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SHORT SYNTHESIS OF 5-SUBSTITUTED-2,3,4,5-TETRAHYDRO-BENZO[*f*][1,4]THIAZEPINES BY USING A MODIFIED PICTET-SPENGLER REACTION

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Abstract – 5-Substituted-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepines (**6**) were synthesized using a modified Pictet-Spengler reaction of *N*-formyliminium ion (**4**) as the key step. The cyclization of **4** was found to be affected by the acidity of the reaction media, which depended on the structure of the benzene ring. The cyclization of the substrates (**4a-g**) lacking an electron-donating substituent at the benzene ring proceeded smoothly by using a mixed acid catalyst of trifluoroacetic acid and a small amount of trifluoromethanesulfonic acid, thus giving *N*-formylbenzothiazepines (**5a-g**) in good yields. On the other hand, in the case of substrates (**4h-j**) with the OMe group at the benzene ring, although the cyclization proceeded by use of trifluoroacetic acid as the sole catalyst to give the products (**5h-j**), the mixed acid catalyst did not induce the cyclization reaction to any extent. The modified Pictet-Spengler reaction, which constitutes imination of 2-(phenylthio)ethanamine (**1a**) with aldehydes (**2**), and formylation of the resulting imines (**3**), followed by the acid-catalyzed cyclization of *N*-formyliminium ion (**4**), could be carried out as a one-pot procedure, thus providing a convenient methodology for synthesizing various 5-substituted-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepines (**6**).

INTRODUCTION

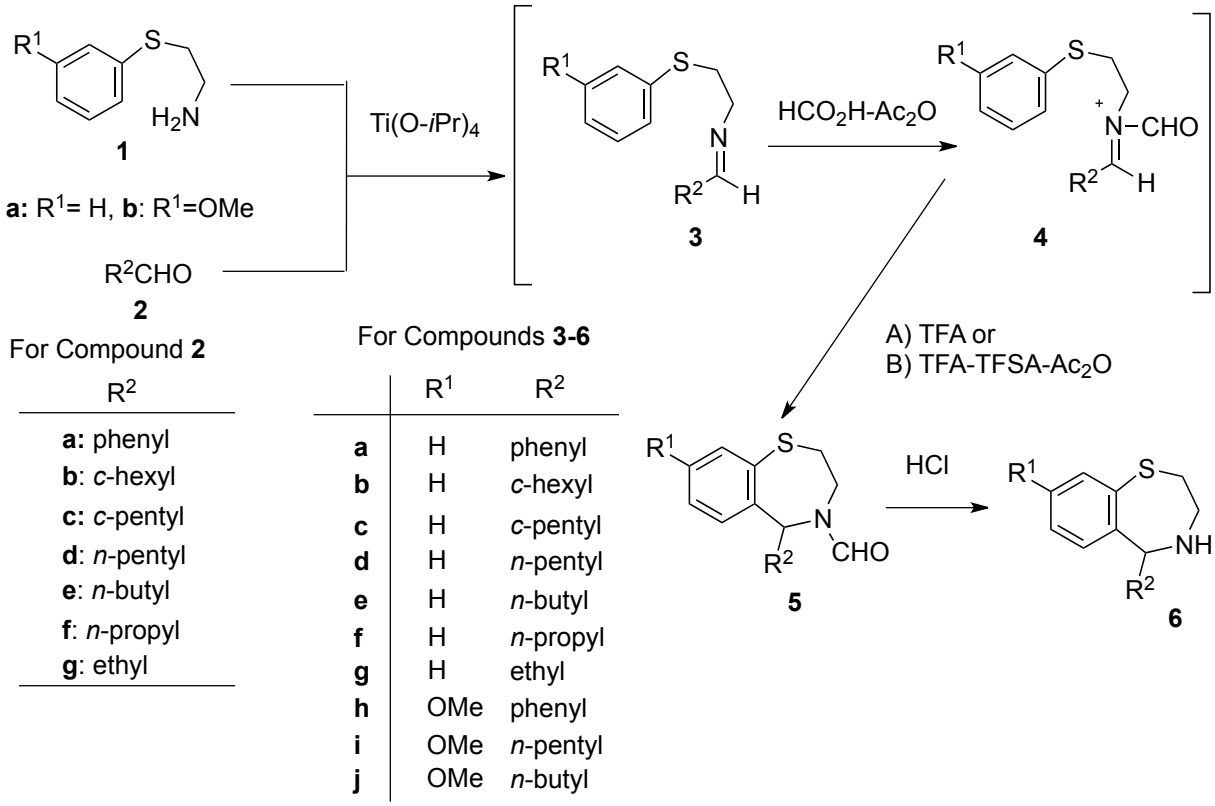
The Pictet-Spengler reaction is one of the key reactions for synthesizing 1,2,3,4-tetrahydroisoquinoline and heteroaryl homologs, which constitute an important class of naturally occurring bioactive substances.[1] The reaction involves an acid-catalyzed cyclization of the intermediate imine formed by condensation of an arylethylamine with an aldehyde. We recently improved this key cyclization reaction by substituting *N*-formyliminium ion for the imine. This modified Pictet-Spengler reaction provides a highly efficient and convenient method for synthesizing 1-substituted and 1,1-disubstituted-1,2,3,4-tetrahydroisoquinolines,[2,3] 1-substituted and 1,1-disubstituted-1,2,3,4-tetrahydro-β-carbolines,[4,5] 1-substituted-2,3-dihydro-1*H*-isoindoles (isoindolines),[6] 4-substituted and 4,4-disubstituted-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines,[7] and 5-substituted-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepines.[8] In the synthesis of these compounds, the *N*-formyliminium ion, as anticipated, exhibits stronger electrophilic properties than the imine. Thus, the modified Pictet-Spengler reaction proceeds under mild acidic conditions, even with substrates in which the aromatic ring lacks electron-donating groups and with sterically congested substrates derived from ketones. Furthermore, we have demonstrated that this reaction can be applied to construct not only a six-membered ring system but also five- and seven-membered ones.

In this report, we describe the synthesis of 5-substituted-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepines using the modified Pictet-Spengler reaction. Although several methods have previously been reported for the synthesis of benzothiazepines,[9-12] this approach to constructing the benzothiazepine ring system using the Pictet-Spengler reaction is hitherto unknown. Development of this new method for the synthesis of benzothiazepines should contribute not only to heterocyclic chemistry but also to pharmacology.

RESULTS AND DISCUSSION

The substrate for the modified Pictet-Spengler reaction, the *N*-formyliminium ion (**4**), was prepared in a one-pot procedure as follows (Scheme 1).

The condensation reaction of 2-(phenylthio)ethanamine (**1a**) (1.0 mol equiv) and aldehyde (**2**) (1.3 mol equiv) to form imine (**3**) was carried out by heating in titanium(IV) tetraisopropoxide (1.2 mol equiv) at 70 °C for 2 h without using any solvent. The imine (**3**) thus formed *in situ*, upon heating in a solution of a large amount of acetic-formic anhydride (30 mol equiv) at 70 °C for 2 h, yielded *N*-formyliminium ion (**4**). The reaction mixture of **4** was used as the substrate for the acid-catalyzed cyclization reaction, after removal of excess acetic-formic anhydride by evaporation *in vacuo*. We found that the cyclization of the *N*-formyliminium ion (**4a**) was difficult compared with that of the oxa-analog (**8**) reported in the preceding paper.[8] Thus, heating of **4a** with trifluoroacetic acid (TFA) (60 mol equiv) at 70 °C for 16 h gave the *N*-formylbenzothiazepine (**5a**) only in 25% yield (run 1). A longer reaction time (48 h) did not improve the yield. However, addition of acetic anhydride (1 mol equiv) did improve the yield of **5a** (54%)



For Compound **2**

R^2
a: phenyl
b: *c*-hexyl
c: *c*-pentyl
d: *n*-pentyl
e: *n*-butyl
f: *n*-propyl
g: ethyl

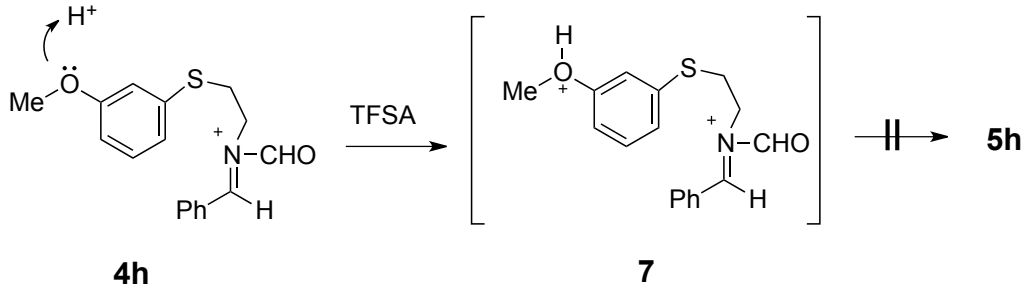
For Compounds **3-6**

	R^1	R^2
a	H	phenyl
b	H	*c*-hexyl
c	H	*c*-pentyl
d	H	*n*-pentyl
e	H	*n*-butyl
f	H	*n*-propyl
g	H	ethyl
h	OMe	phenyl
i	OMe	*n*-pentyl
j	OMe	*n*-butyl

Scheme 1. Synthesis of 5-substituted-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepines

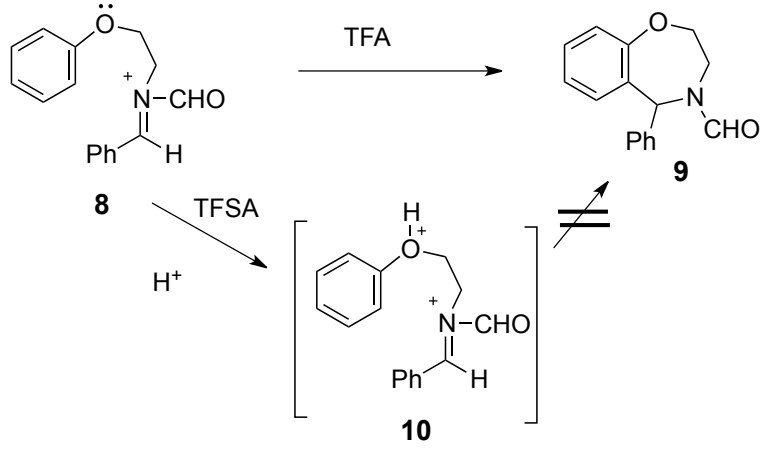
(run 2). This suggested that the benzene ring carrying a sulfur atom does not have enough nucleophilic character to induce this cyclization reaction. T. Ohwada and colleagues demonstrated in their investigations of dication chemistry that the Pictet-Spengler cyclization reaction was greatly facilitated by increasing acidity in the reaction media, and that a super acid such as trifluoromethanesulfonic acid (TFSA) activated the electrophilic carbon of the C=N group.[13,14] Thus, reaction of **4a** with a mixed acid catalyst consisting of TFA (60 mol equiv), acetic anhydride (1 mol equiv) and TFSA (1 mol equiv) at 70 °C for 16 h proceeded smoothly to give **5a** in quantitative yield (run 3). The reaction of other *N*-formyliminium ions (**4b-g**) with the mixed acid catalyst under similar conditions also provided the corresponding *N*-formylbenzothiazepines (**5b-g**). The substrates having *c*-hexyl (**4b**), *c*-pentyl (**4c**), *n*-pentyl (**4d**), *n*-butyl (**4e**), *n*-propyl (**4f**), and ethyl (**4g**) yielded the corresponding 5-alkyl-substituted benzothiazepines (**5b-g**) in 72, 27, 72, 76, 62, and 30% yields, respectively (runs 4, 5, 9-12) (Table 1). In the case of *c*-pentyl (**4c**), the use of two molar equivalents of TFSA slightly improved the yield of **5c** (36%) (run 6). However, a longer reaction time (24 h) at 70 °C completely decomposed the product (**5c**). This suggested that the decreased yield of **5c** may be attributed to the thermal instability of **5c**. In order to improve the yield, we examined the cyclization under lower temperature. The use of one molar equivalent of TFSA did not induce the cyclization at room temperature for 48 h at all (run 7). However, the reaction proceeded at room temperature for 48 h by using five molar equivalents of TFSA to give the product (**5c**) in 62% yield (run 8).

In the case of **4h** containing an electron-donating OMe group on the benzene ring, as expected, the cyclization proceeded smoothly by use of TFA as the sole catalyst at 70 °C for 16 h to give the *N*-formylbenzothiazepine (**5h**) in 78% yield (run 14). The cyclizations of *n*-pentyl (**4i**) and *n*-butyl (**4j**) analogs also occurred upon treatment with TFA under similar conditions to give the corresponding *N*-formylbenzothiazepines (**5i**) and (**5j**) in yields of 82% and 55%, respectively (runs 15, 16). In contrast, the TFSA-catalyzed reaction of **4h** under similar conditions induced extensive decomposition and no identifiable products could be obtained. The expected product (**5h**) was not detected by TLC (run 13). This failure of the cyclization in stronger acidic media using TFSA can be ascribed to protonation of the electron-rich OMe group on the benzene ring, since the formed oxonium cation (**7**) reduces the nucleophilic character of the benzene ring. Thus, TFSA greatly deactivates the nucleophilic center of the cyclized carbon and inhibits the cyclization reaction (Scheme 2).



Scheme 2. Cyclization reaction of *N*-formyliminium ion (**4h**) under mixed acid catalyzed (TFA-TFSA-Ac_2O) reaction condition

A similar phenomenon was observed in the TFSA-catalyzed reaction of the oxa-analog (**8**) carrying an oxygen at the benzene ring. As reported in the preceding paper, the reaction of **8** with TFA smoothly induced the cyclization to yield the product (**9**).[8] However, the reaction of **8** by TFSA as an additional reagent did not produce the cyclized product (**9**) to any extent. This failure of the cyclization can also be attributed to the protonation of an electron-rich oxygen moiety on the benzene ring, which reduced its



Scheme 3. Cyclization reaction of *N*-formyliminium ion (**8**) under acidic reaction condition

nucleophilic character (Scheme 3). The hydrolysis of **5** with hydrochloric acid afforded the 5-substituted-2,3,4,5-tetrahydrobenzothiazepines (**6**) in good yields, as shown in Table 1.

The structures of the products were determined using MS, IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy.[15]

Table 1. Synthesis of 5-substituted-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepines (**6**) using the Modified Pictet-Spengler reaction

Run	Modified Pictet-Spengler Reaction									Hydrolysis of **5**	
	Substrates (**4**)			Reagents (mol eq)			Conditions		Products (**5**)	Products (**6**)	
		R^1	R^2	TFA	TFSA	Ac_2O	Temp (°C)	Time (h)	Yield (%)		Yield (%)
1	**4a**	H	phenyl	60	_	_	70	16	**5a** 25	**6a**	80
2	**4a**	H	phenyl	60	_	1	70	16	**5a** 54		
3	**4a**	H	phenyl	60	1	1	70	16	**5a** 100		
4	**4b**	H	*c*-hexyl	60	1	1	70	16	**5b** 72	**6b**	100
5	**4c**	H	*c*-pentyl	60	1	1	70	16	**5c** 27	**6c**	100
6	**4c**	H	*c*-pentyl	60	2	1	70	16	**5c** 36		
7	**4c**	H	*c*-pentyl	60	1	1	rt	48	**5c** 0		
8	**4c**	H	*c*-pentyl	60	5	1	rt	48	**5c** 62		
9	**4d**	H	*n*-pentyl	60	1	1	70	10	**5d** 72	**6d**	100
10	**4e**	H	*n*-butyl	60	1	1	70	10	**5e** 76	**6e**	95
11	**4f**	H	*n*-propyl	60	1	1	70	10	**5f** 62	**6f**	70
12	**4g**	H	ethyl	60	1	1	70	10	**5g** 30	**6g**	80
13	**4h**	OMe	phenyl	60	1	1	70	16	**5h** 0		
14	**4h**	OMe	phenyl	60	_	_	70	16	**5h** 78	**6h**	94
15	**4i**	OMe	*n*-pentyl	60	_	_	70	16	**5i** 82	**6i**	86
16	**4j**	OMe	*n*-butyl	60	_	_	70	16	**5j** 55	**6j**	96

Thus, the modified Pictet-Spengler reaction of 2-(arylthio)ethanamines and aldehydes *via* *N*-formyliminium ions presents a convenient method for synthesizing various 5-substituted 2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepines. Furthermore, this study demonstrates that the cyclization is greatly affected by the acidity of the reaction media, which depended on the structure of the substrate, and therefore, the selection of acid catalysts is critically important to the modified Pictet-Spengler reaction.

EXPERIMENTAL

Unless otherwise noted, the following procedures were adopted. Melting points were determined using a Yanagimoto SP-M1 hot-stage melting point apparatus and are uncorrected. IR spectra were acquired on

KBr disks using a HORIBA FT-710 spectrophotometer, and the values are given in cm^{-1}. NMR spectra were acquired using a JEOL JNM-AL 300 (^{1}H-NMR, 300 MHz; ^{13}C-NMR, 75 MHz) NMR spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard, and the chemical shifts are given as δ values. HRFAB-MS spectra were recorded using a JEOL-MS700 spectrometer with glycerol as the matrix. TLC was performed on Merck precoated Silica gel 60 F_{254} plates. Column chromatography was carried out with silica gel (Wakogel C-200). The organic extract from each reaction mixture was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to dryness.

Modified Pictet-Spengler reaction of 2-(phenylthio)ethanamine (1a) and aldehyde (2). General procedure: A mixture of **1a** (0.5 g, 3.26 mmol), aldehyde (**2**) (1.2 mol equiv), and Ti(O-*i*Pr)$_4$ (1.2 mol equiv) was heated at 70 °C for 2 h under an argon atmosphere. A solution of acetic-formic anhydride (30 mol equiv) (prepared from HCO_2H [30 mol equiv] and Ac_2O [30 mol equiv]) was added to the reaction mixture at 0 °C, then the mixture was heated at 70 °C for 2 h. After removal of excess acetic-formic anhydride by heating *in vacuo*, TFA (60 mol equiv), TFSA (1-5 mol equiv) and acetic anhydride (1 mol equiv) were added to the reaction mixture and heated at 70 °C or stirred at room temperature for 10-48 h (as shown in Table 1). The reaction mixture was diluted with MeOH (100 mL) and passed through a short SiO_2 column ($CHCl_3$-MeOH) to remove TiO_2. The eluent was concentrated *in vacuo* to *ca*. 50 mL, and the resulting residue was extracted with $CHCl_3$. After removal of the extraction solvent *in vacuo*, the residue was purified by chromatography over SiO_2 and elution with AcOEt-hexane (1:1-1:3) to give (**5**).

***N*-Formyl-5-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (5a):** Yellow plates recrystallized from Et_2O, mp 127-129 °C. IR: 1658, 1596. ^{1}H-NMR: 2.67-2.74, (2H, m, C2-H), 3.25-3.33, 3.64-3.81, 4.52-4.60 (total 2H, each m, C3-H), 6.16, 6.95 (total 1H, each s, C5-H), 7.04-7.51 (9H, m, Ar-H), 8.24, 8.57 (total 1H, each s, CHO). HR-FABMS *m/z* MH^+: Calcd for $C_{16}H_{16}NOS$: 270.0953. Found: 270.0964.

***N*-Formyl-5-cyclohexyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (5b):** Yellow gum. IR: 1671, 1589. ^{1}H-NMR: 0.78-1.80 (11H, m, cyclohexyl-CH_2 and C1'-H), 2.78-3.12 (3H, m, C2-H and C3-H), 3.79-3.88 (1H, m, C3-H), 4.07-4.17 (0.5H, m, C5-H), 5.11 (0.5H, d, J = 11 Hz, C5-H), 7.09-7.51 (4H, m, Ar-H), 8.10, 8.19 (total 1H, each s, CHO). HR-FABMS *m/z* (MH^+): Calcd for $C_{16}H_{22}NOS$: 276.1422. Found: 276.1433.

***N*-Formyl-5-cyclopentyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (5c):** Yellow gum. IR: 1670, 1560. ^{1}H-NMR: 1.00-1.89 (9H, m, cyclopentyl-CH_2 and C1'-H), 2.80, 2.86 (2H, dt, J = 5, 6 Hz, C2-H), 3.42-3.69 (1H, m, C3-H), 3.93 (1H, d, J = 4 Hz, C3-H), 4.21 (0.5H, d, J = 13 Hz, C5-H), 5.13 (0.5H, d, J = 12 Hz, C5-H), 7.13-7.54 (4H, m, Ar-H), 8.10, 8.21 (total 1H, each s, CHO). HR-FABMS *m/z* (MH^+): Calcd for $C_{15}H_{20}NOS$: 262.1265. Found: 262.1272.

***N*-Formyl-5-pentyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (5d):** Yellow gum. IR: 1670, 1590, 1540. ^{1}H-NMR: 0.84-0.91 (3H, m, CH_3), 1.20-1.34 (6H, m, pentyl-CH_2), 2.05-2.45 (2H, m, C1'-H), 2.79-2.83

(1H, m, C2-H), 2.86-2.90 (1H, m, C2-H), 3.82-3.97 (2H, m, C3-H), 4.62-4.67, 5.36-5.41 (total 1H, each m, C5-H), 7.11-7.54 (4H, m, Ar-H), 8.08, 8.21 (total 1H, each s, CHO). HR-FABMS *m/z* (MH^+): Calcd for $C_{15}H_{22}NOS$: 264.1423. Found: 264.1429.

***N*-Formyl-5-butyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (5e):** Yellow gum. IR: 1677, 1664, 1465. ^{1}H-NMR: 0.89, 0.91 (total 3H, each t, J = 7 Hz, CH_3), 1.24-1.43 (4H, m, butyl-CH_2), 2.16-2.46 (2H, m, C1'-H), 2.80-2.90 (2H, m, C2-H), 3.82-3.92 (2H, m, C3-H), 4.62-4.67, 5.38-5.43 (total 1H, each m, C5-H), 7.13-7.54, (4H, m, Ar-H), 8.08, 8.20 (total 1H, each s, CHO). HR-FABMS *m/z* (MH^+): Calcd for $C_{14}H_{20}NOS$: 250.1265. Found: 250.1276.

***N*-Formyl-5-propyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (5f):** Yellow plates recrystallized from Et_2O. mp 87-88 °C. IR: 1670, 1652, 1585. ^{1}H-NMR: 0.95, 0.97 (total 3H, each t, J = 7 Hz, CH_3), 1.18-1.43 (2H, m, propyl-CH_2), 2.13-2.38 (1H, m, C1'-H), 2.35-2.46 (1H, m, C1'-H), 2.79-2.90, 3.82-3.92 (total 4H, each m, C2-H and C3-H), 4.64-4.69, 5.38-5.43 (total 1H, each m, C5-H), 7.13-7.54, (4H, m, Ar-H), 8.08, 8.20 (total 1H, each s, CHO). HR-FABMS *m/z* (MH^+): Calcd for $C_{13}H_{18}NOS$: 236.1109. Found: 236.1096.

***N*-Formyl-5-ethyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (5g):** Yellow gum. IR: 1671, 1589. ^{1}H-NMR: 0.89, 0.97 (3H, each t, J = 7 Hz, CH_3), 2.21-2.58 (2H, m, C1'-H), 2.80-2.90 (2H, m, C2-H), 3.87-3.92 (2H, m, C3-H), 4.52-4.58, 5.30-5.32 (total 1H, each m, C5-H), 7.12-7.55 (4H, m, Ar-H), 8.09, 8.21 (total 1H, each s, CHO). HR-FABMS *m/z* (MH^+): Calcd for $C_{12}H_{16}NOS$: 222.0953. Found: 222.0960.

Modified Pictet-Spengler reaction of 2-(3-methoxyphenylthio)ethanamine (1b) and aldehyde (2). General procedure: A mixture of (**1b**) (0.5 g, 2.73 mmol), aldehyde (**2**) (1.2 mol equiv), and Ti(O-*i*Pr)$_4$ (1.2 mol equiv) was heated at 70 °C for 2 h under an argon atmosphere. A solution of acetic-formic anhydride (30 mol equiv) (prepared from HCO_2H [30 mol equiv] and Ac_2O [30 mol equiv]) was added to the reaction mixture at 0 °C, then the mixture was heated at 70 °C for 2 h. After removal of excess acetic-formic anhydride by heating *in vacuo*, TFA (60 mol equiv) was added to the reaction mixture and heated at 70 °C for 16 h. The reaction mixture was diluted with MeOH (100 mL) and passed through a short SiO_2 column ($CHCl_3$-MeOH) to remove TiO_2. The eluent was concentrated *in vacuo* to *ca*. 50 mL, and the resulting residue was extracted with $CHCl_3$. After removal of the extraction solvent *in vacuo*, the residue was purified by chromatography over SiO_2 and elution with AcOEt-hexane (1:1-1:3) to give (**5**).

***N*-Formyl-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (5h):** Yellow prisms recrystallized from Et_2O, mp 132-139 °C. IR: 1681, 1660, 1641, 1594. ^{1}H-NMR: 2.71-2.95 (2H, m, C2-H), 3.16-3.76, 4.52-4.57 (total 2H, each m, C3-H), 3.78, 3.82 (total 3H, each s, OCH_3), 6.03, 6.90 (total 1H, each s, C5-H), 6.78-7.38 (8H, m, Ar-H), 8.31, 8.47 (total 1H, each s, CHO). HR-FABMS *m/z* (MH^+): Calcd for $C_{17}H_{18}NO_2S$: 300.1059. Found: 300.1053.

***N*-Formyl-8-methoxy-5-pentyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (5i):** Yellow oil. IR: 1671, 1596. ^{1}H-NMR: 0.84-0.91 (3H, m, CH_3), 1.26-1.33 (7H, m, pentyl-CH_2 and C1'-H), 2.10-2.44 (2H, m, C2-H and C1'-H), 2.80-2.90 (2H, m, C2-H and C3-H), 3.77, 3.78 (total 3H, each s, OCH_3), 3.85-3.95 (1H, m, C3-H), 4.56-4.61, 5.32-5.36 (total 1H, each m, C5-H), 6.73, 7.76 (total 1H, each dd, *J* = 9, 3 Hz, C7-H), 7.03, 7.08 (total 1H, each d, *J* = 3 Hz, C9-H), 7.14, 7.31 (total 1H, each d, *J* = 9 Hz, C6-H), 8.06, 8.19 (total 1H, each s, CHO). HR-FABMS *m/z* (MH^+): Calcd for $C_{16}H_{24}NO_2S$: 294.1527. Found: 294.1537.

***N*-Formyl-5-butyl-8-methoxy-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (5j):** Yellow oil. IR: 1671, 1596. ^{1}H-NMR: 0.94, 0.97 (total 3H, each t, *J* = 7 Hz, CH_3), 1.27-1.42 (4H, m, butyl-CH_2), 2.10-2.41 (2H, m, C1'-H), 2.82-2.90 (2H, m, C2-H), 3.77, 3.78 (total 3H, each s, OCH_3), 3.84-4.00 (2H, m, C3-H), 4.58-4.63, 5.33-5.39 (total 1H, each m, C5-H), 6.73, 6.76 (total 1H, each dd, *J* = 8, 3 Hz, C7-H), 7.03, 7.08 (total 1H, each d, *J* = 3 Hz, C9-H), 7.14, 7.31 (total 1H, each d, *J* = 8 Hz, C6-H), 8.06, 8.19 (total 1H, each s, CHO). HR-EIMS *m/z* (M^+): Calcd for $C_{15}H_{21}NO_2S$: 279.1293. Found: 279.1282.

Hydrolysis of *N*-formyl -2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (5). General procedure:

A solution of (**5**) (100 mg) in EtOH (5 mL) and 10% HCl aqueous solution (5 mL) was refluxed for 16-48 h under an argon atmosphere. The reaction mixture was diluted with water, made alkaline with 10% NaOH solution, and extracted with $CHCl_3$. The residue was purified by column chromatography over SiO_2 with MeOH-$CHCl_3$ (9:1) to give (**6**).

5-Phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (6a): Reaction time: 16 h. Yellow gum. IR: 1646, 1600, 1565. ^{1}H-NMR: 2.95-3.01 (1H, m, C2-H), 3.13-3.18 (1H, m, C2-H), 3.44 (2H, t, *J* = 4 Hz, C3-H), 5.94 (1H, s, C5-H), 6.85-6.88 (1H, m, Ar-H), 7.09-7.53 (8H, m, Ar-H). ^{13}C-NMR: 28.9 (C2), 46.8 (C3), 63.7 (C5), 128.4 (Ph-CHx2), 128.7 (Ar-CH), 128.8 (Ar-CH), 129.0 (Ph-CHx2), 129.5 (Ar-CH), 131.2 (Ar-CH), 134.8 (Ph-C), 135.2 (C5a), 137.7 (C9a). HR-FABMS *m/z* (MH^+): Calcd for $C_{15}H_{16}NS$: 242.0102. Found: 242.0092.

5-Cyclohexyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (6b): Reaction time: 16 h. Yellow gum. IR: 1670, 1596. ^{1}H-NMR: 0.80-0.88 (1H, m, cyclohexyl-CH_2), 1.12-1.43 (5H, m, cyclohexyl-CH_2), 1.62-1.66 (2H, m, cyclohexyl-CH_2), 1.87-1.90 (1H, m, cyclohexyl-CH_2), 2.27-2.30 (1H, m, cyclohexyl-CH_2), 2.83-2.85 (1H, m, C1'-H), 3.00-3.05 (1H, m, C2-H), 3.30-3.41 (2H, m, C2-H and C3-H), 3.61-3.65 (1H, m, C3-H), 4.36 (1H, d, *J* = 11 Hz, C5-H), 7.23-7.32 (3H, m, Ar-H), 7.43 (1H, dd, *J* = 6, 2 Hz, Ar-H). ^{13}C-NMR: 25.0 (cyclohexyl-CH_2), 25.1 (cyclohexyl-CH_2), 25.4 (cyclohexyl-CH_2), 28.4 (C2), 29.8 (cyclohexyl-CH_2), 29.9 (cyclohexyl-CH_2), 34.3 (C1'), 43.0 (C3), 66.1 (C5), 128.0 (Ar-CH), 128.9 (Ar-CH), 131.4 (Ar-CH), 133.7 (Ar-CH), 133.8 (C5a), 135.7 (C9a). HR-FABMS *m/z* (MH^+): Calcd for $C_{16}H_{22}NS$: 248.1473. Found: 248.1469.

5-Cyclopentyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (6c): Reaction time: 16 h. Yellow gum. IR: 1571, 1540. ^{1}H-NMR: 1.01-1.07 (1H, m, cyclopentyl-CH_2), 1.57-1.83 (6H, m, cyclopentyl-CH_2), 2.02-2.27 (1H, m, cyclopentyl-CH_2), 3.04 (1H, m, C1'-H), 3.21-3.34 (3H, m, C2-H and C3-H), 3.54-3.60 (1H, m, C3-H), 4.48 (1H, d, *J* = 11 Hz, C5-H), 7.23-7.40 (3H, m, Ar-H), 7.53 (1H, dd, *J* = 8, 1 Hz, Ar-H). ^{13}C-NMR: 25.1 (cyclopentyl-CH_2), 25.7 (cyclopentyl-CH_2), 28.6 (C2), 31.31 (cyclopentyl-CH_2), 31.4 (cyclopentyl-CH_2), 39.1 (C1'), 44.2 (C3), 66.2 (C5), 128.8 (Ar-CH), 129.5 (Ar-CH), 130.4 (Ar-CH), 134.1 (Ar-CH), 134.4 (C5a), 137.0 (C9a). HR-FABMS *m/z* (MH^+): Calcd for $C_{14}H_{20}NS$: 234.1316. Found: 234.1321.

5-Pentyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (6d): Reaction time: 16 h. Yellow gum. IR: 1623, 1598. ^{1}H-NMR: 0.86-0.88 (3H, m, CH_3), 1.10-1.48 (6H, m, pentyl-CH_2), 2.15-2.30 (1H, m, C1'-H), 2.40-2.55 (1H, m, C1'-H), 2.95-3.05 (1H, m, C2-H), 3.15-3.22 (2H, m, C2-H, and C-3-H), 3.45-3.60 (1H, m, C3-H), 4.81 (1H, d, *J* = 5 Hz, C5-H), 7.30-7.44 (3H, m, Ar-H), 7.56 (1H, d, *J* = 8 Hz, Ar-H). ^{13}C-NMR: 13.9 (CH_3), 22.4 (pentyl-CH_2), 26.0 (pentyl-CH_2), 28.5 (pentyl-CH_2), 29.4 (C1'), 31.3 (C2), 44.2 (C3), 60.1 (C5), 128.8 (Ar-CH), 129.7 (Ar-CHx2), 133.9 (Ar-CH), 135.2x2 (C5a and C9a). HR-FABMS *m/z* (MH^+): Calcd for $C_{14}H_{22}NS$: 236.1473 Found: 236.1484.

5-Butyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (6e): Reaction time: 16 h. Yellow gum. IR: 1654, 1571. ^{1}H-NMR: 0.97 (3H, t, *J* = 7 Hz, CH_3), 1.19-1.42 (4H, m, butyl-CH_2), 2.24-2.35 (1H, m, C1'-H), 2.42-2.55 (1H, m, C1'-H), 3.02-3.08 (1H, m, C2-H), 3.20-3.36 (2H, m, C2-H and C3-H), 3.52-3.58 (1H, m, C3-H), 4.80 (1H, dd, *J* = 9, 6 Hz, C5-H), 7.29-7.43 (3H, m, Ar-H), 7.56 (1H, dd, *J* = 7, 1 Hz, Ar-H). ^{13}C-NMR: 13.8 (CH_3), 19.6 (butyl-$\underline{C}H_2$), 22.2 (butyl-CH_2), 28.3 (C1'), 29.6 (C2), 44.3 (C3), 60.2 (C5), 128.8x2 (Ar-CH), 129.6 (Ar-CH), 133.9 (Ar-CH), 135.0 (C5a), 135.4 (C9a). HRMS *m/z* (MH^+): Calcd for $C_{12}H_{18}NS$: 222.1316. Found: 222.1306.

5-Propyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (6f): Reaction time: 16 h. Yellow gum. IR: 1654. ^{1}H-NMR: 0.98 (3H, t, *J* = 7 Hz, CH_3), 1.10-1.40 (4H, m, propyl-CH_2), 2.24-2.35 (1H, m, C1'-H), 2.48-2.60 (1H, m, C1'-H), 3.02-3.09 (1H, m, C2-H), 3.20-3.36 (2H, m, C2-H and C3-H), 3.52-3.58 (1H, m, C3-H), 4.78-4.83 (1H, m, C5-H), 7.27-7.54 (4H, m, Ar-H). ^{13}C-NMR: 13.8 (CH_3), 22.3 (propyl-CH_2), 28.4 (C1'), 29.6 (C2), 44.3 (C3), 60.2 (C5), 128.8 (Ar-CH), 129.6x2 (Ar-CH), 133.9 (Ar-CH), 135.2 (C5a), 135.5 (C9a). HR-FABMS *m/z* (MH^+): Calcd for $C_{12}H_{18}NS$: 208.1160. Found: 208.1155.

5-Ethyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (6g): Reaction time: 16 h. Yellow oil. IR: 1670. ^{1}H-NMR: 0.97 (3H, t, *J* = 7 Hz, CH_3), 1.75-2.00 (2H, m, C1'-H), 2.54-2.74 (2H, m, C2-H), 3.15-3.23 (1H, m, C3-H), 3.36-3.44 (1H, m, C2-H), 4.09 (1H, dd, *J* = 8, 6 Hz, C5-H), 7.01-7.08 (1H, m, Ar-H), 7.16-7.18 (2H, m, Ar-H), 7.50 (1H, d, *J* = 7 Hz, Ar-H). ^{13}C-NMR: 11.8 (CH_3), 26.9 (CH_2), 35.5 (C2), 50.5 (C3), 62.3 (C5), 126.0 (Ar-CH), 126.4 (Ar-CH), 127.8 (Ar-CH), 133.4 (Ar-CH), 136.2 (C5a), 148.4 (C9a). HR-FABMS *m/z* (MH^+): Calcd for $C_{11}H_{16}NS$: 194.1004. Found: 194.1011.

8-Methoxy-5-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (6h): Reaction time: 24 h. Colorless solid. IR: 1594, 1560. ^{1}H-NMR: 2.71-2.92 (2H, m, C2-H), 3.34 (1H, ddd, *J* = 13, 10, 3 Hz, C3-H), 3.51-3.58 (1H, m, C3-H), 3.74 (3H, s, OCH_3), 5.59 (1H, s, C5-H), 6.51 (1H, d, *J* = 8 Hz, C6-H), 6.58 (1H, dd, *J* = 8, 3 Hz, C7-H), 7.17 (1H, d, *J* = 3 Hz, C9-H), 7.25-7.39 (5H, m, Ph-H). ^{13}C-NMR: 35.5 (C2), 51.3 (C3), 55.4 (OCH_3), 63.9 (C5), 109.2 (C9), 112.9 (C6), 118.4 (C7), 126.8 (Ph-CH), 127.5 (Ph-CH), 128.3 (Ph-CH), 129.3 (Ph-CH), 124.3 (Ph-CH), 137.0 (Ph-C), 141.5 (C5a), 143.5 (C9a), 157.6 (C8). HR-FABMS *m/z* (MH^+): Calcd for $C_{16}H_{18}ONS$: 272.1109. Found: 272.1104

8-Methoxy-5-pentyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (6i): Reaction time: 48 h. Yellow oil. IR: 1675, 1596, 1565. ^{1}H-NMR: 0.96 (3H, t, *J* = 7 Hz, CH_3), 1.25-1.52 (6H, m, pentyl-CH_2), 1.78-1.98 (2H, m, C1'-H), 2.63-2.88 (2H, m, C2-H), 3.20-3.28 (1H, m, C3-H), 3.41-3.48 (1H, m, C3-H), 3.78 (3H, s, OCH_3), 4.18 (1H, dd, *J* = 8, 6 Hz, C5-H), 6.77 (1H, dd, *J* = 8, 3 Hz, C7-H), 7.14 (1H, d, *J* = 3 Hz, C9-H), 7.16 (1H, d, *J* = 8 Hz, C6-H). ^{13}C-NMR: 14.1 (CH_3), 22.6 (pentyl-CH_2), 26.9 (pentyl-CH_2), 32.0 (pentyl-CH_2), 34.3 (C1'), 35.7 (C2), 50.4 (C3), 55.3 (OCH_3), 60.0 (C5), 113.2 (C7), 118.4 (C9), 127.0 (C6), 137.2 (C5a), 140.9 (C9a), 157.5 (C8). HR-FABMS *m/z* (MH^+): Calcd for $C_{15}H_{24}ONS$: 266.1579. Found: 266.1573.

5-Butyl-8-methoxy-2,3,4,5-tetrahydrobenzo[*f*][1,4]thiazepine (6j): Reaction time: 48 h. Yellow oil. IR: 1596, 1565, 1540. ^{1}H-NMR: 0.93 (3H, t, *J* = 7 Hz, CH_3), 1.25-1.53 (4H, m, butyl-CH_2), 1.76-2.09 (2H, m, C1'-H), 2.56-2.81 (2H, m, C2-H), 3.11-3.20 (1H, m, C3-H), 3.32-3.41 (1H, m, C2-H), 3.77 (3H, s, OCH_3), 4.10 (1H, dd, *J* = 8, 6 Hz, C5-H), 6.70 (1H, dd, *J* = 8, 3 Hz, C7-H), 7.06 (1H, d, *J* = 3 Hz, C9-H), 7.09 (1H, d, *J* = 8 Hz, C6-H). ^{13}C-NMR: 14.1 (CH_3), 22.8 (butyl-CH_2), 29.4 (butyl-CH_2), 34.0 (C1'), 35.7 (C2), 50.4 (C3), 55.3 (OCH_3), 59.9 (C5), 113.2 (C7), 118.4 (C9), 127.0 (C6), 137.0 (C5a), 140.8 (C9a), 157.5 (C8). HR-FABMS *m/z* (MH^+): Calcd for $C_{13}H_{20}ONS$: 252.1422. Found: 252.1419.

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15. The ^{1}H- and ^{13}C-NMR spectra of *N*-formyl compounds (**5**) exhibited complex signals attributable to rotational isomerism of the N-CO bond. Therefore, ^{13}C-NMR spectra of cyclized products were assigned based on measurements of *N*-deformyl derivatives (**6**).