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Novel rearrangement of 1*H*-2,3-benzoxazines to cyclic *N*-acyl hemiaminals: application to the synthesis of 1-arylnaphthalene skeletal congeners

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Abstract

The rearrangement of 1*H*-2,3-benzoxazine derivatives has been investigated. The reaction affords cyclic hemiaminal derivatives for their conversion to the corresponding 1-arylisobenzofurans, which can be trapped by various dienophiles to afford skeletal congeners of 1-arylnaphthalene lignans.

Keywords: 1*H*-2,3-Benzoxazine; Rearrangement; Hemiaminal; 1-Arylisobenzofuran

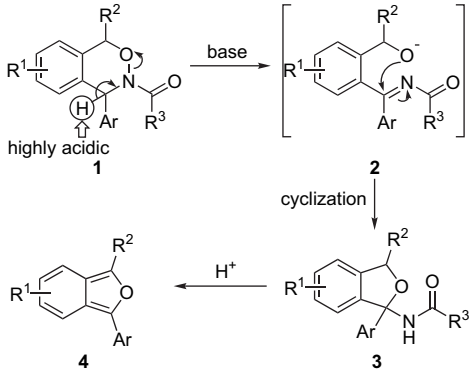
1. Introduction

Many imaginative routes have been delineated for the synthesis of 1-arylnaphthalene lignans.[1,2] The formation of C–C bond in these established routes involves Friedel–Crafts, Diels–Alder, Michael, and aldol reactions. A flexible generation of this C–C bond would aid in the synthesis of these natural targets and their evaluation as drug scaffolds.

Recently, a concise synthesis of 4-substituted 1*H*-2,3-benzoxazines through the Pictet–Spengler cyclization of hydroxamates with aldehydes has been reported by our group.[3] This strategy improved the scope of the Pictet–Spengler reaction, giving access to a new family of compounds, some of which are otherwise difficult to obtain.

2. Results and discussion

One of the purposes for preparing this new class of compounds is to execute base-promoted rearrangement shown in Scheme 1. The 4-proton of 1*H*-2,3-benzoxazine **1** is acidic and therefore may easily be abstracted in the presence of base leading to ring-opened intermediate **2** after the cleavage of N–O bond. Spontaneous cyclization to five-membered ring may give a cyclic *N*-acyl hemiaminal species **3**, which are traditionally available by lithiation of aryl bromides bearing an *ortho* hydroxymethyl group followed by reaction with benzonitrile.[4]



Scheme 1.

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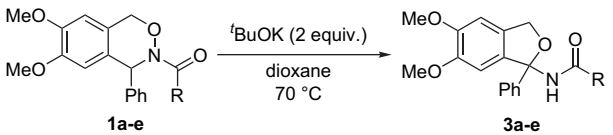
Cyclic *N*-acyl hemiaminals might be useful precursors to generate substituted isobenzofurans **4** (Scheme 1). Although isobenzofurans are unstable, they have proven to be effective for the preparation of natural products.[5,6] Motivated by these results, we report herein an efficient preparation of skeletal congeners of 1-arylnaphthalene lignans from 1*H*-2,3-benzoxazines. This method uses a novel rearrangement to cyclic *N*-acyl hemiaminal derivatives followed by acid-catalyzed elimination to 1-arylisobenzofurans, which were trapped by a Diels–Alder reaction with several dienophiles.

First, for the investigation of the rearrangement, **1a** was selected as the substrate, leading to compound **3a**. This transformation was next explored using Cs_2CO_3, KOH, DBU, NaH, and *t*-BuOK as bases and different solvent systems ($ClCH_2CH_2Cl$, PhMe, THF, dioxane, and DMSO). To our delight, the desired cyclic *N*-acyl hemiaminal **3a** was obtained when strong bases were employed. As shown in Table 1, the rearrangement of **1a** to its cyclic *N*-acyl hemiaminal **3a** was performed smoothly upon treatment with *t*-BuOK in dioxane at 70 °C for 0.5 h (Table 1, entry 1). Similar reactions were observed in the rearrangement of **1b** and **1c**, and the corresponding hemiaminals **3b** and **3c** were obtained in excellent yields (entries 2 and 3). The aroyl group on the nitrogen of benzoxazine **1** could be replaced by acetyl group without decreasing the yield of hemiaminal **3d** (entry 4).

The cyclic *N*-acyl hemiaminal was the exclusive product of the reaction after purification using silica gel. No hydrolysis to ketone or hemiketal was observed in this reaction. Hemiaminals are usually very reactive and not isolable, but like the closely related hemiacetals, are relatively stable in cyclic forms.[4] However, a complex reaction mixture resulted when **1e** was treated with *t*-BuOK at 70 °C (Table 1, entry 5). A control experiment has shown the decomposition of **3e** via heating in the presence of *t*-BuOK in dioxane.

To avoid this problem, NaH was employed to promote the reaction at room temperature. In this reaction, the polar solvent such as DMSO is efficient and the corresponding product **3e** was obtained in good yield (Table 2, entry 1). These optimized conditions were subsequently applied to the rearrangement of different benzoxazines **1**, generally furnishing very good yields of hemiaminals **3**, as shown in Table 2. Moreover, this method is compatible with a variety of R^1 and R^2 substituents differing in number, type, and position (entries 6–8).

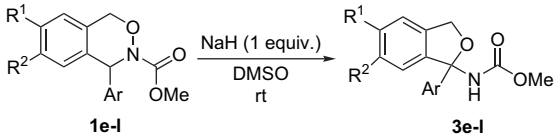
Table 1
Rearrangement of **1** to **3** in the presence of *t*-BuOK



1a-e **3a-e**

Entry	R	Time (h)	Product	Yield (%)
1	C_6H_5	1	**3a**	98
2	4-MeO–C_6H_4	1	**3b**	97
3	4-NO_2–C_6H_4	1	**3c**	97
4	Me	0.5	**3d**	98
5	OMe	2	**3e**	57

Table 2
Rearrangement of **1** to **3** in the presence of NaH



1e-l **3e-l**

Entry	R^1	R^2	Ar	Time (h)	Product	Yield (%)
1	MeO	MeO	C_6H_5	3	**3e**	75
2	MeO	MeO	2-Cl–C_6H_4	6	**3f**	85
3	MeO	MeO	4-Cl–C_6H_4	1	**3g**	85
4	MeO	MeO	4-NO_2–C_6H_4	1	**3h**	99
5	MeO	MeO	furan-2-yl	9	**3i**	80
6	MeO	MeO	3,4,5-$(MeO)_3$–C_6H_2	5	**3j**	75
7	OCH_2O		3,4,5-$(MeO)_3$–C_6H_2	2.5	**3k**	96
8	MeO	H	C_6H_5	1	**3l**	80

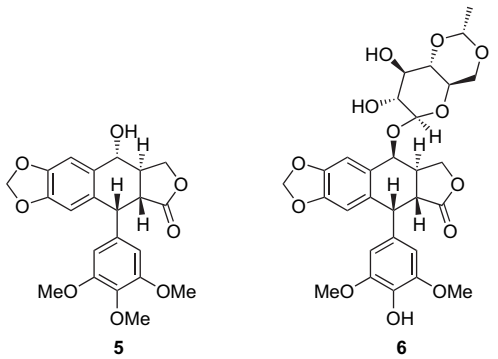
In addition, the rearrangement of 1,4-disubstituted 1*H*-2,3-benzoxazines, using the conditions in Table 2, was investigated (Scheme 2). The reactions of **1m** and **1n** provided diastereomeric mixtures of the corresponding cyclic *N*-acyl hemiaminals **3m** and **3n** in good yields and can be used for isobenzofuran generation without purification.

1m-n **3m-n**

m: R = Et, 2.0 h, 56 %
n: R = Ph, 2.0 h, 87 %

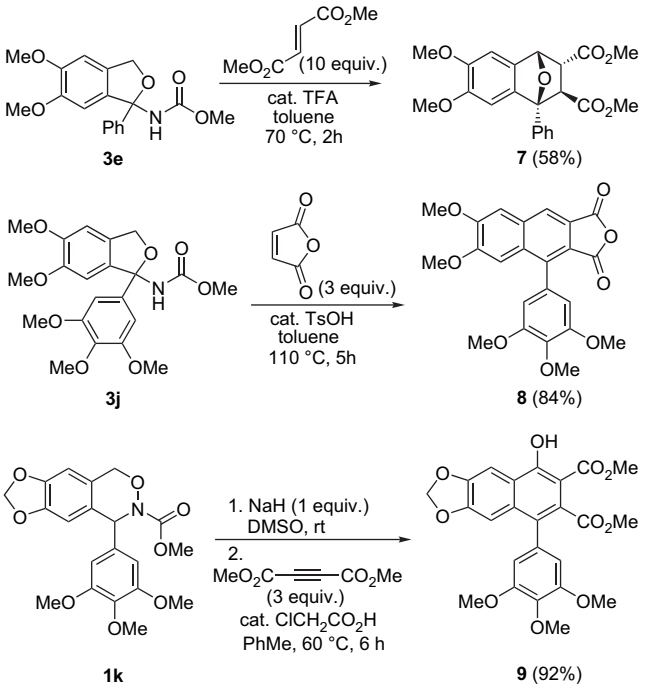
Scheme 2.

Aryl tetrahydronaphthalene lignan lactones have retained the interest of synthetic, medicinal, and biological chemists for over 50 years,[7,8] whereas the natural product podophyllotoxin **5** (Fig. 1) is a potent tubulin binding antimitotic agent for inhibiting microtubule formation and semisynthetic derivatives such as etoposide **6** are effective topoisomerase II poisons.[9] As with the synthetic derivatives, 1-arylnaphthalene lignans have potent and specific phosphodiesterase 4 inhibitory activities.[10] Not surprisingly, there has been significant activity toward the synthesis of these molecules in pursuit of preparing analogs with improved biological profiles.



5 **6**

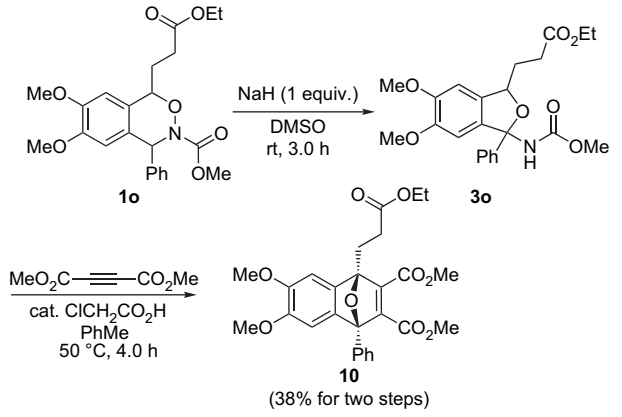
Figure 1. Selected aryl tetrahydronaphthalene lactones.



Scheme 3.

Hemiaminals can be converted into naphthalenic compounds through isobenzofuran intermediates. A mixture of **3e**, dimethyl fumarate, and catalytic amount of TFA was heated in toluene for 2 h to afford bridged compound **7** in 58% yield (Scheme 3).[11] A likely mechanism in this reaction is the formation of isobenzofuran derivative **4** (Scheme 1), followed by Diels–Alder reaction with dienophile to give the Diels–Alder adduct. Similar coupling using **3j** and maleic anhydride in the presence of TsOH afforded adduct **8** without isolation of the bridged intermediate. Indeed, the 1*H*-2,3-benzoxazines are capable of generating hemiaminals under base promotion, which in turn can react with dienophile without isolation in 'one-pot' process, such as the transformation of **1k** to **9**[12] (Scheme 3).

Moreover, compound **1o** was prepared and rearrangement was carried out with NaH at room temperature (Scheme 4). A mixture of diastereomers **3o** was detected and trapped in Diels–Alder reaction with excess of dimethyl acetylenedicarboxylate



Scheme 4.

(DMAD) and catalytic amount of $ClCH_2CO_2H$. The bridged arylnaphthalene lignan **10** was obtained in 38% yield in two steps.

3. Conclusions

In summary, a novel method of generating cyclic *N*-acyl hemiaminals from 1*H*-2,3-benzoxazine using base-mediated rearrangement has been developed. The products from this synthesis were reacted further to give 1-arylisobenzofurans and trapped in Diels–Alder reaction with different dienophiles. The features of the present method include the availability of the starting materials, the mild reaction conditions, and the simplicity of the workup. This method should be useful for the preparation of interesting molecular scaffolds as well as has potential application in the synthesis of podophyllotoxin and related structures.

4. Experimental section

4.1. General

All reactions were carried out under nitrogen. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). ^1H and ^{13}C NMR spectra were recorded on Varian Inova 500 MHz instrument or Varian Unity plus 400 MHz instrument, with chemical shifts reported in parts per million relative to the residual deuterated solvent. IR spectra were recorded on Bio-Red FTS 6000 instrument. High-resolution mass spectra (HRMS) were recorded on Q-TOF micro (water) spectrometer. All melting points are uncorrected. All reagents were used as obtained commercially.

4.2. Typical experimental procedure for the preparation of *1*[3]

To the solution of hydroxamate (0.6 mmol) in 6 mL of dry MeCN was added aldehyde (0.9 mmol) in one portion followed by NaI (1.8 mmol) and then TMSCl (1.8 mmol) was added dropwise under a N_2 atmosphere. The resulting mixture was stirred until all the hydroxamate was consumed and was treated with 6 mL of 20% $NaHSO_3$ and extracted three times with EtOAc (10 mL each time). The organic phases were collected, washed with saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was isolated by chromatography on a silica gel column to afford the desired benzoxazines.

4.2.1. Methyl 1-ethyl-6,7-dimethoxy-4-phenyl-1H-benzo[d]-[1,2]oxazine-3(4H)-carboxylate *1m*

Yield 89%, colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ=1.02 (t, J=7.0 Hz, 3H), 1.88–1.97 (m, 1H), 2.16–2.24 (m, 1H), 3.77 (s, 3H), 3.79 (s, 3H), 3.90 (s, 3H), 5.15 (dd, J=7.0, 2.5 Hz, 1H), 6.10 (s, 1H), 6.52 (s, 1H), 6.66 (s, 1H), 7.26–7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=9.02,

26.27, 53.34, 56.19, 56.29, 59.37, 80.31, 107.18, 110.65, 125.78, 127.89, 128.12, 128.55, 129.15, 140.80, 148.35, 148.71, 155.47; ESI-HRMS calcd for $C_{20}H_{23}NO_5$ $(M+Na)^+$ requires: 380.1468, found: 380.1483.

4.2.2. Methyl 6,7-dimethoxy-1,4-diphenyl-1H-benzo[d]-[1,2]oxazine-3(4H)-carboxylate **1n**

Yield 31%, white solid, mp=113–115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=3.66 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 6.10 (s, 1H), 6.24 (s, 1H), 6.25 (s, 1H), 6.59 (s, 1H), 7.32–7.51 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=53.48, 56.15, 56.24, 59.32, 83.32, 109.38, 110.21, 125.44, 128.12, 128.23, 128.72, 128.96, 129.06, 129.54, 129.68, 138.07, 140.98, 148.48, 148.70, 155.47; ESI-HRMS calcd for $C_{24}H_{23}NO_5$ $(M+Na)^+$ requires: 428.1468, found: 428.1471.

4.2.3. Methyl 1-(3-ethoxy-3-oxopropyl)-6,7-dimethoxy-4-phenyl-1H-benzo[d][1,2]oxazine-3(4H)-carboxylate **1o**

Yield 77%, colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.24 (t, J=7.0 Hz, 3H), 2.50–2.55 (m, 1H), 2.53 (m, 3H), 3.76 (s, 3H), 3.78 (s, 3H), 3.90 (s, 3H), 4.12 (q, J=7.0 Hz, 2H), 5.20 (d, J=8.0 Hz, 1H), 6.10 (s, 1H), 6.52 (s, 1H), 6.71 (s, 1H), 7.29–7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ= 14.21, 28.21, 29.28, 53.14, 55.99, 56.09, 59.15, 60.50, 78.33, 106.86, 110.46, 125.32, 127.06, 127.98, 128.40, 128.86, 140.47, 148.32, 148.56, 155.18, 173.41; ESI-HRMS calcd for $C_{23}H_{27}NO_7$ $(M+Na)^+$ requires: 452.1680, found: 452.1685.

4.3. Typical experimental procedure for the preparation of **3a–3d**

To a solution of 1*H*-2,3-benzoxazine (0.32 mmol) in dry dioxane (3 mL) was added *t*-BuOK (0.64 mmol) at room temperature under N_2 atmosphere. The resulting mixture was stirred at 70 °C for 1.0 h and then isolated by chromatography on silica gel column to afford the desired cyclic *N*-acyl hemiaminal.

4.3.1. N-(5,6-Dimethoxy-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)benzamide **3a**

Yield 98%, white solid, mp=156–158 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ=3.67 (s, 3H), 3.74 (s, 3H), 5.13, 5.22 (AB, J=12.0 Hz, 2H), 6.92 (s, 1H), 6.95 (s, 1H), 7.25–7.85 (m, 10H), 9.05 (br, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ=56.40, 56.50, 72.96, 97.63, 104.91, 107.42, 125.78, 127.89, 128.53, 128.73, 128.78, 131.54, 131.99, 134.00, 135.42, 144.73, 149.24, 150.27, 167.02; IR (KBr) 3341, 1677, 1506, 1342, 1281, 1216, 1134, 1022; ESI-HRMS calcd for $C_{23}H_{21}NO_4$ $(M+Na)^+$ requires: 398.1363, found: 398.1373.

4.3.2. N-(5,6-Dimethoxy-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-4-methoxybenzamide **3b**

Yield 97%, white solid, mp=186–188 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ=3.68 (s, 3H), 3.75 (s, 3H), 3.79 (s, 3H), 5.13, 5.22 (AB, J=11.7 Hz, 2H), 6.93–7.36 (m, 7H), 7.56 (d, J=6.9 Hz, 2H), 7.84 (d, J=8.4 Hz, 2H), 8.90 (br, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ=56.03, 56.40, 56.50, 72.90, 97.65, 104.90, 107.43, 113.91, 125.77, 127.60, 127.82, 128.74, 130.42, 131.52, 134.15, 144.92, 149.21, 150.22, 162.39, 166.41; IR (KBr) 3361, 1641, 1480, 1342, 1252, 1181, 1112, 1041; ESI-HRMS calcd for $C_{24}H_{23}NO_5$ $(M+Na)^+$ requires: 428.1468, found: 428.1468.

4.3.3. N-(5,6-Dimethoxy-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)-4-nitrobenzamide **3c**

Yield 86%, pale yellow solid, mp=102–104 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ=3.68 (s, 3H), 3.75 (s, 3H), 5.15, 5.24 (AB, J=12.0 Hz, 2H), 6.93 (s, 1H), 6.97 (s, 1H), 7.26 (t, J=7.5 Hz, 1H), 7.35 (t, J=7.5 Hz, 2H), 7.60 (d, J= 7.5 Hz, 2H), 8.07 (d, J=8.5 Hz, 2H), 8.25 (d, J=8.5 Hz, 2H), 9.48 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ=56.40, 56.52, 73.09, 97.65, 104.92, 107.34, 123.89, 125.78, 128.05, 128.85, 130.08, 131.54, 133.60, 141.14, 144.33, 149.30, 149.72, 150.37, 165.61; IR (KBr) 3340, 1683, 1522, 1344, 1283, 1214, 1113, 1027; ESI-HRMS calcd for $C_{23}H_{20}N_2O_6$ $(M+Na)^+$ requires: 443.1214, found: 443.1215.

4.3.4. N-(5,6-Dimethoxy-1-phenyl-1,3-dihydro-isobenzofuran-1-yl)acetamide **3d**

Yield 98%, white solid, mp=172–174 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ=1.99 (s, 3H), 3.68 (s, 3H), 3.74 (s, 3H), 5.08, 5.14 (AB, J=12.0 Hz, 2H), 6.81 (s, 1H), 6.90 (s, 1H), 7.24–7.50 (m, 5H), 8.68 (br, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ=24.10, 56.40, 56.46, 72.76, 96.89, 104.97, 106.86, 125.76, 127.88, 128.74, 131.26, 134.14, 144.67, 149.26, 150.14, 169.86; IR (KBr) 3350, 1699, 1503, 1341, 1268, 1216, 1127, 1024; ESI-HRMS calcd for $C_{18}H_{19}NO_4$ $(M+Na)^+$ requires: 336.1206, found: 336.1211.

4.4. Typical experimental procedure for the preparation of **3e–3n**

To a solution of 1*H*-2,3-benzoxazine (0.61 mmol) in dry DMSO (6 mL) was added NaH (0.61 mmol) at room temperature under N_2 atmosphere. After the completion of benzoxazine, the resulting mixture was poured into water, extracted with EtOAc. The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was recrystallized from Et_2O to afford the desired cyclic *N*-acyl hemiaminal.

4.4.1. (5,6-Dimethoxy-1-phenyl-1,3-dihydroisobenzofuran-1-yl)carbamic acid methyl ester **3e**

Yield 75%, white solid, mp=150–152 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ=3.44 (s, 3H), 3.67 (s, 3H), 3.73 (s, 3H), 5.10, 5.16 (AB, J=12.0 Hz, 2H), 6.77 (s, 1H), 6.88 (s, 1H), 7.23–7.55 (m, 5H), 8.14 (br, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ=51.67, 56.36, 56.45, 72.86, 97.34, 104.90, 106.60, 125.68, 127.96, 128.77, 130.92, 133.92, 144.83, 149.31, 150.18, 155.61; IR (KBr) 3351, 1750, 1730, 1503, 1340, 1251, 1106, 1025; ESI-HRMS calcd for $C_{18}H_{19}NO_5$ $(M+Na)^+$ requires: 352.1155, found: 352.1167.

*4.4.2. [1-(2-Chloro-phenyl)-5,6-dimethoxy-1,3-dihydro-isobenzofuran-1-yl]carbamic acid methyl ester **3f***

Yield 85%, white solid, mp=153–155 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ=3.44 (s, 3H), 3.65 (s, 3H), 3.73 (s, 3H), 5.08, 5.13 (AB, J=12.0 Hz, 2H), 6.90 (s, 1H), 7.06 (s, 1H), 7.25–7.30 (m, 2H), 7.38 (dd, J=7.4, 1.8 Hz, 1H), 7.64 (dd, J=7.6, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ=51.83, 56.30, 72.50, 96.91, 104.79, 106.80, 127.58, 129.35, 129.82, 130.91, 131.77, 132.06, 132.73, 140.67, 149.02, 150.57, 155.29, 155.34.

*4.4.3. [1-(4-Chloro-phenyl)-5,6-dimethoxy-1,3-dihydro-isobenzofuran-1-yl]carbamic acid methyl ester **3g***

Yield 85%, white solid, mp=112–114 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ=3.42 (s, 3H), 3.66 (s, 3H), 3.71 (s, 3H), 5.09, 5.13 (AB, J=12.0 Hz, 2H), 6.76 (s, 1H), 6.88 (s, 1H), 7.35 (d, J=8.0 Hz, 2H), 7.54 (d, J=8.0 Hz, 2H), 8.21 (br, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ=51.73, 56.36, 56.47, 72.84, 96.93, 104.94, 106.57, 127.71, 128.70, 130.89, 132.57, 133.42, 143.90, 149.46, 150.37, 155.60; IR (KBr) 3335, 1737, 1504, 1339, 1256, 1104, 1027; ESI-HRMS calcd for $C_{18}H_{18}ClNO_5$ $(M+Na)^+$ requires: 386.0766, found: 386.0771.

*4.4.4. Methyl 5,6-dimethoxy-1-(4-nitrophenyl)-1,3-dihydroisobenzofuran-1-ylcarbamate **3h***

Yield 99% (after chromatography on silica gel column), white solid, mp=163–165 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ=3.45 (s, 3H), 3.69 (s, 3H), 3.73 (s, 3H), 5.18 (s, 2H), 6.83 (s, 1H), 6.92 (s, 1H), 7.83 (dd, J=7.0, 2.0 Hz, 2H), 8.17 (d, J=7.0, 2.0 Hz, 2H), 8.43 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ=51.88, 56.39, 56.52, 72.99, 96.81, 105.06, 106.64, 124.07, 127.05, 130.96, 132.45, 147.32, 149.59, 150.67, 152.18, 155.69; IR (KBr) 3351, 1734, 1503, 1344, 1262, 1104, 1027; ESI-HRMS calcd for $C_{18}H_{18}N_2O_7$ $(M+Na)^+$ requires: 397.1006, found: 397.1011.

*4.4.5. Methyl 1-(furan-2-yl)-5,6-dimethoxy-1,3-dihydroisobenzofuran-1-ylcarbamate **3i***

Yield 80%, white solid, mp=158–160 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ=3.45 (s, 3H), 3.69 (s, 3H), 3.76 (s, 3H), 4.98, 5.09 (AB, J=12.0 Hz, 2H), 6.30–6.45 (m, 2H), 6.75 (s, 1H), 6.90 (s, 1H), 7.57 (t, J=1.5 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ=51.76, 56.37, 72.72, 93.51, 104.90, 106.11, 106.84, 110.98, 131.62, 131.69, 143.23, 149.32, 150.48, 154.76, 155.26; IR (KBr) 3349, 1734, 1507, 1340, 1285, 1216, 1104, 1003; ESI-HRMS calcd for $C_{16}H_{17}NO_6$ $(M+Na)^+$ requires: 342.0948, found: 342.0957.

*4.4.6. [5,6-Dimethoxy-1-(3,4,5-trimethoxy-phenyl)-1,3-dihydroisobenzofuran-1-yl]carbamic acid methyl ester **3j***

Yield 75%, white solid, mp=140–142 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ=3.42 (s, 3H), 3.61 (s, 3H) 3.69 (s, 3H), 3.72 (s, 3H), 3.76 (s, 6H), 5.09, 5.13 (AB, J=12.0 Hz, 2H), 6.806 (s, 1H), 6.809 (s, 1H), 6.84 (s, 1H), 6.88 (s, 1H), 8.08 (br, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ=51.64, 56.35, 56.49, 56.60, 60.57, 72.99, 97.32, 103.14, 104.82, 106.54, 130.92, 133.75, 137.44, 140.47, 149.32, 150.12, 153.25, 155.57; IR (KBr) 3365, 1739, 1504, 1338, 1235, 1127, 1027; ESI-HRMS calcd for $C_{21}H_{25}NO_8$ $(M+Na)^+$ requires: 442.1472, found: 442.1471.

*4.4.7. [5,6-Methylenedioxy-1-(3,4,5-trimethoxy-phenyl)-1,3-dihydroisobenzofuran-1-yl]carbamic acid methyl ester **3k***

Yield 96%, white solid, mp=133–135 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ=3.43 (s, 3H), 3.61 (s, 3H) 3.77 (s, 6H), 5.08 (s, 2H), 5.94 (s, 1H), 6.01 (s, 1H), 6.781 (s, 1H), 6.784 (s, 2H), 6.89 (s, 1H), 8.12 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ=51.67, 56.58, 60.57, 72.97, 97.06, 101.81, 102.08, 103.12, 103.69, 132.24, 135.28, 137.55, 140.32, 147.77, 148.42, 153.28, 155.63; IR (KBr) 3350, 1737, 1474, 1341, 1248, 1125, 1036; ESI-HRMS calcd for $C_{20}H_{21}NO_8$ $(M+Na)^+$ requires: 426.1159, found: 426.1169.

*4.4.8. Methyl 5-methoxy-1-phenyl-1,3-dihydroisobenzofuran-1-ylcarbamate **3l***

Yield 80%, white solid, mp=96–98 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ=3.42 (s, 3H), 3.71 (s, 3H), 5.10, 5.18 (AB, J=12.5 Hz, 2H), 6.76 (dd, J=8.5, 2.5 Hz, 1H), 6.84 (d, J=1.5 Hz, 1H), 7.12 (d, J=8.5 Hz, 1H), 7.23 (t, J=7.5 Hz, 1H), 7.31 (t, J=7.5 Hz, 2H), 7.51 (d, J=7.5 Hz, 2H), 8.19 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ=51.66, 56.01, 72.63, 96.82, 106.33, 114.56, 124.18, 125.65, 127.99, 128.77, 134.63, 141.13, 144.85, 155.66, 160.28; IR (KBr) 3339, 1717, 1515, 1269, 1147, 1098, 1025; ESI-HRMS calcd for $C_{17}H_{17}NO_4$ $(M+Na)^+$ requires: 322.1050, found: 322.1053.

*4.4.9. Methyl 3-ethyl-5,6-dimethoxy-1-phenyl-1,3-dihydroisobenzofuran-1-ylcarbamate **3m***

Yield 56%. A 5:1 mixture of diastereomers: minor diastereomer R_f=0.44 (40% EtOAc in petroleum ether), major diastereomer R_f=0.37; ^{1}H NMR (500 MHz, DMSO-d_6) δ=0.99 (t, J=7.5 Hz, 0.6H), 1.06 (t, J=7.5 Hz, 3H), 1.63–1.73 (m, 1H), 1.76–1.80 (m, 0.2H), 1.91–1.97 (m, 0.2H), 1.98–2.05 (m, 1H), 3.42 (s, 3H), 3.43 (s, 0.6H), 3.66 (s, 3H), 3.69 (s, 0.6H), 3.73 (s, 0.6H), 3.75 (s, 3H), 5.19 (dd, J=7.5, 4.0 Hz, 0.2H), 5.22 (dd, J=8.5, 3.5 Hz, 1H), 6.74 (s, 1H), 6.80 (s, 0.4H), 6.84 (s, 1H), 7.20 (t, J=7.0 Hz, 0.2H), 7.25 (t, J=7.0 Hz, 1H), 7.30 (t, J=7.5 Hz, 0.4H), 7.35 (t, J=7.5 Hz, 2H), 7.53 (d, J=7.0 Hz, 0.4H), 7.58 (d, J=7.0 Hz, 2H), 8.05 (s, 1H), 8.11 (s, 0.2H); IR (KBr) 3333, 1731, 1510, 1255, 1002; ESI-HRMS calcd for $C_{20}H_{23}NO_5$ $(M+Na)^+$ requires: 380.1468, found: 380.1479.

*4.4.10. Methyl 5,6-dimethoxy-1,3-diphenyl-1,3-dihydroisobenzofuran-1-ylcarbamate **3n***

Two diastereomers were separated, yield of one of which was 45% after chromatography on silica gel column, white solid, mp=78–80 °C; R_f=0.41 (40% EtOAc in petroleum ether); ^{1}H NMR (500 MHz, DMSO-d_6) δ=3.46 (s, 3H), 3.60 (s, 3H), 3.73 (s, 3H), 6.21 (s, 1H), 6.42 (s, 1H), 6.93 (s, 1H), 7.24 (tt, J=7.5, 1.5 Hz, 1H), 7.33 (tt, J=7.5, 1.5 Hz, 3H), 7.39 (tt, J=7.5, 1.5 Hz, 2H), 7.54 (dt, J=7.5, 1.5 Hz, 2H), 7.62 (dt, J=8.5, 1.5 Hz, 2H), 8.45 (s, 1H). The yield of

the other one was 42.5% after chromatography on silica gel column, white solid, mp=153–155 °C; R_f=0.31 (40% EtOAc in petroleum ether); ^{1}H NMR (500 MHz, DMSO-d_6) δ=3.44 (s, 3H), 3.64 (s, 3H), 3.70 (s, 3H), 6.27 (s, 1H), 6.47 (s, 1H), 6.84 (s, 1H), 7.20–7.48 (m, 8H), 7.50–7.62 (m, 2H), 8.23 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ=51.78, 56.40, 56.55, 85.30, 96.69, 105.47, 106.40, 125.58, 127.82, 128.30, 128.66, 128.84, 128.94, 133.37, 134.16, 142.72, 145.26, 149.87, 150.50, 155.55; IR (KBr) 3347, 1746, 1502, 1308, 1250, 1003; ESI-HRMS calcd for $C_{24}H_{23}NO_5$ $(M+Na)^+$ requires: 428.1468, found: 428.1481.

*4.5. Experimental procedure for the preparation of **10***

To a solution of **1o** in dry DMSO was added NaH (1.0 equiv) at room temperature under N_2 atmosphere. After the completion of benzoxazine, the resulting mixture was poured into water, extracted with EtOAc. The organic phase was separated, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in toluene, and DMAD (3.0 equiv) and catalytic amount of $ClCH_2CO_2H$ were added, and then the resulting mixture was stirred at 50 °C for 4 h. The bridged compound **10** was obtained as colorless oil after chromatography on silica gel column. The yield was 38% in two steps.

^{1}H NMR (500 MHz, $CDCl_3$) δ=1.25 (t, J=7.0 Hz, 3H), 2.57–2.63 (m, 1H), 2.66–2.72 (m, 1H), 2.79–2.85 (m, 1H), 2.98–3.04 (m, 1H), 3.70 (s, 3H), 3.75 (s, 3H), 3.83 (s, 3H), 3.90 (s, 3H), 4.16 (q, J=7.0 Hz, 2H), 6.99 (s, 1H), 7.01 (s, 1H), 7.42–7.49 (m, 3H), 7.61–7.64 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ=14.44, 23.68, 29.96, 52.53, 52.55, 56.76, 56.84, 60.76, 92.70, 94.21, 106.09, 108.00, 127.15, 128.99, 129.22, 133.50, 141.96, 142.25, 146.90, 147.33, 149.35, 159.02, 163.06, 165.56, 173.35.

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