Electrophilic Cyclization of *o*-Anisole- and *o*-Thioanisole-Substituted Ynamides: Synthesis of 2-Amidobenzofurans and 2-Amidobenzothiophenes

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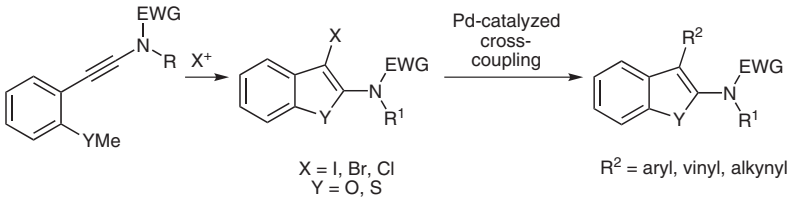
Abstract: A facile synthesis of 3-substituted 2-amidobenzofurans and 2-amidobenzothiophenes via electrophilic cyclization reaction of *o*-anisole- and *o*-thioanisole-substituted ynamides with I_2, NBS and NCS was developed. The products 3-iodo-2-amidobenzofurans were further transferred into 3-aryl-, 3-alkynyl, and 3-vinyl-2-amidobenzofurans via Pd-catalyzed reactions such as Suzuki–Miyaura and Sonogashira cross-coupling reactions and the Heck reaction.

Key words: 2-amidobenzofurans, 2-amidobenzothiophenes, electrophilic cyclization, ynamide, cross-coupling reaction

Benzofuran[1] and benzothiophene[2] are the fundamental motifs in both synthetic and naturally occurring compounds that exert a wide range of pharmacological activities. Thus, various methods have been established for the synthesis of these heterocycles, including electrophilic cyclization chemistry.[3] As their functionalized derivatives, 2-amidobenzofurans[4] and 2-amidobenzothiophenes,[5] attract considerable interest for biological and physiological effects. While several methods have been reported for the synthesis of these derivatives,[6,7] they are generally limited with respect to the availability of starting materials and the types and locations of substituents in products.

In recent years, ynamides have emerged as important synthons in modern organic synthesis.[8] The ready availability[9] and high reactivity[10] of these specially functionalized alkynes makes them ideal as starting materials for the synthesis of various heterocyclic compounds. Recently, 2-amidobenzofurans were constructed via transition metal-catalyzed reactions of ynamides by the groups of Hsung[11] and Skrydstrup,[12] respectively. Our group also developed a carbocation-induced electrophilic cyclization reaction of *o*-anisole-substituted ynamides for the synthesis of 3-alkyl- and 3-allenyl-2-amidobenzofurans.[13] In continuation of the study on electrophilic cyclization reaction of ynamides, we wish to report herein a halocyclization reaction of *o*-anisole- and *o*-thioanisole-substituted ynamides for the synthesis of 3-halogenated-2-amidobenzofurans and -benzothiophenes, which could be readily transferred into 3-aryl-, 3-vinyl, and 3-alkynyl-2-amidobenzofurans and -2-amidobenzothiophenes via Pd-catalyzed cross-coupling reactions (Scheme 1). This two-step protocol may be well complementary to our previous carbocation-induced electrophilic cyclization strategy.

The *o*-anisole- and *o*-thioanisole-substituted ynamides are readily prepared via the Cu-catalyzed cross-coupling reactions of alkynyl bromides and amides.[9c] We initially examined the reaction of *o*-anisole-substituted ynamide **1a** (0.5 mmol in 4 mL of CH_2Cl_2) with I_2 (1.5 equiv). To our delight, **1a** reacted in less than one hour at room temperature to afford 3-iodo-2-amidobenzofuran **2a** in excellent yield (Table 1, entry 1). Other common solvents such as THF, MeCN, and toluene were effective as well, although lower yields were obtained (entries 2–4). Besides I_2, ynamide **1a** reacted smoothly with the mild halogenated reagents *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) to form 3-bromo-2-amidobenzofuran **2b** (entry 6) and 3-chloro-2-amidobenzofuran **2c** (entry 8), respectively. Other electrophiles such as NIS, and $CuBr_2$ were less effective (entries 5, 7) and corresponding halocyclization with $CuCl_2$ and Selectfluor was unsuccessful (entries 9, 10).



Scheme 1 Two-step synthesis of 2-amidobenzofurans and benzothiophenes

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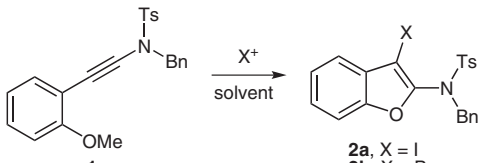
Table 1 Effect of Reaction Conditions on the Cyclization Reaction[a]



1a

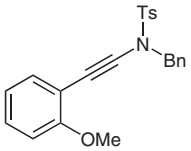
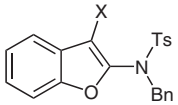
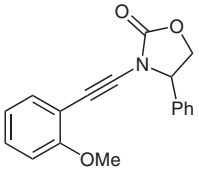
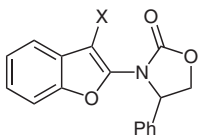
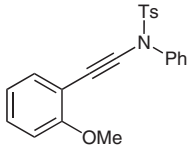
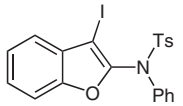
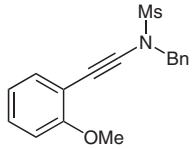
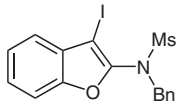
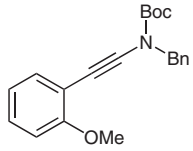
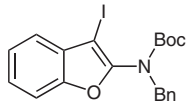
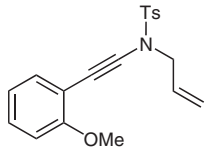
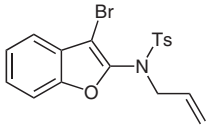
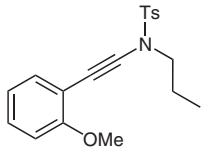
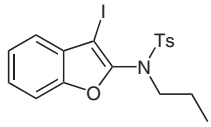
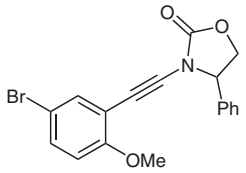
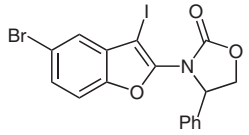
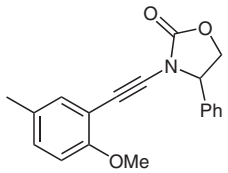
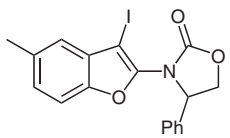
2a, X = I
2b, X = Br
2c, X = Cl

Entry	Electrophile	Solvent	Yield (%) of product
1	I_2	CH_2Cl_2	**2a**, 97
2	I_2	toluene	**2a**, 85
3	I_2	THF	**2a**, 50
4	I_2	MeCN	**2a**, 17
5	NIS	CH_2Cl_2	**2a**, 48
6	NBS	CH_2Cl_2	**2b**, 79
7	$CuBr_2$	CH_2Cl_2	**2b**, 70
8	NCS	CH_2Cl_2	**2c**, 65
9	$CuCl_2$	CH_2Cl_2	0
10	selectfluor	CH_2Cl_2	0

[a] Unless otherwise specified, the reaction was carried out using **1** (0.5 mmol) and electrophile (0.75 mmol) in CH_2Cl_2 (4 mL) at r.t.

The scope of ynamides **1** was further investigated. As shown in Table 2, the reactions were successful for sulfonamides (Table 2, entries 1, 7, 8, 10, 11), oxazolidinone (entry 4) and acyclic carbamate (entry 9), and substituent on the benzene ring did not affect the yield significantly (entries 12, 13).

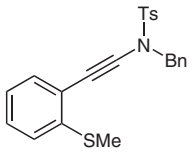
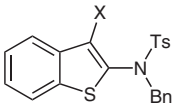
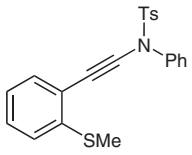
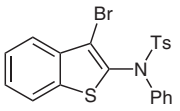
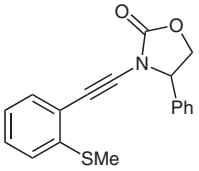
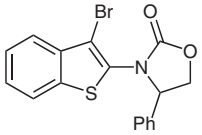
Table 2 Synthesis of 2-Amidobenzofurans **2**[a]

Entry	Ynamide	Electro-phile	Yield (%) of product
1	 **1a**	I_2	 **2a**, X = I, 97
2	**1a**	NBS	**2b**, X = Br, 79
3	**1a**	NCS	**2c**, X = Cl, 65
4	 **1b**	I_2	 **2d**, X = I, 92
5	**1b**	NBS	**2e**, X = Br, 74
6[b]	**1b**	NCS	**2f**, X =Cl, 87
7	 **1c**	I_2	 **2g**, 88
8	 **1d**	I_2	 **2h**, 77
9	 **1e**	I_2	 **2i**, 74
10	 **1f**	NBS	 **2j**, 55
11	 **1g**	I_2	 **2k**, 57
12	 **1h**	I_2	 **2l**, 77
13	 **1i**	I_2	 **2m**, 83

[a] Unless otherwise specified, the reaction was carried out using **1** (0.5 mmol) and electrophile (0.75 mmol) in CH_2Cl_2 (4 mL) at r.t.
[b] NCS used: 1.5 mmol.

This halocyclization strategy was extended to the synthesis of 2-amidobenzothiophenes. As expected, *o*-thioanisole-substituted ynamide **3a** reacted smoothly with I_2 to form 2-amido-3-iodobenzothiophene **4a** in a 90% yield (Table 3, entry 1). Bromocyclization and chlorocyclization with NBS and NCS afforded the 3-bromo-2-amidobenzothiophene **4b** (entry 2) and 3-chloro-2-amidobenzothiophene **4c** (entry 3), respectively. Besides *N*-benzylsulfonamide **3a**, *N*-phenylsulfonamide **3b** and oxazolidinone **3c** also gave 3-halo-2-amidobenzothiophenes **4d** (entry 4) and **4e** (entry 5) in good yields.

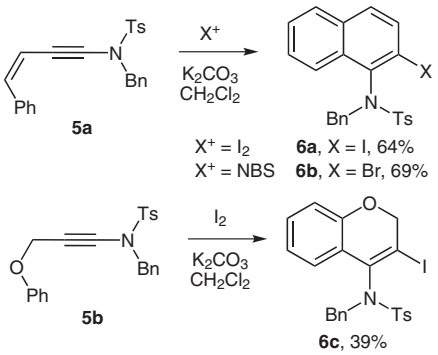
Table 3 Synthesis of 2-Amidobenzothiophenes **4**[a]

Entry	Ynamide	Electrophile	Yield (%) of product
1	 **3a**	I_2	 **4a**, X = I, 90
2	**3a**	NBS	**4b**, X = Br, 91
3	**3a**	NCS	**4c**, X = Cl, 75
4	 **3b**	NBS	 **4d**, 63
5	 **3c**	NBS	 **4e**, 88

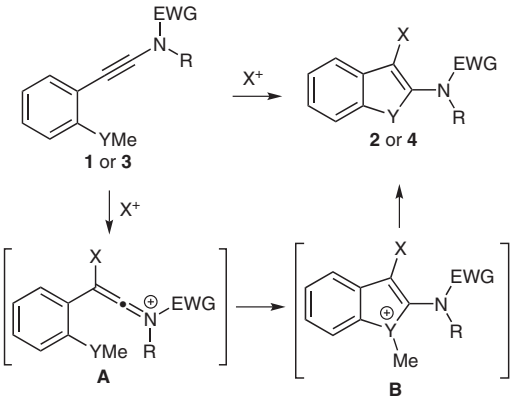
[a] Unless otherwise specified, the reaction was carried out using **3** (0.5 mmol) and electrophile (0.75 mmol) in CH_2Cl_2 (4 mL) at r.t.

This approach is not limited to the construction of heterocycles. When an aryl group acts as a nucleophile, carbocyclic system can also be obtained via the formation of a C–C bond.[14] As shown in Scheme 2, in the presence of K_2CO_3, *N*-tosylenynamine **5a** reacted with electrophiles smoothly to afford 2-halo-1-amidonaphthalenes **6a** and **6b**. 1-Amidobenzopyran **6c** could also be constructed from ynamide **5b**, although in lower yield.

A possible mechanism is given in Scheme 3. Electrophilic addition of the electrophile with *o*-anisyl/*o*-thioanisyl ynamide **1**/**3** gives the intermediate keteniminium ions **A**. Subsequent cyclization occurs to afford *O*/*S*-methylbenzofuran/benzothiophene **B**, which is demethylated by nucleophile to produce 2-amidobenzofuran/2-amidobenzothiophene **2**/**4**.



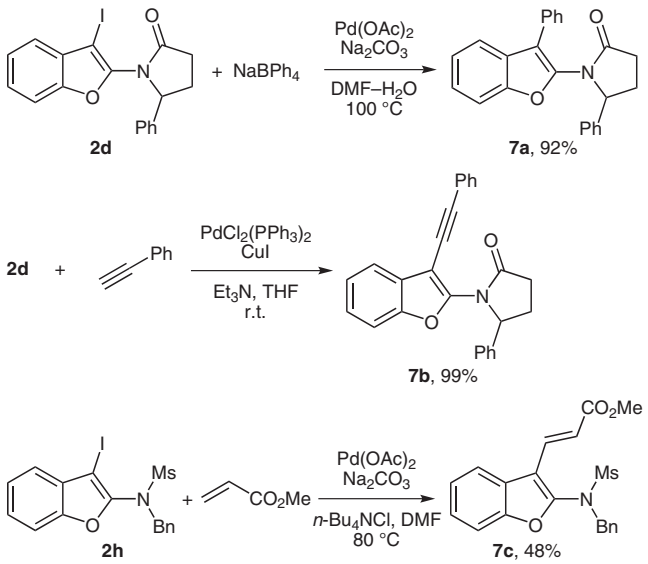
Scheme 2 Synthesis of amidonaphthalenes and amidobenzopyrans



Scheme 3 Proposed reaction mechanism

The 3-iodo-2-amidobenzofurans and -benzothiophenes obtained by this approach should be very useful for the synthesis of 3-functionalized 2-amidobenzofurans and 2-amidobenzothiophenes. For example, 3-iodo-2-amidobenzofurans **2d** and **2h** can be further transferred into 3-aryl-, 3-alkynyl-, and 3-vinyl-2-amidobenzofurans **7a**, **7b**, and **7c** via Pd-catalyzed reactions such as Suzuki–Miyaura and Sonogashira cross-coupling reactions, and the Heck reaction (Scheme 4).

In conclusion, we have described a novel synthesis of 2-amidobenzofurans and 2-amidobenzothiophenes via electrophilic cyclization reaction of *o*-anisole- and *o*-thioanisole-substituted ynamides with I_2, NBS, and NCS. 1-Amidonaphthalenes and 1-amidobenzopyrans were also constructed by this strategy from ynamides via the formation of a C–C bond. The 3-iodo-2-amidobenzofurans were further transferred into 3-aryl-, 3-alkynyl- and 3-vinyl-2-amidobenzofurans via Pd-catalyzed Suzuki–Miyaura and Sonogashira cross-coupling reactions, and the Heck reaction. This two-step strategy is well complementary to our previous synthesis of 2-amidobenzofurans via carbocation-induced electrophilic cyclization reaction.



Scheme 4 Synthesis of 3-aryl-, 3-vinyl-, and 3-alkynyl-2-amidobenzofurans

All commercially available chemicals and reagents were used without any further purification. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using TMS as the internal standard and $CDCl_3$ as the solvent. Chemical shifts were expressed in ppm and *J* values are given in Hz. High-resolution mass spectra (HRMS) were obtained using the ESI-TOF method. Flash column chromatography was carried out using 300–400 mesh silica gel.

Preparation of the ynamides was done according to Hsung's method.[9c] Characterization of unreported ynamides is listed below.

N-Benzyl-N-[2-(2-methoxyphenyl)ethynyl]methanesulfonamide (1d)
Yield: 2.924 g (81%); brown oil.

IR (neat): 3032, 2935, 2237, 1704, 1495, 1356, 1162, 756 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.58 (2 H, m), 7.25–7.42 (5 H, m), 6.84–6.91 (2 H, m), 4.72 (2 H, s), 3.83 (3 H, s), 2.95 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 134.8, 132.9, 129.5, 129.2, 128.8, 128.7, 120.5, 111.8, 110.8, 86.1, 68.1, 55.9, 55.8, 38.7.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{17}NO_3S$ + Na (M + Na)$^+$: 338.0826; found: 338.0827.

***tert*-Butyl Benzyl-[2-(2-methoxyphenyl)ethynyl]carbamate (1e)**
Yield: 5.889 g (75%); brown oil.

IR (neat): 2978, 2245, 1719, 1390, 1248, 1156, 748 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.48 (2 H, m), 7.18–7.38 (5 H, m), 6.83–6.88 (2 H, m), 4.69 (2 H, s), 3.84 (3 H, s), 1.54 (9 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 153.9, 136.6, 132.3, 128.6, 128.4, 128.3, 127.8, 120.4, 113.1, 110.7, 82.6, 55.7, 53.4, 28.1.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{23}NO_3$ + Na (M + Na)$^+$: 360.1571; found: 360.1576.

N-Benzyl-4-methyl-N-{2-[2-(methylthio)phenyl]ethynyl}benzenesulfonamide (3a)
Yield: 0.4922 g (61%); brown oil.

IR (neat): 2920, 2228, 1434, 1361, 1166, 751 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (2 H, d, *J* = 8.4 Hz), 7.00–7.40 (11 H, m), 4.63 (2 H, s), 2.43 (3 H, s), 2.41 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 140.7, 134.8, 134.5, 131.8, 129.7, 128.9, 128.5, 128.3, 128.0, 127.8, 124.5, 124.3, 121.3, 88.8, 69.1, 55.9, 21.7, 15.3.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{22}NO_2S_2$ (M + H)$^+$: 408.1086; found: 408.1091.

4-Methyl-N-{2-[2-(methylthio)phenyl]ethynyl}-N-phenylbenzenesulfonamide (3b)
Yield: 1.637 g (52%); brown oil.

IR (neat): 2921, 2233, 1593, 1490, 1370, 1169, 688 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.71 (2 H, d, *J* = 8.0 Hz), 7.24–7.42 (9 H, m), 7.04–7.15 (2 H, m), 2.45 (3 H, s), 2.42 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.0, 141.7, 138.9, 133.1, 132.4, 129.6, 129.1, 128.6, 128.4, 128.2, 126.3, 124.35, 124.32, 120.9, 88.9, 68.3, 21.7, 15.2.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{19}NO_2S_2$ + Na (M + Na)$^+$: 416.0749; found: 416.0762.

3-{2-[2-(Methylthio)phenyl]ethynyl}-4-phenyloxazolidin-2-one (3c)
Yield: 1.111 g (45%); brown oil.

IR (neat): 2920, 2246, 1765, 1395, 1193, 1062, 746 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.42 (5 H, m), 7.15–7.22 (2 H, m), 6.94–7.04 (2 H, m), 5.12 (1 H, dd, *J* = 7.2 Hz), 4.72 (1 H, dd, *J* = 7.2 Hz), 4.24 (1 H, dd, *J* = 7.2 Hz), 2.27 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.4, 141.3, 136.2, 132.1, 129.4, 129.3, 128.6, 127.2, 124.4, 124.2, 120.4, 84.4, 70.9, 70.4, 62.2, 15.1.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}NO_2S$ + Na (M + Na)$^+$: 332.0716; found: 332.0723.

(*Z*)-N-Benzyl-4-methyl-N-(4-phenylbut-3-en-1-ynyl)benzenesulfonamide (5a)
Yield: 2.224 g (63%); brown oil.

IR (neat): 3030, 2921, 2211, 1596, 1362, 1165, 720 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (2 H, d, *J* = 8.4 Hz), 7.68–7.71 (2 H, m), 7.25–7.33 (10 H, m), 6.48 (1 H, d, *J* = 12.0 Hz), 5.71 (1 H, d, *J* = 12.0 Hz), 4.60 (2 H, s), 2.42 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.8, 136.5, 135.6, 134.8, 134.5, 129.9, 128.7, 128.5, 128.4, 128.3, 128.2, 128.1, 127.6, 106.5, 89.2, 71.0, 55.7, 21.7.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{21}NO_2S$ + Na (M + Na)$^+$: 410.1185; found: 410.1190.

N-Benzyl-4-methyl-N-(3-phenoxyprop-1-ynyl)benzenesulfonamide (5b)
Yield: 4.834 g (87%); brown oil.

IR (neat): 3032, 2244, 1597, 1494, 1364, 1212, 1168 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (2 H, d, *J* = 8.0 Hz), 7.16–7.31 (9 H, m), 6.87–7.01 (3 H, m), 4.74 (2 H, s), 4.44 (2 H, s), 2.40 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 144.7, 134.4, 134.3, 129.7, 129.4, 128.7, 128.6, 128.3, 127.6, 121.2, 115.0, 80.8, 67.3, 55.9, 55.3, 21.7.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{22}NO_3S$ (M + H)$^+$: 392.1315; found: 392.1316.

2-Amidobenzofurans 2 and 2-Amidobenzothiophenes 4; N-Benzyl-N-(3-iodobenzofuran-2-yl)-4-methylbenzenesulfonamide (2a); Typical Procedure
To a solution of **1a** (0.5 mmol, 195.7 mg) in CH_2Cl_2 (4 mL) was added I_2 (0.75 mmol, 190.4 mg, 1.5 equiv). The reaction mixture was allowed to stir at r.t. After the consumption of **1a** (TLC, eluent: hexane–EtOAc, 9:1), the mixture was concentrated, and the residue

was purified by flash chromatography on silica gel (eluent: hexane–EtOAc, 9:1–6:1) to afford **2a**; yield: 246.1 mg (97%); pale solid; mp 123–125 °C.

IR (KBr): 3030, 1598, 1447, 1351, 1169, 741, 666 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.83 (2 H, d, *J* = 8.0 Hz), 7.21–7.37 (11 H, m), 4.77 (2 H, s), 2.48 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 148.0, 144.6, 135.8, 134.4, 130.5, 130.0, 129.1, 128.5, 128.3, 126.5, 123.7, 122.1, 111.5, 67.6, 54.1, 21.8.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{18}INO_3S$ + Na (M + Na)$^+$: 525.9966; found: 525.9950.

_N_-Benzyl-_N_-(3-bromobenzofuran-2-yl)-4-methylbenzenesulfonamide (2b)
Yield: 180.8 mg (79%); pale solid; mp 104–106 °C.

IR (KBr): 3035, 1613, 1448, 1358, 1167, 744, 666 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.82 (2 H, d, *J* = 8.4 Hz), 7.21–7.45 (11 H, m), 4.77 (2 H, s), 2.48 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.7, 144.7, 144.6, 135.8, 134.5, 129.9, 128.8, 128.5, 128.2, 128.1, 127.6, 126.4, 123.6, 120.3, 111.6, 97.7, 53.8, 21.7.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{18}BrNO_3S$ + Na (M + Na)$^+$: 478.0090; found: 478.0088.

_N_-Benzyl-_N_-(3-chlorobenzofuran-2-yl)-4-methylbenzenesulfonamide (2c)
Yield: 133.6 mg (65%); pale solid; mp 112–114 °C.

IR (KBr): 3064, 1450, 1358, 1168, 740, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (2 H, d, *J* = 8.4 Hz), 7.20–7.49 (11 H, m), 4.75 (2 H, s), 2.48 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.1, 144.6, 143.0, 135.8, 134.5, 129.9, 128.6, 128.5, 128.2, 128.1, 126.3, 126.1, 123.5, 119.4, 111.7, 110.7, 53.6, 21.7.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{18}ClNO_3S$ + Na (M + Na)$^+$: 434.0593; found: 434.0594.

3-(3-Iodobenzofuran-2-yl)-4-phenyloxazolidin-2-one (2d)
Yield: 185.5 mg (92%); pale solid; mp 157–159 °C.

IR (KBr): 2969, 1759, 1617, 1394, 1205, 1040, 757 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.48 (2 H, m), 7.19–7.36 (7 H, m), 5.59 (1 H, dd, *J* = 8.4 Hz), 4.87 (1 H, dd, *J* = 8.4 Hz), 4.37 (1 H, dd, *J* = 8.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 152.1, 146.0, 136.3, 130.4, 129.5, 129.2, 127.3, 126.1, 123.8, 121.5, 111.4, 71.1, 62.6, 61.4.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{12}INO_3$ + Na (M + Na)$^+$: 427.9751; found: 427.9760.

3-(3-Bromobenzofuran-2-yl)-4-phenyloxazolidin-2-one (2e)
Yield: 132.7 mg (74%); pale solid; mp 121–123 °C.

IR (KBr): 2968, 1760, 1630, 1396, 1205, 1048, 757 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.46 (9 H, m), 5.55 (1 H, dd, *J* = 8.4 Hz), 4.88 (1 H, dd, *J* = 8.4 Hz), 4.37 (1 H, dd, *J* = 8.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 151.5, 142.5, 136.3, 129.5, 129.2, 127.6, 127.1, 126.0, 123.7, 119.9, 111.5, 93.8, 71.2, 61.2.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{12}BrNO_3$ + Na (M + Na)$^+$: 379.9892; found: 379.9898.

3-(3-Chlorobenzofuran-2-yl)-4-phenyloxazolidin-2-one (2f)
Yield: 136.2 mg (87%); pale solid; mp 125–127 °C.

IR (KBr): 2919, 1775, 1641, 1395, 1210, 1053, 757 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.49 (9 H, m), 5.53 (1 H, dd, *J* = 8.4 Hz), 4.89 (1 H, dd, *J* = 8.4 Hz), 4.37 (1 H, dd, *J* = 8.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 150.9, 140.8, 136.3, 129.5, 129.2, 127.0, 126.2, 125.9, 123.6, 119.1, 111.6, 107.3, 71.2, 61.2.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{12}ClNO_3$ + Na (M + Na)$^+$: 336.0410; found: 336.0403.

_N_-(3-Iodobenzofuran-2-yl)-4-methyl-_N_-phenylbenzenesulfonamide (2g)
Yield: 216.3 mg (88%); pale solid; mp 159–161 °C.

IR (KBr): 3056, 1597, 1446, 1354, 1170, 751, 667 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.74 (13 H, m), 2.44 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.6, 148.8, 144.6, 138.5, 135.8, 130.5, 129.6, 129.4, 128.7, 128.6, 126.7, 123.8, 122.2, 111.7, 67.2, 21.8.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{16}INO_3S$ + Na (M + Na)$^+$: 511.9788; found: 511.9793.

_N_-Benzyl-_N_-(3-iodobenzofuran-2-yl)methanesulfonamide (2h)
Yield: 165.1 mg (77%); pale solid; mp 144–146 °C.

IR (KBr): 3032, 1602, 1449, 1338, 1159, 797 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.43 (9 H, m), 4.90 (2 H, s), 3.13 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 148.2, 134.6, 130.4, 129.3, 128.7, 128.5, 126.7, 123.9, 122.2, 111.6, 67.1, 54.9, 41.2.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{14}INO_3S$ + Na (M + Na)$^+$: 449.9632; found: 449.9637.

***tert*-Butyl Benzyl(3-iodobenzofuran-2-yl)carbamate (2i)**
Yield: 167.0 mg (74%); pale solid; mp 101–103 °C.

IR (KBr): 2977, 1715, 1610, 1379, 1152, 760 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.42 (9 H, m), 4.89 (2 H, s), 1.49 (9 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 151.9, 151.0, 136.9, 130.8, 128.5, 128.4, 127.7, 125.6, 123.5, 121.5, 111.4, 82.2, 62.4, 52.3, 28.3.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{20}INO_3$ + Na (M + Na)$^+$: 472.0380; found: 472.0386.

_N_-Allyl-_N_-(3-bromobenzofuran-2-yl)-4-methylbenzenesulfonamide (2j)
Yield: 111.3 mg (55%); pale solid; mp 83–85 °C.

IR (KBr): 2918, 1616, 1448, 1354, 1164, 754, 674 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.78 (2 H, d, *J* = 8.4 Hz), 7.29–7.52 (6 H, m), 5.75–5.85 (1 H, m), 5.04–5.18 (2 H, m), 4.18–4.20 (2 H, m), 2.47 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.7, 144.8, 144.5, 135.8, 131.4, 129.8, 128.1, 127.6, 126.4, 123.6, 120.3, 119.9, 111.7, 97.5, 52.8, 21.7.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{16}BrNO_3S$ + Na (M + Na)$^+$: 429.9927; found: 429.9911.

_N_-(3-Iodobenzofuran-2-yl)-4-methyl-_N_-propylbenzenesulfonamide (2k)
Yield: 128.9 mg (57%); pale solid; mp 110–112 °C.

IR (KBr): 2966, 1597, 1447, 1355, 1167, 746, 665 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.77 (2 H, d, *J* = 8.4 Hz), 7.30–7.43 (6 H, m), 3.53 (2 H, t, *J* = 8.4 Hz), 2.46 (3 H, s), 1.47–1.56 (2 H, m), 0.92 (3 H, t, *J* = 8.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 148.3, 144.3, 135.8, 130.6, 129.8, 128.2, 126.5, 123.7, 122.1, 111.5, 67.1, 52.1, 21.71, 21.70, 11.2.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{18}INO_3S$ + Na (M + Na)$^+$: 477.9958; found: 477.9950.

3-(5-Bromo-3-iodobenzofuran-2-yl)-4-phenyloxazolidin-2-one (2l)
Yield: 187.1 mg (77%); brown oil.

IR (neat): 2917, 1767, 1610, 1390, 1205, 1044, 729 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.44 (7 H, m), 7.15 (1 H, d, *J* = 8.8 Hz), 5.57 (1 H, dd, *J* = 8.8 Hz), 4.89 (1 H, dd, *J* = 8.8 Hz), 4.38 (1 H, dd, *J* = 8.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1, 150.8, 147.0, 135.9, 132.3, 129.6, 129.3, 128.9, 127.2, 124.2, 116.9, 112.9, 71.1, 61.3, 61.1.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{11}BrINO_3$ + Na $(M + Na)^+$: 505.8859; found: 505.8858.

3-(3-Iodo-5-methylbenzofuran-2-yl)-4-phenyloxazolidin-2-one (2m)
Yield: 174.0 mg (83%); brown oil.

IR (neat): 2918, 1768, 1390, 1205, 1043, 699 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.47 (2 H, m), 7.28–7.37 (3 H, m), 7.19 (1 H, d, *J* = 8.4 Hz), 7.08 (2 H, d, *J* = 8.4 Hz), 5.57 (1 H, dd, *J* = 8.4 Hz), 4.86 (1 H, dd, *J* = 8.4 Hz), 4.36 (1 H, dd, *J* = 8.4 Hz), 2.38 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.4, 150.5, 145.9, 136.2, 133.4, 130.4, 129.5, 129.2, 127.3, 127.28, 121.3, 111.0, 71.1, 62.4, 61.4, 21.3.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{14}INO_3$ + Na $(M + Na)^+$: 441.9911; found: 441.9903.

***N*-Benzyl-*N*-(3-iodobenzo[*b*]thiophen-2-yl)-4-methylbenzenesulfonamide (4a)**
Yield: 233.7 mg (90%); brown oil.

IR (neat): 2920, 1354, 1161, 1088, 812, 741 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (2 H, d, *J* = 8.0 Hz), 7.23–7.69 (11 H, m), 4.85 (2 H, s), 2.47 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.5, 140.0, 138.8, 137.9, 135.6, 134.6, 129.9, 129.5, 128.5, 128.4, 128.3, 126.7, 126.5, 125.4, 122.6, 86.4, 56.4, 21.8.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{18}INO_2S_2$ + Na $(M + Na)^+$: 541.9716; found: 541.9718.

***N*-Benzyl-*N*-(3-bromobenzo[*b*]thiophen-2-yl)-4-methylbenzenesulfonamide (4b)**
Yield: 214.0 mg (91%); brown oil.

IR (neat): 2922, 1432, 1354, 1162, 1089, 812, 748 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (2 H, d, *J* = 8.0 Hz), 7.23–7.72 (11 H, m), 4.87 (2 H, s), 2.47 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.4, 137.0, 136.4, 135.9, 135.7, 134.8, 129.9, 129.2, 128.5, 128.3, 128.2, 126.5, 125.2, 124.0, 122.6, 110.5, 55.8, 21.7.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{18}BrNO_2S_2$ + Na $(M + Na)^+$: 493.9855; found: 493.9856.

***N*-Benzyl-*N*-(3-chlorobenzo[*b*]thiophen-2-yl)-4-methylbenzenesulfonamide (4c)**
Yield: 161.5 mg (75%); pale solid; mp 155–157 °C.

IR (KBr): 2922, 1353, 1162, 1089, 935, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (2 H, d, *J* = 8.0 Hz), 7.23–7.72 (11 H, m), 4.85 (2 H, s), 2.47 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.4, 136.2, 135.7, 134.9, 134.6, 134.4, 129.8, 129.0, 128.5, 128.2, 126.4, 125.0, 122.7, 122.5, 121.6, 55.6, 21.7.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{18}ClNO_2S_2$ + Na $(M + Na)^+$: 450.0360; found: 450.0355.

***N*-(3-Bromobenzo[*b*]thiophen-2-yl)-4-methyl-*N*-phenylbenzenesulfonamide (4d)**
Yield: 139.2 mg (63%); pale solid; mp 164–166 °C.

IR (KBr): 2922, 2851, 1361, 1166, 1089, 754, 692 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.78 (4 H, m), 7.29–7.51 (9 H, m), 2.54 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 139.9, 137.2, 136.9, 135.83, 135.78, 129.6, 129.3, 128.8, 128.6, 128.3, 126.7, 125.4, 124.2, 122.6, 111.2, 21.7.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{16}BrNO_2S_2$ + Na $(M + Na)^+$: 479.9698; found: 479.9707.

3-(3-Bromobenzo[*b*]thiophen-2-yl)-4-phenyloxazolidin-2-one (4e)
Yield: 164.7 mg (88%); brown oil.

IR (neat): 2920, 1759, 1389, 1182, 1035, 751 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.72 (1 H, d, *J* = 8.0 Hz), 7.58 (1 H, d, *J* = 8.0 Hz), 7.29–7.41 (7 H, m), 5.51 (1 H, dd, *J* = 8.0 Hz), 4.89 (1 H, dd, *J* = 8.0 Hz), 4.41 (1 H, dd, *J* = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3, 136.6, 136.2, 135.9, 133.4, 129.5, 129.3, 127.4, 126.2, 125.3, 123.3, 122.5, 106.5, 70.8, 62.6.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{12}BrNO_2S$ + Na $(M + Na)^+$: 395.9664; found: 395.9663.

***N*-Benzyl-*N*-(2-iodonaphthalen-1-yl)-4-methylbenzenesulfonamide (6a); Typical Procedure**
To a solution of **5a** (0.609 mmol, 236.2 mg) in CH_2Cl_2 (4 mL) was added I_2 (0.671 mmol, 170.2 mg, 1.1 equiv) and K_2CO_3 (1.218 mmol, 169.3 mg, 2.0 equiv). The reaction mixture was allowed to stir at r.t. After the consumption of **5a** (TLC, eluent: hexane–EtOAc, 9:1), the mixture was filtered over a plug of silica gel, washed with EtOAc (50 mL), and the filtrate was concentrated. The residue was purified by flash chromatography on silica gel (eluent: hexane–EtOAc, 9:1–6:1) to afford **6a**; yield: 163.0 mg (64%); brown oil.

IR (neat): 3031, 2923, 1344, 1157, 1088, 1036, 774 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.86 (4 H, m), 7.31–7.53 (5 H, m), 7.05–7.20 (6 H, m), 5.04 (1 H, d, *J* = 14.0 Hz), 4.90 (1 H, d, *J* = 14.0 Hz), 2.47 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 138.56, 138.48, 136.5, 134.8, 134.6, 133.9, 130.6, 130.2, 129.7, 128.4, 128.1, 127.7, 126.64, 126.56, 125.5, 100.5, 54.9, 21.7.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{21}INO_2S$ $(M + H)^+$: 514.0332; found: 514.0320.

***N*-Benzyl-*N*-(2-bromonaphthalen-1-yl)-4-methylbenzenesulfonamide (6b)**
Yield: 146.6 mg (69%); brown oil.

IR (neat): 2923, 2853, 1345, 1159, 1089, 810, 775 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (2 H, d, *J* = 8.4 Hz), 7.54–7.72 (4 H, m), 7.25–7.41 (4 H, m), 7.05–7.12 (5 H, m), 5.09 (1 H, d, *J* = 14.0 Hz), 4.79 (1 H, d, *J* = 14.0 Hz), 2.47 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 138.2, 135.0, 134.9, 134.3, 133.2, 130.33, 130.29, 130.2, 129.6, 128.2, 128.1, 128.0, 127.6, 126.9, 126.4, 125.4, 123.6, 54.3, 21.7.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{20}BrNO_2S$ + K $(M + K)^+$: 504.0030; found: 504.0033.

***N*-Benzyl-*N*-(3-iodo-2*H*-chromen-4-yl)-4-methylbenzenesulfonamide (6c)**
Yield: 100.1 mg (39%); brown oil.

IR (neat): 2922, 2852, 1599, 1453, 1347, 1159, 938 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (2 H, d, *J* = 8.4 Hz), 7.34 (2 H, d, *J* = 8.4 Hz), 7.09–7.25 (6 H, m), 6.69–6.84 (3 H, m), 4.96 (1

H, d, J = 14.8 Hz), 4.84 (1 H, d, J = 14.8 Hz), 4.75 (1 H, d, J = 14.8 Hz), 4.54 (1 H, d, J = 14.8 Hz), 2.47 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2, 144.0, 138.2, 137.8, 134.6, 130.3, 130.1, 129.7, 128.3, 125.0, 121.9, 121.4, 115.9, 95.0, 75.7, 53.1, 21.7.

HRMS (ESI): m/z calcd for $C_{23}H_{20}INO_3S$ + K $(M + K)^+$: 555.9840; found: 555.9861.

4-Phenyl-3-(3-phenylbenzofuran-2-yl)oxazolidin-2-one (7a)

A vial was charged with **2d** (0.25 mmol, 101.3 mg), $NaBPh_4$ (0.0625 mmol, 21.4 mg), $Pd(OAc)_2$ (0.0125 mmol, 3.2 mg), and Na_2CO_3 (0.25 mmol, 26.5 mg). The vial was evacuated under high vacuum and backfilled with N_2. DMF–H_2O (1:0.5 mL) was added next and the solution was stirred at 100 °C. After the consumption of **2d** (TLC, eluent: hexane–EtOAc, 6:1), the mixture was filtered over a plug of silica gel and washed with EtOAc (50 mL). The filtrate was washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (eluent: hexane–EtOAc, 6:1) to afford **7a**; yield: 81.5 mg (92%); brown oil.

IR (neat): 3061, 1767, 1453, 1394, 1210, 1043, 750, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.53 (8 H, m), 7.01–7.23 (6 H, m), 5.23 (1 H, dd, J = 8.8 Hz), 4.76 (1 H, dd, J = 8.8 Hz), 4.27 (1 H, dd, J = 8.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.6, 152.2, 140.7, 135.8, 130.5, 129.1, 128.9, 128.83, 128.81, 128.0, 127.8, 127.2, 125.3, 123.1, 120.4, 117.5, 111.5, 70.8, 62.0.

HRMS (ESI): m/z calcd for $C_{23}H_{17}NO_3$ + Na $(M + Na)^+$: 378.1101; found: 378.1104.

4-Phenyl-3-[3-(2-phenylethynyl)benzofuran-2-yl]oxazolidin-2-one (7b)

A vial was charged with **2d** (0.5 mmol, 202.5 mg), $PdCl_2(PPh_3)_2$ (0.025 mmol, 17.5 mg), and CuI (0.0125 mmol, 2.4 mg). The vial was evacuated under high vacuum and backfilled with N_2. Et_3N–THF (4:4 mL) and phenylacetylene (0.75 mmol, 76.6 mg) were added next and the solution was stirred at r.t. After the consumption of **2d** (TLC, eluent: hexane–EtOAc, 6:1), the mixture was filtered over a plug of silica gel and washed with EtOAc (50 mL). The filtrate was concentrated and the residue was purified by flash chromatography on silica gel (eluent: hexane–EtOAc, 6:1) to afford **7b**; yield: 188.1 mg (99%); brown oil.

IR (neat): 3061, 1771, 1454, 1205, 1045, 749 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.63 (3 H, m), 7.23–7.47 (11 H, m), 5.74 (1 H, dd, J = 8.0 Hz), 4.90 (1 H, dd, J = 8.0 Hz), 4.37 (1 H, dd, J = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.3, 151.4, 147.2, 136.8, 131.7, 129.3, 129.2, 128.7, 128.5, 128.1, 126.8, 125.3, 123.6, 123.0, 120.3, 111.3, 97.1, 96.9, 78.0, 71.1, 61.1.

HRMS (ESI): m/z calcd for $C_{25}H_{17}NO_3$ + Na $(M + Na)^+$: 402.1101; found: 402.1109.

Methyl (*E*)-3-[2-(*N*-Benzylmethylsulfonamido)benzofuran-3-yl]acrylate (7c)

A vial was charged with **2h** (0.25 mmol, 106.8 mg), $Pd(OAc)_2$ (0.0125 mmol, 3.2 mg), Na_2CO_3 (0.25 mmol, 26.5 mg), and n-Bu_4NCl (0.25 mmol, 55.2 mg). The vial was evacuated under high vacuum and backfilled with N_2. DMF (1 mL) and methyl acrylate (0.525 mmol, 45.2 mg) were added next and the solution was stirred at 80 °C. After the consumption of **2h** (TLC, eluent: hexane–EtOAc, 6:1), the mixture was filtered over a plug of silica gel and washed with EtOAc (50 mL). The filtrate was washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography on silica gel (eluent: hexane–EtOAc, 6:1) to afford **7c**; yield: 45.9 mg (48%); pale solid; mp 154–156 °C.

IR (KBr): 2949, 1707, 1641, 1351, 1270, 1157, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (1 H, d, J = 7.6 Hz), 7.25–7.48 (9 H, m), 6.46 (1 H, d, J = 16.4 Hz), 4.86 (2 H, s), 3.79 (3 H, s), 3.11 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 152.3, 147.8, 134.2, 133.4, 129.2, 128.7, 128.6, 126.2, 125.2, 124.1, 121.3, 119.8, 114.5, 111.6, 55.1, 51.7, 40.3.

HRMS (ESI): m/z calcd for $C_{20}H_{19}NO_5S$ + Na $(M + Na)^+$: 408.0876; found: 408.0879.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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