (98)
12					MeOH	1	**21a** (97)

[a] Reaction condition: substrate (1 mmol), 2-aminoethanethiol (6 mmol), and solvent (10 ml) were employed.
[b] Isolated yield.

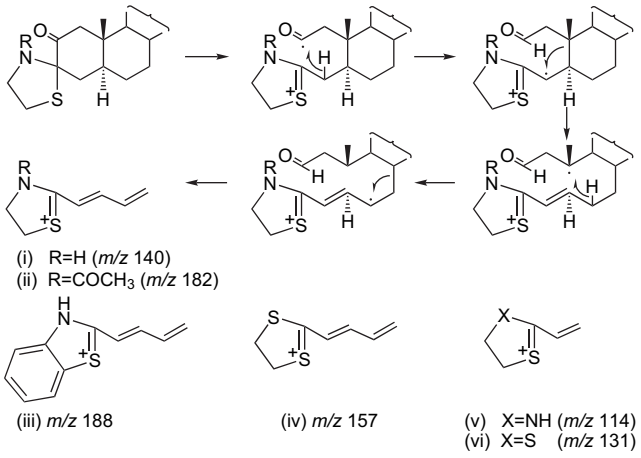
The mass spectrum of **4a** showed peaks at m/z 499 (M^+) and 456 ($M^+-CH_2=C=O^+H$, fission at the C-1,10, C-2,3). The ^{1}H NMR spectrum showed two doublets for H_2-1 at δ 2.480 (J=12.91 Hz, H-1α) and 3.041 (J=12.91 Hz, H-1β). These spectral data clearly supported the presence of the carbonyl group at C-2 and spiro-thiazolidine moiety at C-3. In the case of the substrate having 4,4-dimethyl group, it was found that the condensation also occurs.

In conclusion, it was found that the reaction of 2α-bromo-3-oxo steroids, 2-bromo-4-*tert*-butylcyclohexanone, or 2-bromo-4-methylcyclohexanone, with 2-aminothiol gave diastereomerically pure spiro[steroid-3,2′-thiazolidin]-2-ones,

Table 4. Reaction of α-bromo ketone with 2-aminoethanethiol using microwave or heat at 40 °C

Entry	Substrate	Reaction type	Time	Solvent	Product	Yield[b] (%)
1	**7**[a]	MW	10 min	Water	**6a**	74
2	**7**	Heat	3 h	Benzene	**6a**	91
3	**9**[a]	MW	10 min	Water	**9a**	63
4	**9**	Heat	9 h	Benzene	**9a**	100
5	**10**[a]	MW	10 min	Water	**10a**	71
6	**10**	Heat	5 h	Benzene	**10a**	94
7	**11**[a]	MW	10 min	Water	**11a**	68
8	**11**	Heat	5 h	Benzene	**11a**	65
9	**13**[a]	MW	10 min	Water	**12a**	71
10	**13**	Heat	14 h	Benzene	**12a**	82
11	**14**[a]	MW	10 min	Water	**14a**	68
12	**14**[a]	Heat	62 h	Benzene	**14a**	80

[a] Reaction condition: substrate (0.1 mmol), 2-aminoethanethiol (0.2 mmol), and water (5 ml) were irradiated at 40 °C for 10 min.
[b] Determined by GLC analysis using *n*-dodecane as internal hydrocarbon standard.



Scheme 2. Mass spectra of 2-oxo 3-spiro-thiazolidine derivatives.

1-thia-4-aza-8-*tert*-butylspiro[4.5]-decan-6-one (**9a**) or 1-thia-4-aza-8-methylspiro[4.5]decan-6-one (**10a**). From these results it is evident that the oxo group migrates to the position originally occupied by the bromine atom. Also, this reaction is applicable to acyclic α-halo alkanone. Moreover, it was found that microwave irradiation can shorten significantly the reaction time of the key step using water.

3. Experimental

3.1. General

Melting points were determined with a Yanagimoto apparatus, and are uncorrected. IR spectra were recorded in KBr on a Hitachi Model 270-30 grating infrared spectrometer. Mass spectra were measured with a JEOL JMS-SX102A spectrometer. The NMR spectral data were measured on a JOEL GSX 400 spectrometer in deuteriochloroform with TMS as the internal standard. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck). Column chromatography was performed with silica gel (230–400 mesh).

3.1.1. General procedure for preparation of spiro[steroid-3,2′-thiazolidin]-2-ones. A mixture of 2α-bromo-5α-cholestan-3-one (**1**) (10 mmol), 2-aminoethanethiol (60 mmol), and pyridine (50 ml) was stirred at room temperature. After the appropriate reaction time (best determined by TLC monitoring for unreacted α-bromo ketone), the mixture was diluted with ether and washed successively with 100 ml portions of water. After being dried over Na_2SO_4 and then concentrated, the residue was purified by silica-gel column chromatography. Elution with benzene gave 5α-cholestan-3-one (0.425 g, 11%). Further elution with benzene–ethyl acetate (19:1) gave thiazolidine derivative **1a**, which crystallized from acetone as needles (1.98 g, 43%).

3.1.2. General procedure for prepararion of 1-thia-4-azaspiro[4.5]decan-6-one (6a) using 2-chlorocyclohexanone (6) with 2-aminoethanethiol in benzene. After a mixture of 2-chlorocyclohexanone (**6**) (0.1326 g, 1 mmol) and 2-aminoethanethiol (0.4629 g, 6 mmol) in benzene (10 ml) was stirred at room temperature for 1 h, the solvent was removed under reduced pressure. Water was added to the residue, which was extracted with diethylether (2×25 ml). The ethereal solution was washed successively with saturated aq NaCl (10 ml), aq sodium hydrogencarbonate solution (10 ml), and water (10 ml), dried over Na_2SO_4, and concentrated under vacuum. The resulting oil was chromatographed on silica gel. Elution with hexane–ether (2:1) gave 1-thia-4-azaspiro[4.5]decan-6-one (**6a**) as needles (0.0879 g, 56%).

3.1.3. General procedure for preparation of 1-thia-4-aza-8-methylspiro[4.5]decan-6-one (10a) in water using microwave method. A mixture of 2-bromo-4-methylcyclohexanone (**10**) (0.1 mmol), 2-aminoethanethiol (0.2 mmol), and water (5 ml) was irradiated using a microwave generating equipment Model (DISCOVER®LabMate, CEM Corporation) for 10 min at 40 °C. The progress of the reaction was monitored by GLC; after the irradiation was completed, the reaction mixture was extracted with diethylether and washed with saturated NaCl solution. The ethereal solution was dried over Na_2SO_4 and concentrated in vacuum. The resulting oil was chromatographed on silica gel. Elution with hexane–diethylether (5:1) gave 1-thia-4-aza-7-methylspiro[4.5]decan-6-one (**10a**) as a pale yellow oil (0.0156 g, 87%).

3.1.3.1. 2α-Bromospiro[5α-cholestane-3,2′-thiazolidine] (1b). Needles (from acetone); mp 200–205 °C; IR (KBr)=3300 and 823 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.72 (q, 1H, J=4.0, 13.0 Hz, 2β-H), 3.65 (m, 1H, –CH–NH–), 3.17 (m, 1H, –CH–N–), 2.97 (m, 1H, –CH–S–), 2.80 (m, 1H, –CH–S–), 2.35 (dd, 1H, J=4.0, 13.0 Hz, 1β-H), 0.82 (s, 3H, C19), and 0.65 (s, 3H, C18); HRMS m/z 523.2847 (M^+); calcd for $C_{29}H_{50}BrNS$: M, 523.2849.

3.1.3.2. Spiro[5α-cholestane-3,2′-thiazolidin]-2-one (1a). Needles (from acetone); mp 125–127 °C; IR (KBr)= 3300, 1700, and 792 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.61 (m, 1H, –CH–N–), 3.17 (m, 1H, –CH–N–), 2.99 (m, 1H, –CH–S–), 2.78 (m, 1H, –CH–S–), 2.53 (d, 1H, J=13.89 Hz, 1β-H), 2.41 (d, 1H, J=13.89 Hz, 1α-H), 2.00 (t, 1H, J=12.82 Hz, 4β-H), 0.77 (s, 3H, C19), and 0.64 (s, 3H, C18); ^{13}C NMR ($CDCl_3$) δ: 205.37 (C2), 82.92 (C3), 12.49 (C18), and 11.99 (C19). Anal. Found: C, 75.80%; H, 10.85%. Calcd for $C_{29}H_{49}NOS$: C, 75.76%; H, 10.74%. HRMS m/z 459.3536 (M^+). Calcd for $C_{29}H_{49}NOS$: M, 459.3537.

3.1.3.3. From 2α-bromospiro[5α-cholestan-3,2′-thiazolidine] (1b). A mixture of **1b** (0.200 g, 0.381 mmol), 2-aminoethanethiol (0.176 g, 2.286 mmol), and pyridine (3 ml) was stirred at room temperature. After the appropriate reaction time (best determined by TLC monitoring for starting material), the mixture was diluted with ether and washed successively with 30 ml portions of water. After drying (anhydrous Na_2SO_4) and concentration, the residue was purified by silica-gel column chromatography. Elution with benzene–ethyl acetate (19:1) gave thiazolidine derivative **1a**, which crystallized from acetone (0.085 g, 48%).

3.1.3.4. Spiro[benzothiazole-2(3*H*),3′-(5α-cholestan)]-2′-one (1c). Needles (from ethanol–ether); mp 194–196 °C; IR (KBr)=3290, 1708, 1582, and 735 cm^{-1}; ^1H

NMR ($CDCl_3$) δ: 6.76–7.00 (m, 4H, aromatic protons), 2.54 (d, 1H, J=13.18 Hz, 1β-H), 2.45 (d, 1H, J=13.18 Hz, 1α-H), 2.35 (dd, 1H, J=3.02, 14.01 Hz, 4α-H), 1.95 (t, 1H, J=13.46 Hz, 4β-H), 0.76 (s, 3H, C19), and 0.65 (s, 3H, C18); ^{13}C NMR ($CDCl_3$) δ: 205.82 (C2) and 81.03 (C3). Anal. Found: C, 78.10%; H, 9.79%. Calcd for $C_{33}H_{49}ONS$: C, 78.05%; H, 9.73%. HRMS m/z 507.3549 (M^+). Calcd for $C_{33}H_{49}ONS$: M, 507.3565.

3.1.3.5. Spiro[5β-cholestan-3,2′-thiazolidin]-2-one (2a). Needles (from acetone); mp 108–111 °C; IR (KBr)= 3300, 1716, and 788 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.58 (m, 1H, –CH–N–), 3.20 (m, 1H, –CH–N–), 2.99 (m, 1H, –CH–S–), 2.82 (m, 1H, –CH–S–), 2.63 (t, 1H, J=14.35 Hz, 4α-H), 2.60 (d, 1H, J=14.35 Hz, 1α-H), 2.50 (d, 1H, J=14.35 Hz, 1β-H), 1.07 (s, 3H, C19), and 0.63 (s, 3H, C18); ^{13}C NMR ($CDCl_3$) δ: 205.64 (C2), 82.79 (C3), 22.78 (C19), and 12.09 (18C). Anal. Found: C, 75.82%; H, 10.80%. Calcd for $C_{29}H_{49}ONS$: C, 75.76%; H, 10.74%. HRMS m/z 459.3544 (M^+). Calcd for $C_{29}H_{49}ONS$: M, 459.3537.

3.1.3.6. Spiro[5β-cholestan-3,2′-thiazolidin]-4-one (3a). Plates (from acetone); mp 124–127 °C; IR (KBr)= 3300, 1704, 844, 774, and 724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.68 (m, 1H, –CH–N–), 3.12 (m, 1H, –CH–N–), 2.93 (m, 1H, –CH–S–), 2.75 (m, 1H, –CH–S–), 2.60 (dd, 1H, J=1.91, 4.55 Hz, 5β-H), 2.11 (m, 2H, C2), 1.11 (s, 3H, C19), and 0.63 (s, 3H, C18); ^{13}C NMR ($CDCl_3$) δ: 206.71 (C4), 82.56 (C3), 22.59 (C19), and 11.94 (C18); HRMS m/z 459.3543 (M^+). Calcd for $C_{29}H_{49}ONS$: M, 459.3537.

3.1.3.7. Spiro[5β-cholestan-3,2′-thiazolidine] (3d). Needles (from acetone); mp 82–84 °C; IR (KBr)=3420, 3250, 805, and 785 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 0.973 (s, 3H, C19, C–Nequatorial), 0.936 (s, 3H, C19, C–Naxial), and 0.640 (s, 3H, C18); ^{13}C NMR ($CDCl_3$) δ: 83.87 and 81.24 (C3). Anal. Found: C, 78.20%; H, 11.61%. Calcd for $C_{29}H_{51}NS$: C, 78.13%; H, 11.53%. HRMS m/z 446.3834 (MH^+). Calcd for $C_{29}H_{52}NS$: MH, 446.3823.

3.1.3.8. Spiro[5α-lanost-8-en-3,2′-thiazolidin]-2-one (4a). Needles (from acetone); mp 138–139 °C; IR (KBr)=3304, 1706, and 748 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.312 (m, 2H, –CH_2–N–), 2.786 (m, 2H, –CH_2–S–), 3.041 (d, 1H, J=12.91 Hz, 1β-H), 2.786 (t, 2H, J=5.50 Hz, –CH_2–S–), 2.480 (d, 1H, J=12.91 Hz, 1α-H), 1.132 (s, 3H, CH_3), 0.981 (s, 3H, CH_3), 0.925 (s, 6H, 2×CH_3), and 0.672 (s, 3H, C18); ^{13}C NMR ($CDCl_3$) δ: 207.39 (C2), 135.43 (C8 or C9), 132.91 (C8 or C9), and 90.70 (C3); HRMS m/z 499.3395 (M^+). Calcd for $C_{32}H_{53}ONS$: M, 499.3848.

3.1.3.9. 1-Thia-4-azaspiro[4.5]nonan-6-one (5a). Needles (from hexane–acetone=10:1); mp 55.2–56.2 °C; IR (KBr)=3275 and 1744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.73 (m, 1H), 3.14 (m, 1H), 2.90 (m, 1H), 2.54 (m, 1H), 2.49 (br s, 1H), 2.33 (m, 1H), 2.15 (m, 2H), 1.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 212.82, 83.76, 53.44, 38.55, 36.94, 34.05, and18.18. Anal. Found: C, 53.55%; H, 7.01%. Calcd for $C_7H_{11}ONS$: C, 53.47%; H, 7.05%. HRMS m/z 157.0587 (M^+). Calcd for $C_7H_{11}ONS$: M, 157.0562.

3.1.3.10. 1-Thia-4-azaspiro[4.5]decan-6-one (6a). Needles (from hexane–acetone=10:1); mp 80.2–81.2 °C; IR (KBr)=3291 and 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.63 (m, 1H), 3.13 (m, 1H), 2.99 (m, 1H), 2.93 (br s, 1H), 2.75 (m, 2H), 2.53 (m, 1H), 2.28 (m, 1H), 2.01 (m, 2H), 1.90 (m, 1H), 1.75 (m, 1H), and 1.63 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 205.54, 83.23, 52.25, 41.57, 36.23, 36.91, 25.88, and 22.21. Anal. Found: C, 56.18%; H, 7.59%. Calcd for $C_8H_{13}ONS$: C, 56.10%; H, 7.65%. HRMS m/z 171.0761 (M^+). Calcd for $C_8H_{13}ONS$: M, 171.0719.

3.1.3.11. 1-Thia-4-aza-8-*tert*-butylspiro[4.5]decan-6-one (9a). Needles (from hexane–acetone=10:1); mp 101.0–102.6 °C; IR (KBr)=3222 and 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.63 (m, 1H), 3.14 (m, 1H), 2.98 (m, 1H), 2.95 (br s, 1H), 2.77 (m, 1H), 2.53 (m, 2H), 2.29 (m, 1H), 1.94 (m, 2H), 1.49 (m, 2H), and 0.90 (s, 9H); ^{13}C NMR ($CDCl_3$) δ: 206.31, 82.70, 52.30, 48.32, 40.92, 40.51, 36.92, 32.65, 27.16, and 24.34; HRMS m/z 227.1361 (M^+). Calcd for $C_{12}H_{21}ONS$: M, 227.13453.

3.1.3.12. 1-Thia-4-aza-8-methylspiro[4.5]decan-6-one (10a). Needles (from hexane–acetone=10:1); mp 53.2–53.8 °C; IR (KBr)=3294 and 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.63 (m, 1H), 3.13 (m, 1H), 2.99 (br s, 1H), 2.75 (m, 2H), 2.52 (m, 1H), 2.43 (m, 1H), 2.01 (m, 2H), 1.86 (m, 1H), and 1.03 (d, 3H); ^{13}C NMR ($CDCl_3$) δ: 204.92, 82.45, 52.28, 47.28, 40.46, 36.93, 33.50, 31.62, and 22.11; HRMS m/z 185.0833 (M^+). Calcd for $C_9H_{15}ONS$: M, 185.0876.

3.1.3.13. 1-Thia-4-aza-7,9-dimethylspiro[4.5]decan-6-one (11a). Pale yellow oil; IR (NaCl)=3293 and 1708 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.63 (m, 1H), 3.10 (m, 1H), 2.99 (m, 1H), 2.88 (m, 1H), 2.75 (m, 1H), 2.06 (m, 1H), 1.96 (m, 1H), 1.74 (m, 1H), 1.09 (d, 3H), and 1.00 (d, 3H); ^{13}C NMR ($CDCl_3$) δ: 207.44, 82.16, 52.04, 50.20, 42.94, 41.72, 37.07, 29.29, 21.05, and 14.60; HRMS m/z 199.1063 (M^+). Calcd for $C_{10}H_{17}ONS$: M, 199.1032.

3.1.3.14. 1-Thia-4-azaspiro[4.5]undecan-6-one (12a). Needles (from hexane–acetone=10:1); mp 55.5–56.7 °C; IR (KBr) 3290 and 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.71 (m, 1H), 3.28 (br d, 1H), 3.06 (m, 1H), 3.00 (m, 1H), 2.76 (m, 1H), 2.62 (m, 2H), 2.24 (m, 1H), 1.83 (m, 3H), 1.46 (m, 2H), and 1.27 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: 207.40, 83.91, 52.97, 40.44, 40.30, 37.66, 30.21, 27.04, and 26.21; HRMS m/z 185.0856 (M^+). Calcd for $C_9H_{15}ONS$: M, 185.0876.

3.1.3.15. 1-Thia-4-azaspiro[4.5]dodecan-6-one (14a). Yellow oil; IR (NaCl)=3291 and 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.71 (m, 1H), 3.13 (m, 1H), 3.03 (m, 1H), 2.95 (br s, 1H), 2.79 (m, 1H), 2.65 (m, 1H), 2.51 (m, 2H), 2.16 (m, 1H), 1.93 (m, 1H), 1.78 (m, 3H), 1.67 (m, 1H), 1.36 (m, 2H), and 0.98 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 209.33, 85.24, 53.64, 37.96, 36.96, 36.08, 30.31, 25.78, 25.52, and 24.06. HRMS m/z199.1072 (M^+). Calcd for $C_{10}H_{17}ONS$: M, 199.1032.

3.1.3.16. Spiro[naphthalene-1(2*H*),2′-[1,3]thiazolidine]-3′,4′-dihydro-2′-one (15a). Needles (from hexane–acetone=10:1); mp 86.2–87.1 °C; IR (KBr)=3294, 3066,

3029, and 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.535 (d, 1H), 7.22 (m, 3H), 3.95 (m, 1H), 3.47 (br s, 1H), 3.32 (m, 2H), 3.165 (m, 1H), 3.05 (m, 1H), 2.95 (m, 1H), 2.75 (m, 1H), and 2.28 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: 204.16, 139.48, 136.06, 127.94, 127.66, 127.41, 124.24, 80.30, 55.43, 37.96, 34.14, and 27.31; HRMS *m/z* 219.0747 (M^+). Calcd for $C_{12}H_{13}ONS$: M, 219.0719.

3.1.3.17. Butan-2-oxo-spiro-3-(1′,3′-thiazolidine) (16a). Pale yellow oil; IR (NaCl)=3295 and 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.70 (br s, 1H), 3.57 (m, 1H), 3.21 (m, 1H), 3.07 (m, 1H), 2.76 (m, 1H), 2.34 (s, 3H), and 1.73 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 203.89, 81.47, 52.93, 37.79, 26.97, and 25.30; HRMS *m/z* 145.0567 (M^+). Calcd for $C_6H_{11}ONS$: M, 145.0561.

3.1.3.18. Heptan-3-oxo-spiro-4-(1′,3′-thiazolidine) (17a). Pale yellow oil; IR (NaCl)=3302 and 1707 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.55 (m, 1H), 3.14 (m, 1H), 2.98 (m, 1H), 2.85 (br s, 1H), 2.79 (m, 1H), 2.67 (m, 1H), 2.46 (m, 1H), 1.97 (m, 2H), 1.55 (m, 1H), 1.15 (t, J=7.27 Hz, 3H), 1.09 (m, 1H), and 0.92 (t, J=7.27 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 206.91, 85.61, 53.02, 42.46, 36.82, 30.92, 19.47, 14.25, and 8.49; HRMS *m/z* 187.1060 (M^+). Calcd for $C_9H_{17}ONS$: M, 187.1031.

3.1.3.19. Nonan-4-oxo-spiro-5-(1′,3′-thiazolidine) (18a). Pale yellow oil; IR (NaCl)=3302 and 1706 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.55 (m, 1H), 3.14 (m, 1H), 2.98 (m, 1H), 2.85 (br s, 1H), 2.79 (m, 1H), 2.71 (m, 2H), 2.42 (m, 1H), 1.99 (m, 2H), 1.70 (m, 2H), 1.52 (m, 1H), 1.33 (m, 2H), 1.05 (m, 1H), 0.96 (t, J=7.38 Hz, 3H), and 0.88 (t, J=7.38 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 206.04, 85.69, 52.98, 39.92, 39.59, 36.78, 28.23, 22.91, 17.59, 13.88, and 13.75; HRMS *m/z* 215.1346 (M^+). Calcd for $C_{11}H_{21}ONS$: M, 215.1344.

3.1.3.20. Undecan-5-oxo-spiro-6-(1′,3′-thiazolidine) (19a). Pale yellow oil; IR (NaCl)=3302 and 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.55 (m, 1H), 3.14 (m, 1H), 2.98 (m, 1H), 2.85 (br s, 1H), 2.72 (m, 2H), 2.41 (m, 1H), 1.98 (m, 2H), 1.66 (m, 2H), 1.55 (m, 1H), 1.32 (m, 6H), 1.06 (m, 1H), 0.94 (t, J=7.38 Hz, 3H), and 0.88 (t, J=7.38 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ: 206.24, 85.77, 52.97, 40.19, 37.39, 36.78, 31.97, 26.31, 25.80, 22.45, 22.32, 13.97, and 13.91; HRMS *m/z* 243.1636 (M^+). Calcd for $C_{13}H_{25}ONS$: M, 243.1657.

3.1.3.21. 1-Phenyl-spiro-1-(1′,3′-thiazolidine)propan-2-one (20a). Pale yellow oil; IR (NaCl)=3299 and 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.29–7.71 (m, 5H), 3.53 (m, 1H), 3.06 (m, 1H), 3.07 (br s, 1H), 2.91 (m, 2H), and 2.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 201.13, 140.05, 128.51, 128.37, 128.28, 90.06, 52.31, 37.58, and 25.97; HRMS *m/z* 207.0693 (M^+). Calcd for $C_{11}H_{13}ONS$: M, 207.0718.

3.1.3.22. 1-Phenyl-spiro-1-(1′,3′-thiazolidine)pentan-2-one (21a). Pale yellow oil; IR (NaCl)=3300 and 1709 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.28–7.72 (m, 5H), 3.57 (m, 1H), 3.30 (br s, 1H), 3.06 (m, 1H), 2.87 (m, 2H), 2.42 (m, 1H), 2.02 (m, 1H), 1.49 (m, 2H), and 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: 203.29, 140.31, 128.48, 128.32, 128.25, 89.94, 52.19, 40.29, 37.58, 17.81, and 13.48; HRMS *m/z* 235.1011 (M^+). Calcd for $C_{13}H_{17}ONS$: M, 235.1031.

3.1.4. Spectroscopic (^{13}C NMR) evidence for dihydro-1,4-thiazine intermediate (B). 2α-Bromo-5α-cholestan-3-one (**1**) (50 mg) and 2-aminoethanethiol (50 mg) were added in NMR tube (0.5 ml $CDCl_3$). The ^{13}C NMR spectrum was recorded at 25 °C probe temperature.

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