Tetrahedron 66 (2010) 8837–8845

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Me_3SiCl-promoted intramolecular cyclization of aromatic compounds tethered with *N*,*O*-acetals leading to the facile preparation of 1,4-benzodiazepine skeletons

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ARTICLE INFO

Article history:
Received 18 July 2010
Received in revised form 19 September 2010
Accepted 20 September 2010
Available online 24 September 2010

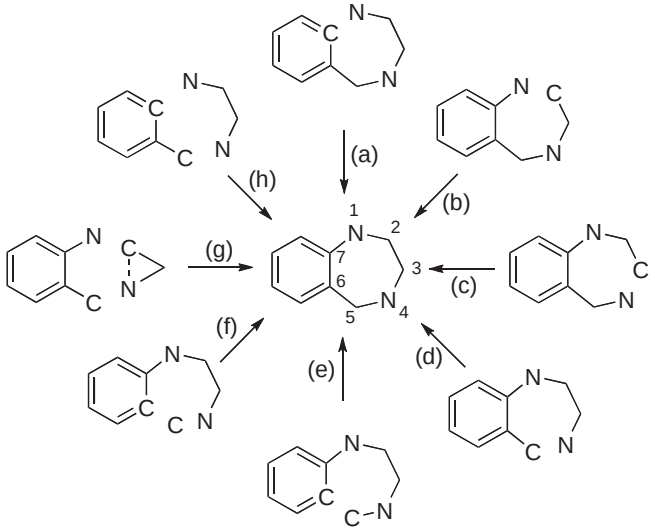
Keywords:
1,4-Benzodiazepine
N,*O*-Acetal
Intramolecular cyclization
Chlorosilane

ABSTRACT

The Me_3SiCl-promoted intramolecular aminomethylation of a novel type of *N*,*O*-acetals, which were prepared via a facile three-step synthesis from *N*-alkylaniline derivatives and *N*-alkyl-2-oxazolidinones that leads to the production of pharmaceutically useful 1,4-benzodiazepine skeletons with a variety of functional groups is described. This method was successfully applied to the facile preparation of both tricyclic benzodiazepine derivatives and a 1,4-benzoxazepine derivative via 7-*exo*-*trig* cyclization.

1. Introduction

1,4-Benzodiazepine skeletons are one of the most important and central building blocks in medicinal and pharmaceutical chemistry. The 1,4-benzodiazepines are found in a wide variety of biologically active substances, which show sedative, anxiolytic, anticonvulsant, and hypnotic activity.[1] A variety of approaches for the synthesis of the 1,4-diazepine skeletons have been developed, which are organized in Scheme 1 based on the position of bond formation: (i) 1,7-bond-forming cyclization via an aromatic substitution with a nitrogen atom (path a);[2] (ii) 1,2-bond-forming cyclization that proceeds via a S_N2-type reaction with a nucleophilic nitrogen atom[3] and a Pd-catalyzed intramolecular N-arylation[4] (path b); (iii) 3,4-bond-forming[5] or 4,5-bond-forming cyclization[6] (paths c and d); (iv) a 5,6-bond-forming reaction via intramolecular cyclization of a substrate with an *N*,*O*- or *N*,*N*-acetal moiety (path e);[7] (v) 4,5- and 5,6-bond-forming annulation via a Pictet–Spengler reaction with an aldehyde as a C1 unit[8] and a Pd-catalyzed intramolecular coupling reaction in the presence of CO gas[9] (path f); (vi) 1,2- and 4,5-bond-forming annulation through a ring-expansion with an aziridine (path g);[10] and (vii) 1,7- and 5,6-bond-forming reaction by direct annulation with an ethylenediamine derivative (path h).[11] Of these synthetic pathways, we focused on the preparation of a 1,4-benzodiazepine framework through intramolecular cyclization



Scheme 1.

of a substrate with an *N*,*O*- or *N*,*N*-acetal moiety in the presence of an acid catalyst (path e), because this facile synthesis of a fused seven-membered ring structure such as a 1,4-benzodiazepine derivative has not been extensively studied. Previously, Katritzky et al. reported intramolecular cyclization of a *N*-arylethylenediamine derivative with a benzotriazole unit in the presence of $AlCl_3$ that led to the

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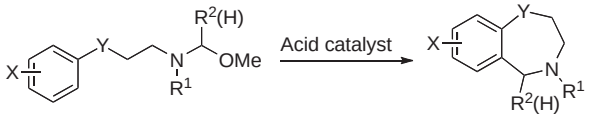
doi:10.1016/j.tet.2010.09.077

production of a 1,4-benzodiazepine derivative.[7d] In addition, several other groups found that a Lewis acid, such as $SnCl_4$, and a strong acid, such as TFA or hydrochloric acid, promoted intramolecular cyclization of a substrate with an *N*,*O*-acetal unit to produce 1,4-benzodiazepine skeletons.[7a–c,7e] However, these methods have several disadvantages, including the use of a strong acid and the use of more than a stoichiometric amount of a Lewis catalyst, which limits the reaction to substrates that are tolerant of these harsh conditions. Therefore, a facile and efficient synthetic reaction that proceeds under milder conditions is required.

In this context, we previously found that the relatively mild Lewis acid trimethylchlorosilane (Me_3SiCl) was a good catalyst to activate *N*,*O*-acetals with a variety of functional group.[12] Thus, to overcome the limitation described above, we attempted to apply intramolecular cyclization of aromatic compounds tethered with an *N*,*O*-acetal moiety in the presence of a mild Lewis acid to the preparation of the 1,4-benzodiazepine framework (Scheme 2). In this paper, we report the results of a Me_3SiCl-promoted intramolecular aminomethylation of novel *N*,*O*-acetals, which were prepared via a three-step synthesis from *N*-alkylaniline derivatives and *N*-alkyl-2-oxazolidinones, leading to the synthesis of 1,4-benzodiazepine skeletons with a variety of functional groups. We also describe the use of this method for the facile preparation of tricyclic benzodiazepine derivatives and a 1,4-benzoxazepine derivative via 7-*exo*-*trig* cyclization.



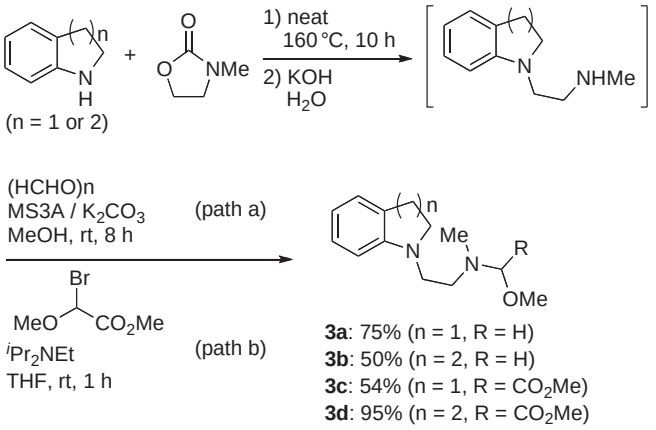
Scheme 2.

2. Results and discussion

2.1. Preparation of *N*,*O*-acetals

Initially, a series of *N*,*O*-acetals **1**,**2** were prepared via the three steps shown in Table 1. For example, a representative reaction was performed as follows: *N*-methylaniline was treated with *N*-methyl-2-oxazolidinone at 160 °C for 10 h without a solvent, followed by a standard work-up with an aqueous solution of KOH, which gave the corresponding ethylenediamine derivative (R^1, R^2=Me).[13] The formed 1,2-ethylenediamine derivative in the crude reaction mixture, i.e., without isolation, was then treated with paraformaldehyde and dehydrating agents in MeOH at room temperature for 8 h to yield the starting material *N*,*O*-acetal **1a** in 72% yield (path a).[14] Also, the ethylenediamine was treated with methyl 2-bromo-2-methoxyacetate[12d] in the presence of diisopropylethylamine in THF at room temperature for 1 h to produce the corresponding *N*,*O*-acetal **2a** in 93% yield (path b).[14]

Moreover, use of indoline and tetrahydroquinoline instead of an aniline derivative gave the *N*,*O*-acetals **3a**–**d** with a nitrogen-containing heterocycle (Scheme 3).

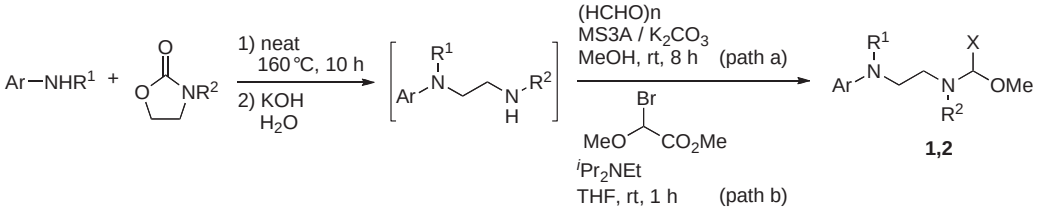


Scheme 3. Preparation of *N*,*O*-acetals **3**.

2.2. Intramolecular cyclization of *N*,*O*-acetals leading to the 1,4-benzodiazepine derivatives

To identify the optimal cyclization conditions, the various catalysts were tested using the intramolecular aminomethylation of *N*,*O*-acetal **1a** in CH_2Cl_2 as a model reaction (Table 2). In a previous

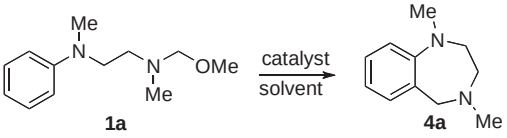
Table 1
Preparation of *N*,*O*-acetals **1** and **2**



Entry	Ar	R^1	R^2	X	Yield[a] (%)	
1	Ph	Me	Me	H	**1a**	72
2	4-Me–C_6H_4	Me	Me	H	**1b**	81
3	2-Me–C_6H_4	Me	Me	H	**1c**	75
4	4-MeO–C_6H_4	Me	Me	H	**1d**	54
5	4-Cl–C_6H_4	Me	Me	H	**1e**	82
6	4-F–C_6H_4	Me	Me	H	**1f**	72
7	3-CF_3–C_6H_4	Me	Me	H	**1g**	74
8	Ph	Et	Me	H	**1h**	60
9	Ph	Me	Allyl	H	**1i**	75
10	Ph	Me	Me	CO_2Me	**2a**	93
11	4-Me–C_6H_4	Me	Me	CO_2Me	**2b**	80
12	4-MeO–C_6H_4	Me	Me	CO_2Me	**2c**	94
13	3-CF_3–C_6H_4	Me	Me	CO_2Me	**2d**	93
14	Ph	Et	Me	CO_2Me	**2e**	95
15	Ph	Bn	Me	CO_2Me	**2f**	78

[a] Isolated yield.

Table 2
Examinations of reaction conditions for intramolecular cyclization



1a **4a**

Run	Catalyst				Solv	Temp (°C)	Time (h)	Yield[a] (%)
1	Me_3SiCl	(1.2)	$Hf(OTf)_4$	(0.1)	CH_2Cl_2	rt	0.5	94
2	Me_3SiCl	(1.2)	—		CH_2Cl_2	rt	0.5	91
3	Me_3SiI	(1.2)	—		CH_2Cl_2	rt	0.5	83
4	Me_3SiOTf	(1.2)	—		CH_2Cl_2	rt	0.5	37
5	Me_3SiCl	(0.2)	—		CH_2Cl_2	rt	6	21
6	Me_3SiCl	(0.1)	—		CH_3CN	Reflux	1	84
7	HCl	(0.1)	—		CH_3CN	Reflux	1	85

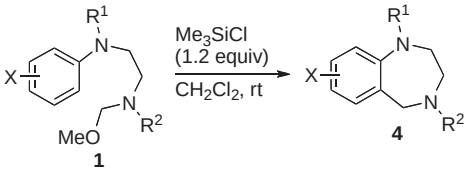
[a] NMR yield.

study, we found that when *N*,*O*-acetal **1a** was reacted with 10 mol % of $Hf(OTf)_4$ and 1.2 equiv of Me_3SiCl in CH_2Cl_2 at room temperature, the desired cyclization was completed within 0.5 h to produce 1,4-dimethyl-2,3,4,5-1*H*-1,4-benzodiazepine (**4a**) in 94% yield (run 1). When Me_3SiCl was used in the absence of $Hf(OTf)_4$, the reaction also proceeded to give the product in 91% yield (run 2). But, use of Me_3SiOTf led to lower reaction yield, because use of the relatively strong Lewis acid resulted in formation of complex mixtures (run 4). In addition, when the amount of Me_3SiCl was decreased to 0.2 equiv of the *N*,*O*-acetal, the product yield was drastically reduced (run 5). On the other hand, it was noted that the reaction was performed under reflux in CH_3CN, a catalytic amount (0.1 equiv) of Me_3SiCl-promoted the intramolecular cyclization to give the corresponding benzodiazepine derivative in good yield (run 6).[15] Because a catalytic amount of HCl was also highly effective for the cyclization, it appears that in situ generation of HCl plays a key role in catalysis of the reaction (run 7).

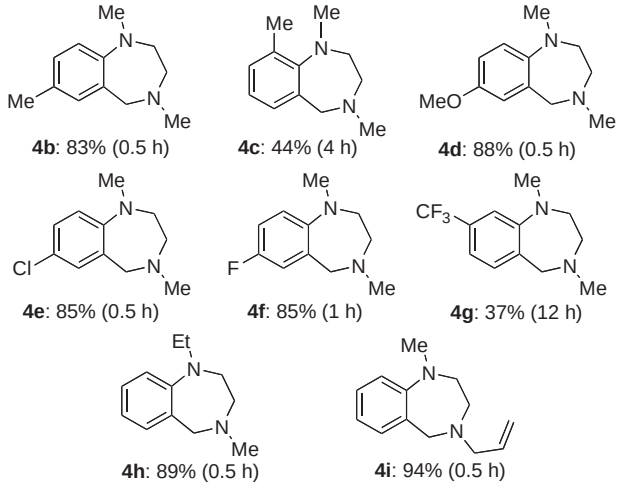
Preparation of a variety of benzodiazepine derivatives starting with a variety of *N*,*O*-acetals was then examined (Table 3). Most of the reactions that involved a substituted benzene ring, which had either an electron-donating group such as an aliphatic group or an electron-withdrawing group as a chloro group, were completed within 0.5 h, yielding the corresponding benzodiazepine derivatives **4** in good to excellent yields. The use of *N*,*O*-acetal **1c**, which has an ortho-substituted methyl group, prolonged the reaction time and reduced the reaction yield due to a steric repulsion between the methyl group and a methyl substituent (R^1=Me) on a nitrogen atom, which negatively affected the configuration of the benzene ring and the *N*,*O*-acetal moiety. Intramolecular cyclization of *N*,*O*-acetal **1g** also required a long reaction time and resulted in a low product yield. Obviously a strong electron-withdrawing group, such as a CF_3 substituent markedly reduced the nucleophilicity of the substituted position.

Similarly, when intramolecular aminomethylation of *N*,*O*-acetals **2** with an ester group was performed with 1.2 equiv of Me_3SiCl in CH_2Cl_2 at room temperature, the corresponding benzodiazepine derivatives **5** were obtained in moderate to good yields (Table 4). In general, although use of a strong acid/base or an excess amount of a Lewis acid as the catalyst resulted in hydrolysis of the ester group and a reduction in the product yield, the relatively mild Lewis acid Me_3SiCl showed no loss in product yield. In the case of a benzene ring without a substituent, the type of R^1 substituent did not affect the reactivity, and the corresponding benzodiazepine derivatives **5e** and **5f** were produced in good yields. On the other hand, the *N*,*O*-acetal **2d** with a CF_3 substituted at the *para* position gave the benzodiazepine derivative **5d** in only 23% yield along with 7% of the 6-trifluoromethylated benzodiazepine derivative **5d′**. Although there are no clear reasons for decrease of the yield, it seems to be a steric repulsion between the carbomethoxy group and the benzene ring.

Table 3
Intramolecular cyclization of *N*,*O*-acetals **1** leading to benzodiazepine derivatives **4**[a]

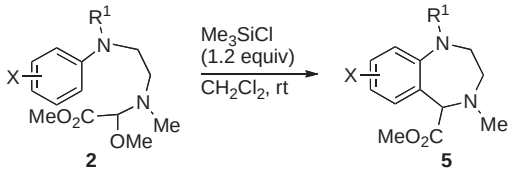


1 **4**

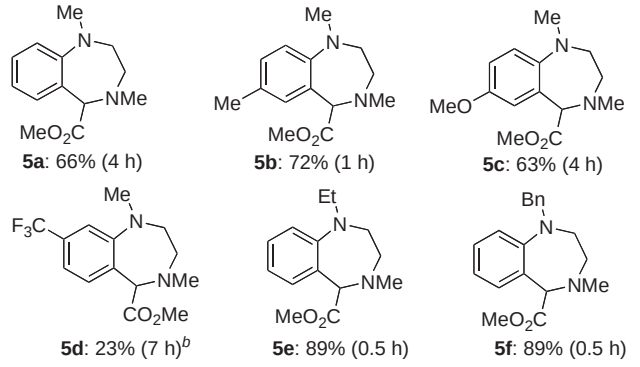


[a] Isolated yield.

Table 4
Intramolecular cyclization of *N*,*O*-acetals **2** leading to benzodiazepine derivatives **5**[a]



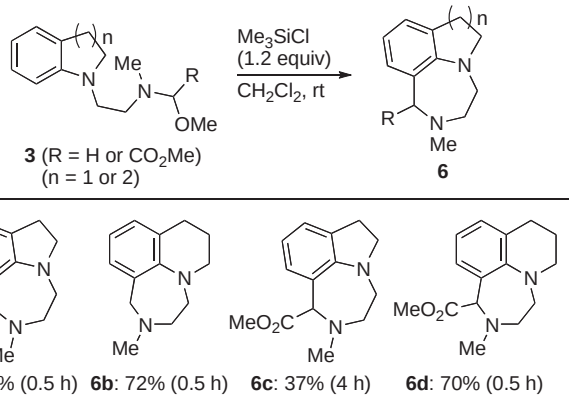
2 **5**



[b] 6-Trifluoromethylated benzodiazepine derivative **5d′** was obtained in 7% yield.
[a] Isolated yield.

Moreover, to prepare a fused benzodiazepine skeleton, intramolecular cyclization of *N*,*O*-acetals **3a**–**d**, which are bound to a nitrogen-containing heterocycle such as indoline and tetrahydroquinoline, was performed in the presence of Me_3SiCl (Table 5). With the exception of the *N*,*O*-acetal **3c**, all intramolecular cyclizations proceeded smoothly to give the corresponding tricyclic benzodiazepine derivatives **6** in good yields. For **3c**, it seemed that both steric hindrance between the benzene ring and the ester group and an unfavorable alignment of the linear *N*,*O*-acetal moiety

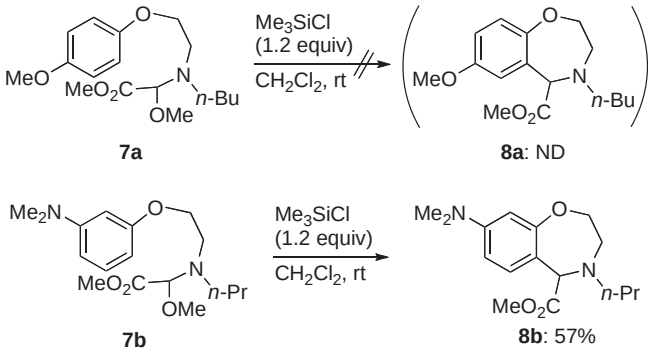
Table 5
Intramolecular cyclization of *N*,*O*-acetals **3** leading to fused benzodiazepine derivatives **6**[a]



[a] Isolated yield.

tethered to the indoline skeleton precluded the approach of the side chain needed for the intramolecular cyclization to occur.

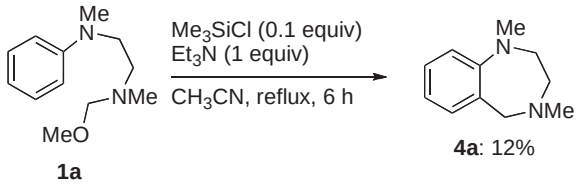
Finally, to illustrate the utility of this method, we examined the preparation of the benzoxazepine derivative **8** by Me_3SiCl-promoted intramolecular cyclization of a new type of *N*,*O*-acetal **7**, which was prepared from a phenol derivative using the three steps described above for the preparation of *N*,*O*-acetals (Scheme 4). When the reaction with the 4-methoxy-substituted *N*,*O*-acetal **7a** was conducted with Me_3SiCl, the desired cyclization gave the hydrolytic product rather than the benzoxazepine derivative **8a**. On the other hand, 3-*N*,*N*-dimethylaminomethylated *N*,*O*-acetal **7b** underwent the expected intramolecular cyclization to give 5-carbomethoxy-8-*N*,*N*-dimethylamino-4-propyl-2,3,4,5-tetrahydro-1,4-benzoxazepine (**8b**) in 57% yield. Evidently, the electron-donating effect of the dimethylamino group markedly increased nucleophilicity at the substituted position of the benzene ring.



Scheme 4. Preparation of 1,4-benzoxazepine derivative **8**.

2.3. Aspect for reaction pathway

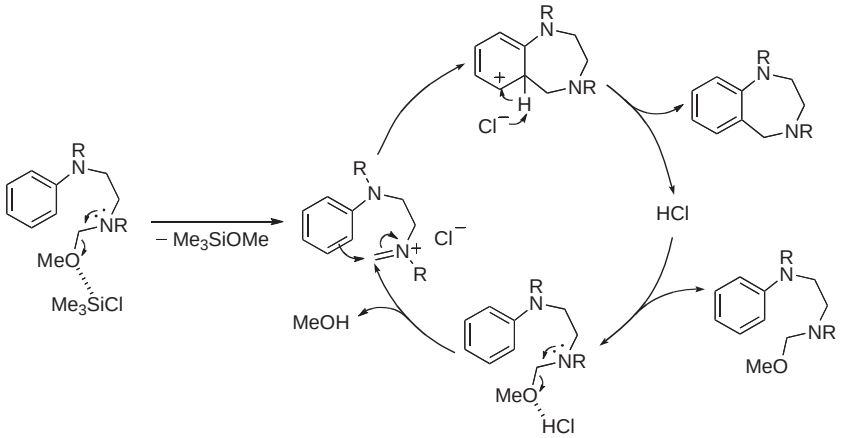
To better understand the mechanism of the cyclization reaction, a control experiment was conducted. When the reaction with *N*,*O*-acetal **1a** was carried out with 0.1 equiv of Me_3SiCl in the presence of 1 equiv of Et_3N as an acid scavenger, the benzodiazepine **4a** was obtained in only 12% yield (Scheme 5).[16] Because the product yield was nearly consistent with the addition equivalent of Me_3SiCl, it shows that in situ generated HCl functions as a catalyst to promote the intramolecular cyclization. In addition, a catalytic amount (10 mol %) of HCl promoted the cyclization (run 7 in Table 2), which strongly supports the catalytic function of HCl. A plausible mechanism for the cyclization, that is, based on these results is shown in Scheme 6.



Scheme 5. Intramolecular cyclization of *N*,*O*-acetal **1a** in the presence of a base.

3. Conclusion

In summary, we demonstrated that the Me_3SiCl-promoted intramolecular cyclization of the *N*,*O*-acetals, which were prepared via a facile three-step synthesis from *N*-alkylaniline derivatives and *N*-alkyl-2-oxazolidinones, leads to the production of pharmaceutically useful 1,4-benzodiazepine derivatives with a variety of functional groups in good yield. Use of Me_3SiCl enabled us to introduce an ester group, which was sensitive to acid conditions, onto the 1,4-benzezodiazepine framework. In addition, this method could be extended to the facile preparation of both tricyclic benzodiazepine derivatives and a benzoxazepine derivative via 7-*exo*-*trig* cyclization. Moreover, we found that when the reaction was conducted in CH_3CN under reflux, Me_3SiCl successfully catalyzed the intramolecular cyclization.



Scheme 6. Plausible mechanism for the intramolecular cyclization of *N*,*O*-acetals.

4. Experimental

4.1. General

All solvents were purified using conventional method prior to use. Column chromatography was performed using silica gel. Anilines, phenols, and 2-oxazolidinone derivatives were commercially available, and anilines were distilled prior to use. Methyl 2-bromo-2-methoxyacetate was prepared as described in our previous study.[12d] All reactions were carried out under a N_2 atmosphere, unless otherwise noted. ^{1}H NMR spectra were measured at 500 (or 300) MHz using tetramethylsilane as the internal standard. ^{13}C NMR spectra were measured at 125 (or 75) MHz using TMS or a center peak of chloroform (77.0 ppm) as an internal standard. High-resolution mass spectra were measured using NBA (3-nitrobenzylalcohol) as the matrix.

4.2. General procedure for the synthesis of *N,O*-acetals

To a reaction flask, an *N*-substituted aniline derivative (50 mmol) and an *N*-substituted 2-oxazolidinone derivative (50 mmol) were successively added and then were heated neat at 160 °C for 10 h with stirring. After completion of the reaction, the resulting solution was cooled to rt. To quench the reaction, an aqueous solution of KOH (10 mL) was added to the mixture. The organic layer was extracted with AcOEt (30 mL×3), dried over Na_2CO_3, and evaporated under reduced pressure to produce the corresponding diamine derivative as a pale brown liquid [path a]. The crude diamine (20 mmol), NaOMe (2.2 g, 40 mmol), and paraformaldehyde (30 mmol) were successively added in dried MeOH (10 mL) with MS3A, and the resulting solution was stirred at rt for 6 h. After completion of the reaction, $NaBH_4$ (1.5 g, 40 mmol) was added to the solution at 0 °C and the solution was stirred for an additional 2 h. After removal of volatile compounds, $CHCl_3$ (15 mL) was added to the crude product. The organic layer was washed with H_2O, dried over Na_2CO_3, and evaporated under reduced pressure. The crude products were distilled (Kugelrohr) to give the corresponding *N,O*-acetal **1** and **3a**,**b** [path b]. The crude diamine (10 mmol), methyl 2-bromo-2-methoxyacetate (10 mmol), and *i*Pr$_2$NEt (12 mmol) were successively added in dried THF (20 mL), and the resulting solution was stirred at rt for 1 h. After removal of volatile compounds, the crude products were distilled (Kugelrohr) to give the corresponding *N,O*-acetal **2** and **7**.

*4.2.1. N,N′-Dimethyl-N-methoxymethyl-N′-phenylethane-1,2-diamine (**1a**).* Yield 72%; yellow oil; IR (neat) 3025, 2941, 1506 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.49 (s, 3H), 2.80 (t, 2H, J=7.3 Hz), 2.94 (s, 3H), 3.28 (s, 3H), 3.45 (t, 2H, J=7.3 Hz), 4.06 (s, 2H), 6.68 (dd, 1H, J=7.5, 7.5 Hz), 6.70 (d, 2H, J=7.5 Hz), 7.21 (dd, 2H, J=7.5, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.5, 39.7, 50.7, 51.2, 55.8, 90.1, 111.9, 116.0, 129.1, 149.1; MS (FAB): *m*/*z* 209 (M^++H); HRMS (FAB): calcd for $C_{12}H_{21}N_2O$ (M^++H): 209.1654, found: 209.1676.

*4.2.2. N,N′-Dimethyl-N-methoxymethyl-N′-(4-methylphenyl)ethane-1,2-diamine (**1b**).* Yield 81%; yellow oil; IR (neat) 3032, 2962, 1510 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.48 (s, 3H), 2.79 (t, 2H, J=7.5 Hz), 2.91 (s, 3H), 3.28 (s, 3H), 3.41 (t, 2H, J=7.5 Hz), 4.06 (s, 2H), 6.64 (d, 2H, J=8.5 Hz), 7.03 (d, 2H, J=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.1, 38.6, 39.7, 50.6, 51.5, 55.8, 90.1, 112.4, 125.3, 129.6, 147.2; MS (FAB): *m*/*z* 223 (M^++H); HRMS (FAB): calcd for $C_{13}H_{21}N_2O$ (M^+−H): 221.1654, found: 221.1656.

*4.2.3. N,N′-Dimethyl-N-methoxymethyl-N′-(2-methylphenyl)ethane-1,2-diamine (**1c**).* Yield 75%; yellow oil; IR (neat) 3020, 2908, 1532 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.49 (s, 3H), 2.80 (t, 2H, J=7.5 Hz), 2.93 (s, 3H), 3.28 (s, 3H), 3.43 (t, 2H, J=7.5 Hz), 4.06 (s, 2H), 6.52 (br, 3H), 7.11 (dd, J=7.2, 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 38.5, 39.7, 50.7, 51.1, 55.8, 90.1, 109.2, 112.7, 117.0, 129.0, 138.7, 149.2; MS (FAB): *m*/*z* 223 (M^++H); HRMS (FAB): calcd for $C_{13}H_{23}N_2O$ (M^++H): 223.1810, found: 223.1829.

*4.2.4. N,N′-Dimethyl-N-methoxymethyl-N′-(4-methoxyphenyl)ethane-1,2-diamine (**1d**).* Yield 82%; yellow oil; IR (neat) 3041, 2942, 1513 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (s, 3H), 2.78 (t, 2H, J=7.5 Hz), 2.88 (s, 3H), 3.28 (s, 3H), 3.36 (t, 2H, J=7.5 Hz), 3.74 (s, 3H), 4.06 (s, 2H), 6.59 (d, 2H, J=9.0 Hz), 7.13 (d, 2H, J=9.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 39.2, 39.6, 50.7, 52.3, 55.7, 55.8, 90.1, 114.2, 114.7, 144.2, 151.5; MS (FAB): *m*/*z* 239 (M^++H); HRMS (FAB): calcd for $C_{13}H_{23}N_2O_2$ (M^++H): 239.1760, found: 239.1751.

*4.2.5. N,N′-Dimethyl-N-methoxymethyl-N′-(4-chlorophenyl)ethane-1,2-diamine (**1e**).* Yield 82%; yellow oil; IR (neat) 3046, 2942, 2819, 1504 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (s, 3H), 2.78 (t, 2H, J=7.2 Hz), 2.91 (s, 3H), 3.27 (s, 3H), 3.42 (t, 2H, J=7.2 Hz), 4.05 (s, 2H), 6.59 (d, 2H, J=9.0 Hz), 7.13 (d, 2H, J=9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.6, 39.6, 50.5, 51.2, 55.7, 90.0, 113.0, 120.7, 128.8, 147.7; MS (FAB): *m*/*z* 242 (M^++H), 240; HRMS (FAB): calcd for $C_{12}H_{18}ClN_2O$ (M^+−H): 241.1108, found: 241.1107.

*4.2.6. N,N′-Dimethyl-N-methoxymethyl-N′-(4-fluorophenyl)ethane-1,2-diamine (**1f**).* Yield 72%; yellow oil; IR (neat) 3054, 2942, 1517 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (s, 3H), 2.78 (t, 2H, J=7.5 Hz), 2.90 (s, 3H), 3.28 (s, 3H), 3.40 (t, 2H, J=7.5 Hz), 4.05 (s, 3H), 6.64 (dd, 2H, J=8.5, 2.5 Hz), 6.92 (dd, 2H, J=8.5, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.9, 39.7, 50.6, 51.9, 55.8, 90.1, 113.3 (d, J_{C-F}=7 Hz), 115.4 (d, J_{C-F}=22 Hz), 146.0, 155.1 (d, J_{C-F}=250 Hz). MS (FAB): *m*/*z* 227 (M^++H); HRMS (FAB): calcd for $C_{12}H_{18}FN_2O$ (M^+−H): 225.1403, found: 225.1403.

*4.2.7. N,N′-Dimethyl-N-methoxymethyl-N′-(3-trifluoromehylphenyl) ethane-1,2-diamine (**1g**).* Yield 74%; yellow oil: IR (neat) 3043, 2893, 1121 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (s, 3H), 2.80 (t, 2H, J=7.2 Hz), 2.98 (s, 3H), 3.28 (s, 3H), 3.48 (t, 2H, J=7.2 Hz), 4.06 (s, 2H), 6.83–6.89 (m, 3H), 7.25–7.28 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.5, 39.7, 50.6, 51.0, 55.7, 90.1, 108.0 (q, J_{C-F}=4 Hz), 112.2 (q, J_{C-F}=5 Hz), 114.7, 124.9 (q, J_{C-F}=241 Hz) 129.5, 131.4 (q, J_{C-F}=31 Hz), 149.1; MS (FAB): *m*/*z* 277 (M^++H); HRMS (FAB): calcd for $C_{13}H_{20}F_3N_2O$ (M^++H): 277.1528, found: 277.1555.

*4.2.8. N′-Ethyl-N-methoxymethyl-N-methyl-N′-phenylethane-1,2-diamine (**1h**).* Yield 60%; yellow oil; IR (neat) 3023, 2970, 1506 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, 3H, J=7.0 Hz), 2.51 (s, 3H), 2.81 (t, 2H, J=7.5 Hz), 3.30 (s, 3H), 3.37 (t, 2H, J=7.5 Hz), 3.41 (q, 2H, J=7.5 Hz), 4.08 (s, 2H), 6.64 (dd, 1H, J=8.5, 8.5 Hz), 6.68 (d, 2H, J=8.5 Hz), 7.20 (dd, 2H, J=8.5, 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.3, 39.8, 45.1, 49.0, 51.3, 55.8, 90.1, 111.7, 115.5, 129.3, 147.8; MS (FAB): *m*/*z* 223 (M^++H); HRMS (FAB): calcd for $C_{13}H_{23}N_2O$ (M^++H): 223.1810, found: 223.1814.

*4.2.9. N-Allyl-N′-ethyl-N-methoxymethyl-N′-phenylethane-1,2-diamine (**1i**).* Yield 75%; yellow oil; IR (neat) 3043, 2934 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.87 (t, 2H, J=7.5 Hz), 2.93 (s, 3H), 3.26 (s, 3H), 3.35 (d, 2H, J=6.5 Hz), 3.43 (t, 2H, J=7.5 Hz), 4.12 (s, 2H), 5.13 (d, 1H, J=10 Hz), 5.20 (d, 1H, J=16 Hz), 5.84 (ddt, J=16, 10, 6.5 Hz, 1H), 6.68 (m, 3H), 7.21 (dd, 2H, J=7.5, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 38.4, 48.2, 51.5, 55.3, 55.4, 87.4, 111.9, 115.9, 117.1, 129.1, 136.2, 149.1; MS (FAB): *m*/*z* 235 (M^++H); HRMS (FAB): calcd for $C_{14}H_{23}N_2O$ (M^++H): 235.1810, found: 235.1824.

*4.2.10. N-[Carbomethoxy(methoxy)methyl]-N,N′-dimethyl-N′-phenylethylamine (**2a**).* Yield 93%; yellow oil; IR (neat) 2950, 1745, 1599 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 2.82 (t, 2H,

J=7.2 Hz), 2.95 (s, 3H), 3.36 (s, 3H), 3.45 (td, 2H, J=7.2, 3.3 Hz), 3.72 (s, 3H), 4.30 (s, 1H), 6.66–6.70 (m, 3H), 7.21 (dd, 2H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.1, 38.5, 49.2, 51.1, 51.8, 55.7, 93.7, 111.8, 116.0, 129.1, 149.0, 168.9; MS (FAB): m/z 267 (M^++H); HRMS (FAB): calcd for $C_{14}H_{22}N_2O_3$ (M^++H): 267.1709, found: 267.1733.

*4.2.11. N-[Carbomethoxy(methoxy)methyl]-N,N′-dimethyl-N′-(4-methylphenyl)ethylamine (**2b**).* Yield 80%; yellow oil; IR (neat) 2960, 1732 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.37 (s, 3H), 2.71–2.73 (m, 2H), 2.83 (s, 3H), 3.28 (s, 3H), 3.32–3.33 (m, 2H), 3.64 (s, 3H), 4.21 (s, 1H), 6.54 (d, 2H, J=8.5 Hz), 6.94 (d, 2H, J=8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.0, 36.9, 38.6, 49.1, 51.3, 51.6, 55.6, 93.5, 112.1, 125.1, 129.5, 129.6, 146.9, 168.8; MS (FAB): m/z 281 (M^++H); HRMS (FAB): calcd for $C_{15}H_{25}N_2O_3$ (M^++H): 281.1865, found: 281.1858.

*4.2.12. N-[Carbomethoxy(methoxy)methyl]-N,N′-dimethyl-N′-(4-methoxyphenyl)ethylamine (**2c**).* Yield 94%; yellow oil; IR (neat) 2946, 1746 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.79 (t, 2H, J=7.5 Hz), 2.88 (s, 3H), 3.35 (s, 3H), 3.36–3.39 (m, 2H), 3.72 (s, 3H), 3.74 (s, 3H), 4.30 (s, 1H), 6.68 (d, 2H, J=9 Hz), 6.81 (d, 2H, J=9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.9, 38.9, 49.1, 51.5, 52.0, 55.5, 93.4, 113.8, 114.5, 143.9, 151.2, 168.8; MS (FAB): m/z 297 (M^++H); HRMS (FAB): calcd for $C_{15}H_{24}N_2O_4$ (M^+): 296.1736, found: 297.1736.

*4.2.13. N-[Carbomethoxy(methoxy)methyl]-N,N′-dimethyl-N′-(3-trifluoromethylphenyl)ethylamine (**2d**).* Yield 93%; yellow oil; IR (neat) 2964, 1733, 1132 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (s, 3H), 2.82 (t, 2H, J=7 Hz), 2.99 (s, 3H), 3.36 (s, 3H), 3.45–3.50 (m, 2H), 3.71 (s, 3H), 4.29 (s, 1H), 6.82 (d, 1H, J=8 Hz), 6.87 (s, 1H), 6.90 (d, 1H, J=8 Hz), 7.29 (dd, 1H, J=8, 8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 37.4, 38.5, 49.0, 51.0, 51.8, 55.8, 93.7, 108.0 (q, J_{C-F}=4 Hz), 112.3 (q, J_{C-F}=4 Hz), 114.6, 124.8 (q, J_{C-F}=252 Hz), 129.5, 131.0 (q, J_{C-F}=25 Hz), 149.1, 168.9; MS (FAB): m/z 335 (M^++H, 40%), 334 (M^+); HRMS (FAB): calcd for $C_{15}H_{22}F_3N_2O_2$ (M^++H): 335.1583, found: 335.1566.

*4.2.14. N-[Carbomethoxy(methoxy)methyl]-N′-ethyl-N-methyl-N′-phenylethylamine (**2e**).* Yield 95%; yellow oil; IR (neat) 2971, 1742, 750 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H, J=7.2 Hz), 2.49 (s, 3H), 2.82 (t, 2H, J=7.5 Hz), 3.36–3.41 (m, 7H, overlap), 3.75 (s, 3H), 4.32 (s, 1H), 6.64 (t, 3H, J=8.0 Hz), 6.67 (m, 3H), 7.20 (dd, 2H, J=8, 8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.2, 37.2, 45.1, 48.9, 49.8, 51.8, 55.8, 93.7, 111.6, 115.6, 129.3, 147.6, 169.0; MS (FAB): m/z 281 (M^++H, 40%), 280 (M^+); HRMS (FAB): calcd for $C_{15}H_{25}N_2O_3$: 281.1787, found: 281.1804.

*4.2.15. N′-Benzyl-N-[Carbomethoxy(methoxy)methyl]-N-methyl-N′-phenylethylamine (**2f**).* Yield 78%; yellow oil; IR (neat) 2944, 1730 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.89 (t, 2H, J=7.5 Hz), 3.37 (s, 3H), 3.54 (t, 2H, J=7.5 Hz), 3.71 (s, 3H), 4.30 (s, 1H), 4.57 (s, 2H), 6.66–6.68 (m, 3H), 7.18–7.29 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.2, 49.4, 51.8, 54.5, 55.8, 67.9, 93.7, 112.0, 116.3, 126.5, 126.7, 128.5, 129.2, 138.8, 148.3, 168.9. MS (FAB): m/z 343 (M^++H); HRMS (FAB): calcd for $C_{20}H_{25}N_2O_3$(M^+−H): 341.1865, found: 341.1879.

*4.2.16. 2-(Indolin-1-yl)-N-methoxymethyl-N-methylethylamine (**3a**).* Yield 75%; yellow oil; IR (neat) 2943, 2813, 1494 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3H), 2.87 (t, 2H, J=7.5 Hz), 2.95 (t, 2H, J=8.1 Hz), 3.20 (t, 2H, J=7.5 Hz), 3.30 (3H, s), 3.38 (t, 2H, J=8.1 Hz), 4.10 (2H, s), 6.48 (d, 1H, J=8.4 Hz), 6.62 (dd, 1H, J=8.4, 8.4 Hz), 7.05–7.03 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 39.7, 47.9, 51.5, 53.4, 55.8, 89.9, 106.8, 117.4, 124.3, 127.2, 129.8, 152.5; MS (FAB): m/z 221 (M^++H); HRMS (FAB): calcd for $C_{13}H_{20}N_2O$ (M^+): 220.1576, found: 221.1582.

*4.2.17. N-Methoxymethyl-N-methyl-2-(1,2,3,4-tetrahydroquinolin-1-yl)ethylamine (**3b**).* Yield 50%; yellow oil; IR (neat) 2951, 1510 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92 (q, 2H, J=6.3 Hz), 2.50 (s, 3H), 2.72 (t, 2H, J=6.3 Hz), 2.82 (t, 2H, J=7.5 Hz), 3.32–3.30 (m, 5H), 3.39 (t, 2H, J=7.5 Hz), 4.08 (s, 2H), 6.58–6.53 (m, 2H), 6.92 (d, 1H, J=7.8 Hz), 7.03 (dd, 1H, J=7.8, 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.2, 28.1, 39.7, 49.8, 49.9, 50.2, 55.8, 90.1, 110.2, 115.4, 122.1, 127.1, 129.1, 145.1; MS (FAB): m/z 235 (M^++H); HRMS (FAB): calcd for $C_{14}H_{21}N_2O$ (M^+−H): 233.1654, found: 233.1653.

*4.2.18. N-[Carbomethoxy(methoxy)methyl]-2-(indolin-1-yl)-N-methylethylamine (**3c**).* Yield 54%; yellow oil; IR (neat) 2952, 1734 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48 (s, 3H), 2.83–2.92 (m, 2H), 2.95 (t, 2H, J=8.5 Hz), 3.16–3.22 (m, 2H), 3.36–3.41 (m, 5H, overlap), 3.75 (s, 3H), 4.36 (s, 1H), 6.46 (d, 1H, J=7.5 Hz), 6.62 (dd, 1H, J=7.5, 7.5 Hz), 7.04 (d, 1H, J=7.5 Hz) 7.05 (dd, 2H, J=7.5, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.5, 36.9, 47.8, 49.9, 51.7, 53.3, 55.6, 93.4, 106.5, 117.2, 124.3, 127.2, 129.6, 152.3, 168.9; MS (FAB): m/z 278 (M^+), 146 (M^+−[indolinyl−CH_2CH_2−]); HRMS (FAB): calcd for $C_{15}H_{23}N_2O_3$ (M^++H): 279.1709, found: 279.1734.

*4.2.19. N-[Carbomethoxy(methoxy)methyl]-N-methyl-2-(1,2,3,4-tetrahydroquinolin-1-yl)ethylamine (**3d**).* Yield 95%; yellow oil; IR (neat) 2913, 1744 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.92 (t, 2H, J=6 Hz), 2.48 (s, 3H), 2.73 (t, 2H, J=6 Hz), 2.83 (t, 2H, J=7.5 Hz), 3.30–3.32 (m, 2H), 3.36–3.39 (m, 5H, overlap), 3.73 (s, 3H), 4.32 (s, 1H), 6.54 (d, 2H, J=7.5 Hz), 6.56 (dd, 2H, J=7.5, 7.5 Hz), 6.92 (d, 1H, J=7.5 Hz), 7.03 (d, 1H, J=7.5, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.1, 28.1, 37.1, 48.8, 49.8, 49.9, 51.8, 55.7, 93.7, 110.1, 115.4, 122.1, 127.0, 129.1, 144.9, 168.9; MS (FAB): m/z 293 (M^++H), 160 (quinolinyl−CH_2CH_2−); HRMS (FAB): calcd for $C_{11}H_{14}N$ (quinolinyl−CH_2CH_2−): 160.1126, found: 160.1141.

*4.2.20. N-Butyl-N-[Carbomethoxy(methoxy)methyl]-2-[(4-methoxy)phenoxy]ethylamine (**7a**).* Yield 98%; yellow oil; IR (neat) 2834, 1749 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, J=7.2 Hz), 1.31 (sext, 2H, J=7.2 Hz), 1.46 (qt, 2H, J=7.2 Hz), 2.73–2.79 (m, 2H), 3.04–3.15 (m, 2H), 3.38 (s, 3H), 3.75 (s, 3H), 3.76 (s, 3H), 3.95–3.98 (m, 2H), 4.47 (s, 1H), 6.82 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 20.2, 31.0, 49.1, 50.6, 51.8, 55.3, 55.7, 68.0, 92.1, 114.6, 115.3, 152.9, 153.8, 169.7; MS (FAB): m/z 326 (M^++H); HRMS (FAB): calcd for $C_{17}H_{28}NO_5$: 326.1967, found: 326.1996.

*4.2.21. N-[Carbomethoxy(methoxy)methyl]-N-propyl-2-[(3-N,N-dimethyl)phenoxy]ethylamine (**7b**).* Yield 99%; yellow oil; IR (neat) 2955, 1731 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, J=8.5 Hz), 1.52 (sext, 2H, J=8.5 Hz), 2.72–2.74 (m, 2H), 2.93 (s, 6H), 3.06–3.17 (m, 2H), 3.39 (s, 3H), 3.76 (s, 3H), 4.01–4.02 (m, 2H), 4.48 (s, 1H), 6.26–6.27 (m, 2H), 6.35 (d, 1H, J=8 Hz), 7.13 (dd, 1H, J=8, 8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.5, 22.0, 40.5, 49.2, 51.8, 52.7, 55.2, 67.2, 92.1, 99.5, 102.0, 105.7, 129.7, 151.9, 159.8, 169.7; MS (FAB): m/z 325 (M^++H); HRMS (FAB): calcd for $C_{17}H_{29}N_2O_4$ (M^++H): 325.2127, found: 325.2145. (Δ+5.5 ppm, Δ+1.8 mmu).

4.3. General procedure for synthesis of 1,4-benzodiazepine derivatives

An *N,O*-acetal (0.5 mmol) and Me_3SiCl (76 μL, 0.060 mmol) were successively mixed in dried CH_2Cl_2 (2 mL) at room temperature under a N_2 atmosphere with stirring. The mixture was stirred at room temperature until the reaction was completed, as verified by TLC (SiO_2/hexane/AcOEt=2:1). After completion of the reaction, the

organic layer was extracted with AcOEt, dried over anhydrous Na_2CO_3, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane–AcOEt) to afford the corresponding 1,4-benzodiazepine derivative.

4.3.1. 1,4-Dimethyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine[7d] (***4a***). Yield 91%; yellow oil; IR (neat) 2958, 1452 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.84 (t, 2H, J=5.0 Hz), 2.89 (s, 3H), 2.99 (t, 2H, J=5.0 Hz), 3.69 (s, 2H), 6.87 (t, 1H, J=7.5 Hz), 6.88 (d, 1H, J=7.5 Hz), 7.13 (d, 1H, J=5.5 Hz), 7.20 (t, 1H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.7, 43.8, 54.6, 58.7, 61.8, 115.4, 120.6, 127.9, 130.3, 130.8; MS (FAB): m/z 177 (M^++H).

4.3.2. 1,4,7-Trimethyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (***4b***). Yield 83%; yellow oil; IR (neat) 29,402, 1508 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.34 (s, 3H), 2.83–2.86 (m, 5H, overlap), 2.94 (t, 2H, J=4.5 Hz), 3.68 (s, 2H), 6.78 (d, 1H, J=8 Hz), 6.95 (s, 1H), 7.00 (d, 1H, J=8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.3, 42.9, 43.5, 54.5, 58.7, 61.6, 115.3, 128.3, 129.9, 130.1, 131.7, 150.2; MS (FAB): m/z 191 (M^++H); HRMS (FAB): calcd for $C_{12}H_{19}N_2$ (M^++H): 191.1548, found: 191.1550.

4.3.3. 1,4,9-Trimethyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (***4c***). Yield 44%; yellow oil; IR (neat) 2926, 1469 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.37 (s, 3H), 2.84 (br s, 5H, overlap), 3.23 (br, 2H), 3.71 (br, 2H), 6.90–6.95 (m, 2H), 7.08 (d, 1H, J=7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.3, 39.3, 43.9, 51.9, 54.6, 61.2, 123.9, 128.3, 128.8, 123.0, 135.5, 149.5; MS (FAB): m/z 191 (M^++H); HRMS (FAB): calcd for $C_{12}H_{19}N_2$ (M^++H): 191.1548, found: 191.1557.

4.3.4. 1,4-Dimethyl-7-methoxy-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (***4d***). Yield 88%; yellow oil; IR (neat) 2956, 2854 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.85 (br s, 5H, overlap), 2.91 (t, 2H, J=5 Hz), 3.69 (s, 2H), 3.77 (s, 3H), 6.75 (s, 1H), 6.76 (d, 2H, J=8 Hz), 6.83 (d, 1H, J=8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.2, 43.5, 54.6, 55.5, 58.9, 61.7, 112.4, 116.3, 116.9, 132.0, 146.3, 153.9; MS (FAB): m/z 207 (M^++H); HRMS (FAB): calcd for $C_{12}H_{19}N_2O$ (M^++H): 207.1497, found: 207.1499.

4.3.5. 7-Chloro-1,4-dimethyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (***4e***). Yield 85%; yellow oil; IR (neat) 2960, 2811 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.83 (t, 2H, J=5 Hz), 2.86 (s, 3H), 2.97 (t, 2H, J=5 Hz), 3.65 (s, 2H), 6.79 (d, 2H, J=8.5 Hz), 7.10 (d, 1H, J=2.5 Hz), 7.14 (dd, 1H, J=8.5, 2.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.8, 43.5, 54.4, 58.4, 61.3, 116.7, 125.3, 127.5, 130.4, 132.0, 151.1; MS (FAB): m/z 211 (M^++H); HRMS (FAB): calcd for $C_{11}H_{16}ClN_2$ (M^++H): 211.1002, found: 211.0979.

4.3.6. 7-Fluoro-1,4-dimethyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (***4f***). Yield 85%; yellow oil; IR (neat) 2942, 2796, 1501 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.83 (t, 2H, J=5 Hz), 2.85 (s, 3H), 2.93 (t, 2H, J=5 Hz), 3.66 (s, 2H), 6.81 (dd, 1H, J=8.5, 5.0 Hz), 6.87–6.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.1, 43.6, 54.5, 58.7, 61.3, 113.6 (d, J_{C-F}=22 Hz), 116.2 (d, J_{C-F}=8 Hz), 117.3 (d, J_{C-F}=23 Hz), 132.4, 148.8, 157.3 (d, J_{C-F}=240 Hz); MS (FAB): m/z 195 (M^++H); HRMS (FAB): calcd for $C_{11}H_{16}FN_2$ (M^++H): 195.1298, found: 195.1292.

4.3.7. 1,4-Dimethyl-8-trifluoromethyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (***4g***). Yield 37%; yellow oil; IR (neat) 2972, 1137 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.85 (t, 2H, J=5 Hz), 2.93 (s, 3H), 3.04 (t, 2H, J=5 Hz), 3.71 (s, 2H), 7.07 (s, 1H), 7.11 (d, 1H, J=8 Hz), 7.21 (d, 1H, J=8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.6, 43.8, 54.5, 58.2, 61.5, 112.1 (q, J_{C-F}=4 Hz), 117.1, 124.3 (q, J_{C-F}=272 Hz), 130.1 (q, J_{C-F}=32 Hz), 131.0, 133.8, 152.8; MS (FAB): m/z 245 (M^++H); HRMS (FAB): calcd for $C_{12}H_{16}F_3N_2$ (M^++H): 245.1266, found: (M^++H): 245.1259.

4.3.8. 1-Ethyl-4-methyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (***4h***). Yield 89%; yellow oil; IR (neat) 2932, 2843, 1492 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.20 (t, 3H, J=7 Hz), 2.36 (s, 3H), 2.78 (t, 2H, J=4.5 Hz), 3.00 (t, 2H, J=4.5 Hz), 3.21 (q, 2H, J=7 Hz), 3.68 (s, 2H), 6.84 (dd, 1H, J=7.5, 7.5 Hz), 6.90 (d, 1H, J=7.5 Hz), 7.13 (d, 1H, J=7.5 Hz), 7.18 (dd, 1H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 43.9, 47.5, 51.1, 59.2, 61.6, 116.5, 120.4, 127.8, 130.8, 130.9, 152.4; MS (FAB): m/z 191 (M^++H); HRMS (FAB): calcd for $C_{12}H_{19}N_2$ (M^++H): 191.1548, found: 191.1557.

4.3.9. 4-Allyl-1-methyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine[7d] (***4i***). Yield 94%; yellow oil; IR (neat) 2952, 1512 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.89 (s, 3H), 2.92 (t, 2H, J=4 Hz), 2.99 (t, 2H, J=4 Hz), 3.10 (d, 2H, J=6.5 Hz), 5.15–5.19 (m, 2H), 5.88–5.91 (m, 1H), 6.87 (d, 1H, J=7 Hz), 6.88 (dd, 1H, J=8, 8 Hz), 7.11 (d, 1H, J=7 Hz), 7.21 (dd, 1H, J=8, 8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.8, 54.5, 56.4, 58.1, 59.0, 115.4, 117.6, 120.6, 127.9, 130.3, 130.9, 135.9, 152.5; (FAB): m/z 203 (M^++H).

4.3.10. 5-Carbomethoxy-1,4-dimethyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (***5a***). Yield 66%; yellow oil; IR (neat) 2947, 1747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.52 (br, 1H, H-3a), 2.77 (s, 3H), 2.89 (ddd, 1H, J=12, 6, 3 Hz, H-3b), 3.00 (ddd, 1H, J=12, 6, 3 Hz, H-2a), 3.17 (dd, 1H, J=12, 3 Hz, H-2b), 3.67 (s, 3H), 4.39 (s, 1H), 6.92 (d, 1H, J=7 Hz), 6.96 (dd, 1H, J=7 Hz), 7.06 (d, 1H, J=7 Hz), 7.30 (dd, 1H, J=7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.8, 42.5, 51.8, 52.5, 52.6, 69.7, 116.9, 121.1, 127.7, 128.9, 129.6, 149.1, 173.3; MS (FAB): m/z 235 (M^++H); HRMS (FAB): calcd for $C_{13}H_{19}N_2O_2$ (M^++H): 235.1447, found: 235.1447.

4.3.11. 5-Carbomethoxy-1,4,7-trimethyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (***5b***). Yield 72%; yellow oil; IR (neat) 2946, 2854, 1740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.39 (s, 3H), 2.47 (br, 1H, H-3a), 2.74 (s, 3H), 2.81 (ddd, 1H, J=12, 6, 3 Hz, H-3b), 2.98 (ddd, 1H, J=12, 6, 3 Hz, H-2a), 3.12 (dd, 1H, J=12, 3 Hz, H-2b), 3.68 (s, 3H), 4.36 (s, 1H), 6.82 (d, 1H, J=8 Hz), 6.88 (s, 1H), 7.10 (d, 1H, J=8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 40.8, 42.5 (br), 51.8, 52.6, 69.6, 116.8, 127.8, 129.4, 130.3, 130.5, 146.7, 173.4; MS (FAB): m/z 249 (M^++H); calcd for $C_{14}H_{21}N_2O_2$ (M^++H): 249.1603, found: 249.1605.

4.3.12. 5-Carbomethoxy-1,4-dimethyl-7-methoxy-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (***5c***). Yield 63%; yellow oil; IR (neat) 2944, 1746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.47 (br, 1H, H-3a), 2.73 (s, 3H), 2.78 (ddd, 1H, J=12, 6, 3 Hz, H-3b), 3.00 (ddd, 1H, J=12, 6, 3 Hz, H-2a), 3.10 (dd, 1H, J=12, 3 Hz, H-2b), 3.69 (s, 3H), 3.78 (s, 3H), 4.36 (s, 1H), 6.68 (d, 1H, J=2.6 Hz), 6.83 (dd, 1H, J=8.7, 2.6 Hz), 6.87 (d, 1H, J=8.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.1, 42.5 (br), 51.9, 52.6, 52.7, 55.4, 69.4, 112.9, 117.7, 129.6, 142.7, 154.4, 173.1; MS (FAB): m/z 265 (M^++H); HRMS (FAB): calcd for $C_{12}H_{16}N_2O_2$ (M^++H): 265.1552, found: 265.1547.

4.3.13. 5-Carbomethoxy-1,4-dimethyl-8-trifluoromethyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (***5d***). Yield 23%; yellow oil; IR (neat) 2932, 1739, 1161 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.43 (s, 3H), 2.56 (m, 1H, H-3a), 2.95 (m, 1H, H-3b), 3.05 (m, 1H, H-2a), 3.25 (m, 1H, H-2b), 3.68 (s, 3H), 4.40 (s, 1H), 7.11 (s, 1H), 7.18–7.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) (a mixture of **5d** and **5d′**) δ 40.2, 40.8, 42.9, 45.8, 50.9, 51.9, 52.0, 52.4, 52.5, 54.1, 64.9, 69.7, 113.6, 113.6, 117.6, 117.6, 119.2, 119.3, 121.8, 123.0, 125.2, 127.4, 128.7, 130.3, 131.0, 131.7, 149.4, 149.6, 172.6, 173.2; MS (FAB): m/z 303 (M^++H); HRMS (FAB): calcd for $C_{14}H_{18}F_3N_2O_2$ (M^++H): 303.1320, found: 303.1292.

4.3.14. 5-Carbomethoxy-1,4-dimethyl-6-trifluoromethyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (***5d′***). Yield 7%; yellow oil; IR (neat)

2932, 1739, 1161 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.27 (m, 1H, H-3a), 2.50 (s, 3H), 2.70 (br s, 3H, overlapping N–Me and H-3b), 2.95 (m, 1H, overlap, H-2a), 3.49 (m, 1H, H-2b), 3.58 (s, 3H), 4.66 (s, 1H), 7.11 (m, 1H), 7.37–7.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) (a mixture of **5d** and **5d′**) δ 40.2, 40.8, 42.9, 45.8, 50.9, 51.9, 52.0, 52.4, 52.5, 54.1, 64.9, 69.7, 113.6, 113.6, 117.6, 117.6, 119.2, 119.3, 121.8, 123.0, 125.2, 127.4, 128.7, 130.3, 131.0, 131.7, 149.4, 149.6, 172.6, 173.2; MS (FAB): *m/z* 303 (M^++H); HRMS (FAB): calcd for $C_{14}H_{18}F_3N_2O_2$ (M^++H): 303.1320, found: 303.1292.

*4.3.15. 5-Carbomethoxy-1-ethyl-4-methyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (**5e**).* Yield 76%; yellow oil; IR (neat) 2945, 1743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, 3H, *J*=7 Hz), 2.41 (s, 3H), 2.45 (br, 1H, H-3a), 2.82 (ddd, 1H, *J*=12, 6, 3 Hz, H-3b), 3.00 (ddd, 1H, *J*=12, 6, 3 Hz, H-2a), 3.20 (q, 2H, *J*=7 Hz), 3.21 (m, 1H, H-2b), 3.67 (s, 3H), 4.33 (s, 1H), 6.93 (d, 1H, *J*=7.5 Hz), 6.96 (dd, 1H, *J*=7.5 Hz), 7.09 (d, 1H, *J*=7.5 Hz), 7.28 (dd, 1H, *J*=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 43.1, 46.8, 50.4, 51.8, 52.5, 69.9, 118.0, 121.2, 128.6, 128.8, 129.9, 148.4, 173.3; MS (FAB): *m/z* 249 (M^++H); HRMS (FAB): calcd for $C_{14}H_{21}N_2O_2$ (M^++H): 249.1603, found: 249.1626.

*4.3.16. 1-Benzyl-5-carbomethoxy-4-methyl-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (**5f**).* Yield 53%; yellow oil; IR (neat) 2940, 1739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.63 (br, 1H, H-2a), 2.91 (t, 2H, *J*=5 Hz, H-3), 3.07 (br, 1H, H-2b), 3.76 (s, 3H), 4.24 (d, 2H, *J*=13.7 Hz), 4.30 (d, 2H, *J*=13.7 Hz), 4.61 (s, 1H), 6.98 (dd, 1H, *J*=7.6, 7.6 Hz), 7.03 (d, 1H, *J*=7.6 Hz), 7.10 (d, 1H, *J*=7.6 Hz), 7.29–7.24 (2H, m), 7.35–7.32 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 41.7 (br), 48.9, 51.9, 53.1 (br), 57.9, 69.9 (br), 117.9, 121.6, 127.1, 128.3, 128.4, 128.8, 128.9, 130.1, 138.6, 150.3, 172.7; MS (FAB): *m/z* 311 (M^++H), 251 (M^+–CO_2Me); HRMS (FAB): calcd for $C_{19}H_{23}N_2O_2$ (M^++H): 311.1760, found: 311.1758.

*4.3.17. 4-Methyl-pyrrolo[3.2.1-jk]2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (**6a**).* Yield 76%; pale yellow oil; IR (neat) 2941, 1492 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.94 (m, 2H), 2.98 (m, 4H), 3.33 (dd, 2H, *J*=8.5 Hz), 3.68 (s, 2H), 6.69 (dd, 1H, *J*=7.5, 7.5 Hz), 6.84 (d, 1H, *J*=7.5 Hz), 7.00 (d, 1H, *J*=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.2, 44.1, 52.9, 56.4, 58.5, 62.7, 119.4, 123.0, 123.2, 127.9, 131.1, 152.3; MS (FAB): *m/z* 189 (M^++H); HRMS (FAB): calcd for $C_{12}H_{17}N_2$ (M^++H): 189.1392, found: 189.1418.

*4.3.18. 4-Methyl-piperidino[3.2.1-jk]2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (**6b**).* Yield 72%; yellow oil; IR (neat) 2934, 1475 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.79–1.87 (m, 2H), 2.35 (s, 3H), 2.75 (t, 2H, *J*=6.3 Hz), 2.83 (t, 2H, *J*=4.8 Hz), 3.06 (t, 2H, *J*=4.8 Hz), 3.21 (t, 2H, *J*=4.8 Hz), 3.65 (s, 2H), 6.73 (dd, 1H, *J*=7.5 Hz), 6.92 (d, 2H, *J*=7.5 Hz), 6.94 (d, 2H, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.6, 28.3, 43.7, 54.8, 55.0, 58.7, 61.6, 119.7, 126.8, 128.5, 128.8, 129.6, 148.2; MS(FAB): *m/z* 203 (M^++H); HRMS (FAB): calcd for $C_{13}H_{19}N_2$ (M^++H): 203.1548, found: 203.1546.

*4.3.19. 5-Carbomethoxy-4-methyl-pyrrolo[3.2.1-jk]2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (**6c**).* Yield 37%; yellow oil; IR (neat) 2928, 1739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.62 (s, 3H), 2.96–3.05 (m, 5H), 3.27 (dd, 1H, *J*=9 Hz), 3.37–3.39 (2H, m), 3.71 (s, 3H), 4.53 (s, 1H), 6.72 (dd, 1H, *J*=7.5 Hz), 6.86 (d, 1H, *J*=7.5 Hz), 7.04 (d, 1H, *J*=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.3, 42.8, 50.9, 51.9, 52.6, 56.4, 70.6, 119.2, 120.1, 123.7, 129.0, 131.9, 152.0, 171.9; MS (FAB): *m/z* 247 (M^++H), 187 (M^+–CO_2Me); HRMS (FAB): calcd for $C_{14}H_{19}N_2O_2$ (M^++H): 247.1447, found: 247.1446.

*4.3.20. 5-Carbomethoxy-4-methyl-piperidino[3.2.1-jk]2,3,4,5-tetrahydro-1H-1,4-benzodiazepine (**6d**).* Yield 70%; yellow oil; IR (neat) 2966, 1731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.75–1.82 (br, 2H), 2.41 (s, 3H), 2.56–2.66 (br, 1H), 2.76 (t, 2H, *J*=6.3 Hz), 2.99–3.00 (br, 1H), 3.08 (br s, 3H), 3.20 (m, 1H), 3.68 (s, 3H), 4.42 (s, 1H), 6.83 (dd, 1H, *J*=7 Hz), 6.88 (d, 1H, *J*=7 Hz), 7.01 (d, 1H, *J*=7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.1, 27.7, 41.9 (br), 51.6, 51.7, 52.1, 53.0, 69.4, 120.1, 126.8, 127.5, 127.8, 129.2, 145.1, 173.3; MS (FAB): *m/z* 261 (M^++H), 201 (M^+–CO_2Me); HRMS (FAB): calcd for $C_{15}H_{21}N_2O_2$ (M^++H): 261.1603, found: 261.1604.

*4.3.21. 5-Carbomethoxy-8-N,N-dimethylamino-4-propyl-2,3,4,5-tetrahydro-1,4-benzoxazepine (**8b**).* Yield 57%; pale yellow oil; IR (neat) 2955, 1735 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J*=7.3 Hz, 3H), 1.54 (q, *J*=7.3 Hz, 2H), 2.55–2.57 (m, 2H), 2.93 (s, 6H), 2.97 (s, 1H), 3.50 (dd, *J*=15.1, 9.6 Hz, 1H), 3.70 (s, 3H), 3.99 (t, *J*=9.6 Hz, 1H), 4.09 (d, *J*=15.1 Hz, 1H), 4.53 (s, 1H), 6.37–6.39 (m, 2H), 6.95 (d, *J*=8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.6, 21.1, 40.3 (br), 51.9, 52.5, 54.7, 67.8, 68.9, 104.9, 107.0, 116.7, 131.5, 151.4, 159.4, 172.2; MS (FAB): *m/z* 293 (M^++H); HRMS (FAB): calcd for $C_{16}H_{25}N_2O_3$ (M^++H): 293.1865, found: 293.1847.

Acknowledgements

This work was partially supported by a grant from the Japan Private School Promotion Foundation supported by MEXT. The authors deeply thank Dow Corning Toray Co., Ltd. for the Me_3SiCl. The authors are grateful to Mr. Kosuke Tamura and Mr. Hitoshi Nakatsuka for their experimental assistance with the spectral measurements.

Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2010.09.077.

References and notes

1. (a) Sternbach, L. H. *J. Med. Chem.* **1979**, *22*, 1 and references cited therein; (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893; (c) Hadjipavlou-Litina, D.; Garg, R.; Hansch, C. *Chem. Rev.* **2004**, *104*, 3751.
2. For selected papers, see: (a) Clement, E. C.; Carlier, P. R. *Tetrahedron Lett.* **2005**, *46*, 3633; (b) Kalinski, C.; Umkehrer, M.; Ross, G.; Kolb, J.; Burdack, C.; Hiller, W. *Tetrahedron Lett.* **2006**, *47*, 3423; (c) Deschrijver, T.; Verwilst, P.; Broos, K.; Deckmyn, H.; Dehaen, W.; De Borggraeve, W. M. *Tetrahedron* **2009**, *65*, 4521.
3. For selected papers, see: (a) Uskokovic, M.; Iacobelli, J.; Wenner, W. *J. Org. Chem.* **1962**, *27*, 3606; (b) Santilli, A. A.; Osdene, T. S. *J. Org. Chem.* **1964**, *29*, 1998; (c) Hardtmann, G. E.; Ott, H. *J. Org. Chem.* **1969**, *34*, 2244; (d) Weidner-Wells, M. A.; DeCamp, A.; Mazzocchi, P. H. *J. Org. Chem.* **1989**, *54*, 5746; (e) Boojamra, C. G.; Burow, K. M.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 5742; (f) Boojamra, C. G.; Burow, K. M.; Thompson, L. A.; Ellman, J. A. *J. Org. Chem.* **1997**, *62*, 1240; (g) Pei, Y.; Lilly, M. J.; Owen, D. J.; D'Souza, L. J.; Tang, X.-Q.; Yu, J.; Nazarbaghi, R.; Hunter, A.; Anderson, C. M.; Glasco, S.; Ede, N. J.; James, I. W.; Maitra, U.; Chandrasekaran, S.; Moos, W. H.; Ghosh, S. S. *J. Org. Chem.* **2002**, *68*, 92; (h) Kamal, A.; Ramana, A. V.; Reddy, K. S.; Ramana, K. V.; Hari Babu, A.; Prasad, B. R. *Tetrahedron Lett.* **2004**, *45*, 8187; (i) Al-awar, R. S.; Ray, J. E.; Hecker, K. A.; Joseph, S.; Huang, J.; Shih, C.; Brooks, H. B.; Spencer, C. D.; Watkins, S. A.; Schultz, R. M.; Considine, E. L.; Faul, M. M.; Sullivan, K. A.; Kolis, S. P.; Carr, M. A.; Zhang, F. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3925; (j) Marcaccini, S.; Miliciani, M.; Pepino, R. *Tetrahedron Lett.* **2005**, *46*, 711; (k) Hemming, K.; Loukou, C. *Tetrahedron* **2004**, *60*, 3349.
4. For a selected paper, see: Beccalli, E. M.; Broggini, G.; Paladino, G.; Zoni, C. *Tetrahedron* **2005**, *61*, 61.
5. For selected papers, see: (a) Sternbach, L. H.; Reeder, E. *J. Org. Chem.* **1961**, *26*, 1111; (b) Sternbach, L. H.; Reeder, E. *J. Org. Chem.* **1961**, *26*, 4936; (c) Hamann, L. G.; Ding, C. Z.; Miller, A. V.; Madsen, C. S.; Wang, P.; Stein, P. D.; Pudzianowski, A. T.; Green, D. W.; Monshizadegan, H.; Atwal, K. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1031.
6. For selected papers, see: (a) Gates, M. *J. Org. Chem.* **1980**, *45*, 1675; (b) Sherrill, R. G.; Sugg, E. E. *J. Org. Chem.* **1995**, *60*, 730; (c) Herrero, S.; Garcia-Lopez, M. T.; Cenarruzabeitia, E.; Del Rio, J.; Herranz, R. *Tetrahedron* **2003**, *59*, 4491; (d) Herrero, S.; Garcia-Lopez, M. T.; Herranz, R. *J. Org. Chem.* **2003**, *68*, 4582; (e) Wiklund, P.; Rogers-Evans, M.; Bergman, J. *J. Org. Chem.* **2004**, *69*, 6371; (f) Hussenether, T.; Hübner, H.; Gmeiner, P.; Troschütz, R. *Bioorg. Med. Chem.* **2004**, *12*, 2625; (g) Ferrini, S.; Ponticelli, F.; Taddei, M. *J. Org. Chem.* **2006**, *71*, 9217.
7. For selected papers, see: (a) Archer, S.; Lewis, T. R.; Unser, M. J.; Hoppe, J. O.; Lape, H. *J. Am. Chem. Soc.* **1957**, *79*, 5783; (b) Kraus, G. A.; Yue, S. *J. Org. Chem.* **1983**, *48*, 2936; (c) Massa, S.; Mai, A.; Artico, M.; Corelli, F.; Botta, M. *Tetrahedron* **1989**, *45*, 2763; (d) Katritzky, A. R.; Xu, Y.-J.; He, H.-Y. *J. Chem. Soc., Perkin Trans. 1*

2002, 592; (e) Cul, A.; Daich, A.; Decroix, B.; Sanz, G.; Van Hijfte, L. *Tetrahedron* **2004**, *60*, 11029.
8. For selected papers, see: (a) Welmaker, G. S.; Sabalski, J. E. *Tetrahedron Lett.* **2004**, *45*, 4851; (b) Duncton, M. A. J.; Smith, L. M.; Burdzovic-Wizeman, S.; Burns, A.; Liu, H.; Mao, Y.; Wong, W. C.; Kiselyov, A. S. *J. Org. Chem.* **2005**, *70*, 9629; (c) Che, X.; Zheng, L.; Dang, Q.; Bai, X. *Tetrahedron* **2006**, *62*, 2563.
9. For a selected paper, see: Ishikura, M.; Mori, M.; Ikeda, T.; Terashima, M.; Ban, Y. *J. Org. Chem.* **1982**, *47*, 2456.
10. For selected papers, see: (a) Hancock, M. T.; Minto, R. E.; Pinhas, A. R. *Tetrahedron Lett.* **2003**, *44*, 8357; (b) Wang, J.-Y.; Guo, X.-F.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2008**, *73*, 1979.
11. For selected papers, see: (a) Kraus, G. A.; Maeda, H. *Tetrahedron Lett.* **1994**, *35*, 9189; (b) Breslin, H. J.; Kukla, M. J.; Ludovici, D. W.; Mohrbacher, R.; Ho, W.; Miranda, M.; Rodgers, J. D.; Hitchens, T. K.; Leo, G. *J. Med. Chem.* **1995**, *38*, 771; (c) Wang, X. L.; Zheng, X. F.; Liu, R. H.; Reiner, J.; Chang, J. B. *Tetrahedron* **2007**, *63*, 3389.
12. (a) Sakai, N.; Hamajima, T.; Konakahara, T. *Tetrahedron Lett.* **2002**, *43*, 4821; (b) Sakai, N.; Hirasawa, M.; Hamajima, T.; Konakahara, T. *J. Org. Chem.* **2003**, *68*, 483; (c) Sakai, N.; Asano, J.; Shimano, Y.; Konakahara, T. *Synlett* **2007**, 2675; (d) Sakai, N.; Asano, J.; Shimano, Y.; Konakahara, T. *Tetrahedron* **2008**, *64*, 9208; (e) Sakai, N.; Sato, A.; Konakahara, T. *Synlett* **2009**, 1449; (f) Sakai, N.; Asano, J.; Kawada, Y.; Konakahara, T. *Eur. J. Org. Chem.* **2009**, 917.
13. Poindexter, G. S.; Owens, D. A.; Dolan, P. L.; Woo, E. *J. Org. Chem.* **1992**, *57*, 6257.
14. Aqueous isolation and silica gel purification of the acetals having an ester resulted in decomposition of the *N*,*O*-acetals.
15. When the intramolecular reaction of **1a** was performed with 1.2 equiv of HCl or 0.6 equiv of TMSCl, the benzodiazepine **4a** was obtained in 49 or 48% yields, respectively. The results show that a stoichiometric amount of a relatively weak Lewis acid TMSCl functions as the best promoter. In this context, one reviewer suggests NMR monitoring of interaction between *N*,*O*-acetal **1a** and TMSCl. However, we could not observe such results.
16. Theoretically, the yield of product **4a** must be identical to the equivalent of Me_3SiCl. Although there are no clear explanations, it seems that the product yield involves an error in experimental handling. However, the important point in the results is that HCl functions as a catalyst to promote the intramolecular cyclization.