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Cs_2CO_3 PROMOTED [3+4] ANNULATION OF SULFUR YLIDES AND ALKENYLTHIAZOLONES: SYNTHESIS OF 5,8-DIHYDROOXEPINO[2,3-*d*]THIAZOLE DERIVATIVES

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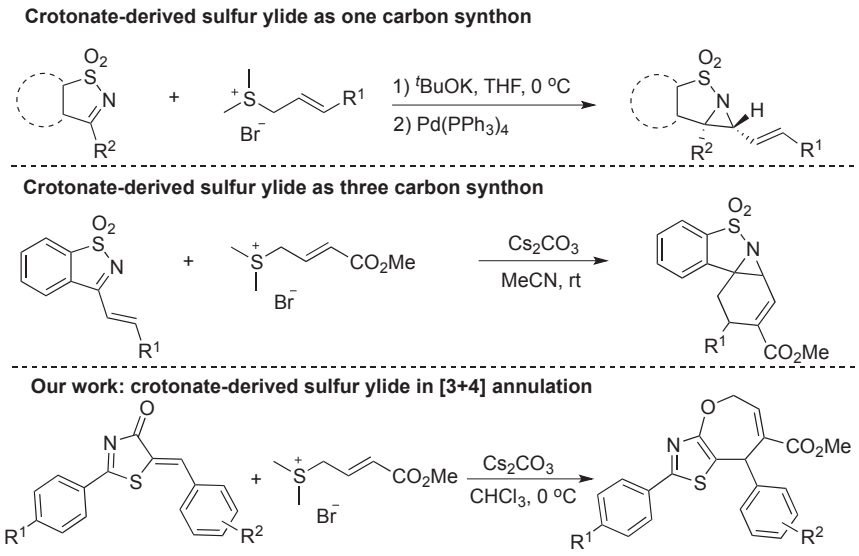
Abstract – An efficient [3+4] annulation reaction of crotonate-derived sulfur ylides and alkenylthiazolones is described. Crotonate-derived sulfur ylides act as a three-carbon synthon in this [3+4] annulation reaction, which was rarely reported before. This new methodology is particularly effective for the synthesis of 5,8-dihydrooxepino[2,3-*d*]thiazole derivatives.

Sulfur ylides have been identified as a versatile C1 synthon and are widely used in [2+1][1] and [4+1][2] annulations to build three- or five-membered rings. This includes epoxides, aziridines, cyclopropanes, indolines, pyrrolines, as well as many other useful compounds. Among these useful sulfur ylides, crotonate-derived sulfur ylides have received much attention due to their unique reaction modes. They can act as one or three carbon synthons in organic reactions (Scheme 1).[3] In addition, chemists also use crotonate-derived sulfur ylides in some domino reactions to produce complex cyclic compounds. Tang and Huang independently reported a novel sequential [3+3] and [1+2] annulation domino reaction to construct bicyclic compounds.[4] Huang and co-workers also developed an efficient domino benzannulation reaction between crotonate-derived sulfur ylides and electron-deficient conjugated dienes.[5] Zhang and co-workers reported an appealing domino approach using crotonate-derived sulfur ylides with electron-deficient enynes to generate bicycle[3.1.0]hexenes.[6] Very recently, we developed a novel [4+3] annulation between thioaurones and crotonate-derived sulfonium salt.[7]



Scheme 1. Examples of crotonate-derived sulfur ylides in domino reactions

Conversely, thiazole, a heterocyclic compound featuring both a nitrogen atom and a sulfur atom as part of the aromatic five membered ring, is a vital motif in various biologically active natural products and pharmaceuticals.[8] In order to further exploit the bioactivities of such compounds, chemists have been trying to design efficient synthetic methods for such scaffolds. Herein, we report the efficient [3+4] annulation of a crotonate-derived sulfur ylide with 5-alkenylthiazolone promoted by Cs_2CO_3.[9] To the best of our knowledge, this is the second example of crotonate-derived sulfonium salt as three carbon synthon in [3+4] annulation. Moreover, this domino reaction afford a convenient method for the synthesis of 5,8-dihydrooxepino[2,3-*d*]thiazole derivatives.

In our initial studies, 5-alkenylthiazolone **1a** and crotonate-derived sulfur ylide **2a** were selected as model substrates. The results are summarized in Table 1. **1a**, **2a** and Cs_2CO_3 were first stirred in MeCN at room temperature. The new product **3a** was obtained in 18% yield (Table 1, entry 1). After careful analysis of **3a** by ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS, a [3+4] annulation reaction occurred and a 5,8-dihydrooxepino[2,3-*d*]thiazole derivative was obtained. Confirmation of the structure of **3a** was obtained by X-ray diffraction measurements (Figure 1).[10] The novel reactivity of the crotonate-derived sulfur ylide, **2a,** promoted us to further optimize the reaction conditions. The yields were improved dramatically in DMSO, dioxane, toluene, and DMF (Table 1, entries 2-5). The yield was improved to 60% when THF was used as a solvent (Table 1, entry 6). With CH_2Cl_2 and $CHCl_3$ as a solvent, the reaction proceeded smoothly to produce **3a** in 70% and 74% yield, respectively (Table 1, entries 7-8). Therefore, $CHCl_3$ is the best choice of solvent for this reaction. Other inorganic or organic bases were then examined, most of which produced inferior yields except for NaH, for which 73% of **3a** was obtained, though still less than that produced using Cs_2CO_3 (Table 1, entries 9-15). Attempts were made

to increase Cs_2CO_3 (3.0 eq.) or decrease Cs_2CO_3 (1.5 eq.), though no better results were observed (Table 1, entries 16-17). The yield of **3a** was increased to 80% when the reaction was carried out at 0 °C (Table 1, entry 18). We also performed the reaction at -15 °C or 61 °C, though it did not exhibit any improvement (Table 1, entries 19-20). Therefore, the optimal reaction conditions are 2.0 equiv Cs_2CO_3 in $CHCl_3$ at 0 °C.

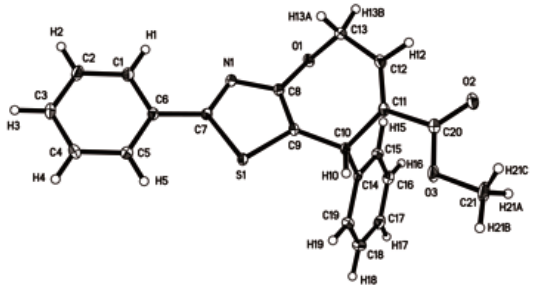
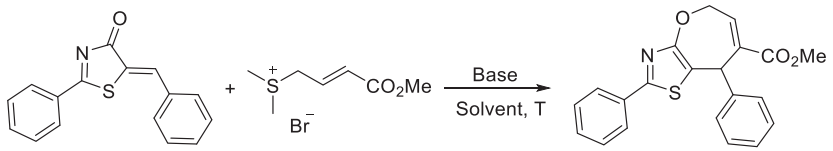


Figure 1. X-Ray crystal structure of **3a**

Table 1. Screening of the reaction conditions[a]



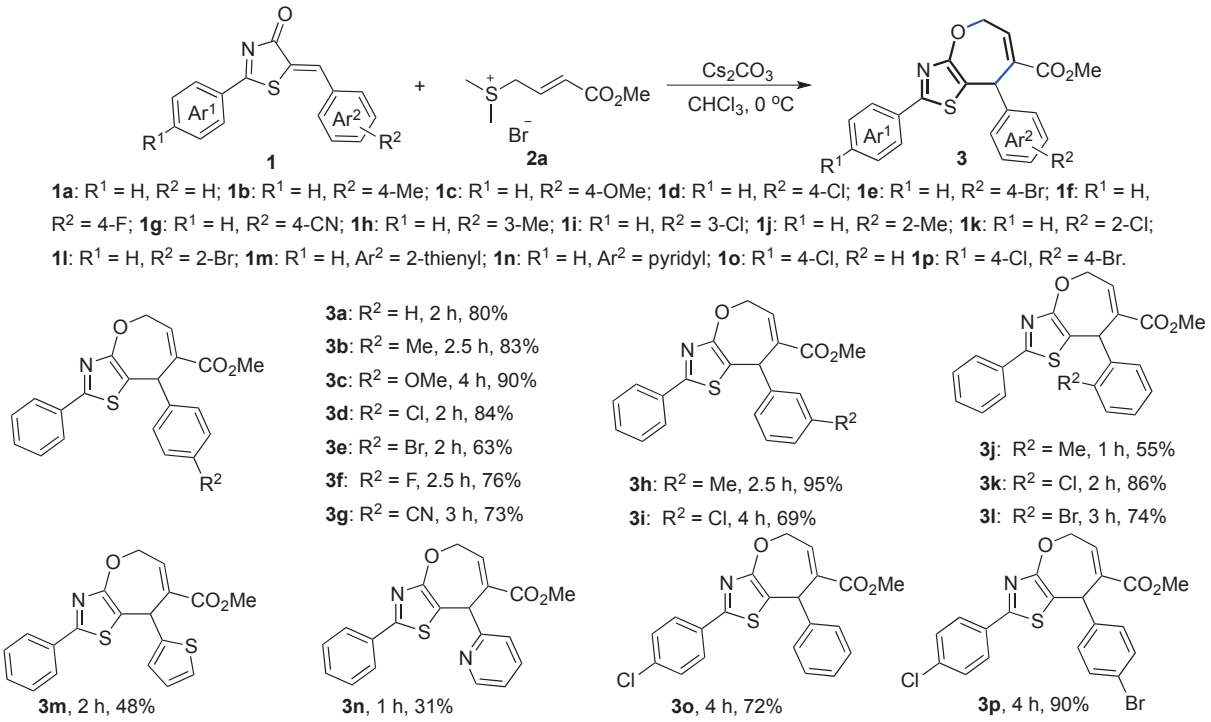
1a **2a** **3a**

Entry	Solvent	Base	Time/min	Yield[b]
1	MeCN	Cs_2CO_3	30	18
2	DMSO	Cs_2CO_3	20	18
3	dioxane	Cs_2CO_3	20	32
4	toluene	Cs_2CO_3	2 h	29
5	DMF	Cs_2CO_3	5	32
6	THF	Cs_2CO_3	20	60
7	CH_2Cl_2	Cs_2CO_3	40	70
8	$CHCl_3$	Cs_2CO_3	20	74
9	$CHCl_3$	DBU	10	34
10	$CHCl_3$	DMAP	1 h	31
11	$CHCl_3$	DABCO	1 h	31
12	$CHCl_3$	DIPEA	30	61
13	$CHCl_3$	Na_2CO_3	1.5 h	35
14	$CHCl_3$	EtONa	4 h	34
15	$CHCl_3$	NaH	10	73
16[c]	$CHCl_3$	Cs_2CO_3	50	69
17[d]	$CHCl_3$	Cs_2CO_3	40	25
18[e]	$CHCl_3$	Cs_2CO_3	2 h	80
19[f]	$CHCl_3$	Cs_2CO_3	5 h	57
20[g]	$CHCl_3$	Cs_2CO_3	1 h	0

[a]Unless otherwise noted, reactions of **1a** (0.30 mmol) and **2a** (0.45 mmol) were carried out in the presence of base (2.0 equiv) in 3 mL of solvent at room temperature. [b]Isolated yield, [c]3.0 equiv Cs_2CO_3 was used, [d]1.5 equiv Cs_2CO_3 was used, [e]Reaction temperature is 0 °C, [f]Reaction temperature is -15 °C, [g]Reflux in $CHCl_3$.

After the reaction conditions were optimized, the substrate scope with respect to substitution on the 5-alkenylthiazolone **1** was screened. As shown in Table 2, diversely substituted **1** bearing alkyl, alkoxy, halogen, cyano, and heterocycles were well tolerated. For example, Ar^2 with electron-donating or electron-withdrawing substituents at the para-position gave the desired products in good to excellent yields (**3a**-**3g**). For example, methoxy-substituted **1c** reacted with **2a** smoothly gave the desired **3c** in 90% yield. In contrast, bromo-, fuloro- cynao-substituted **1e**-**1g** only produced the corresponding products in 63-76% yields. Similarly, meta-substituted Ar^2 was tolerated well in this [3+4] domino reaction (**3h**-**3i**). The efficiency of this [3+4] domino reaction was not significantly affected by ortho-substituted substrates (**3j**-**3l**). Furthermore, 2-thienyl and 2-pyridyl-substituted substrates could give the corresponding [3+4] products in 48% and 31% yields. It was found that chloro-substituted substrates (Ar^1) were tolerable, giving the desired products **3o**, **3p** in good yields.

Table 2. Substrate scope of the [3+4] annulation reaction[a,b]

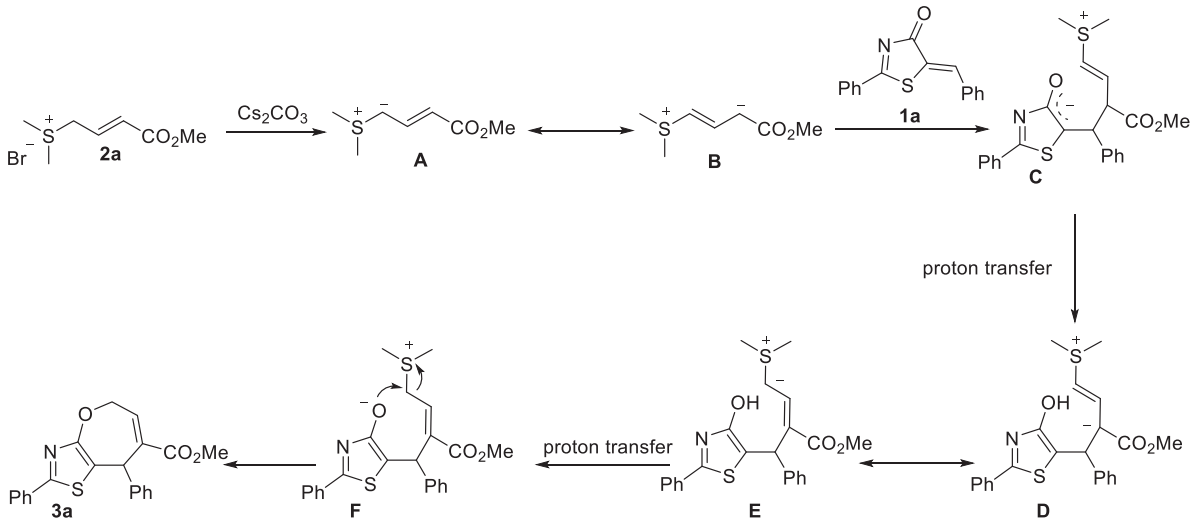


[a]Reactions of **1** (0.5 mmol) and **2** (0.75 mmol) were carried out in the presence of Cs_2CO_3 (1 mmol) in 6 mL of $CHCl_3$. [b]Isolated yields.

To test the practicality of the new methodology, a gram-scale reaction was carried out. A large scale reaction was performed using **1a** (3.8 mmol, 1.0 g) and ylide **2a**, which provided **3a** in 60% yield.

Bearing in mind our experimental results and the related literature, we proposed a possible reaction mechanism. First, the crotonate-derived sulfur ylide was transformed to intermediate **A** and **B** in the

presence of Cs_2CO_3, and then intermolecular Michael addition occurred between intermediate **B** and **1a** to generate intermediate **C**. Subsequently, two proton transfer reactions led to intermediates **D**, **E** and **F**. Finally, intramolecular nucleophilic addition and elimination of the dimethyl sulfide generated the final product, **3a** (Scheme 2).



Scheme 2. Proposed mechanism

We have successfully developed an intermolecular [3+4] annulation reaction between crotonate-derived sulfur ylides and alkenylthiazolones. In this domino reaction, crotonate-derived sulfur ylides act as a three carbon synthon. Furthermore, a series of 5,8-dihydrooxepino[2,3-*d*]thiazole derivatives was synthesized. Our future efforts will focus on an asymmetric version of this domino reaction and apply this new methodology to the construction of natural products.

SUPPORTING INFORMATION

Supplementary data (copies of NMR spectra for all products) associated with this article can be found in the online version.

EXPERIMENTAL

General information

All reactions were performed under Ar atmospheres in oven-dried glassware with magnetic stirring. Unless otherwise stated, all reagents were purchased from commercial suppliers (Aldrich, TCI or Alfa Aesar) and used without further purification. All solvents were purified and dried according to standard methods prior to use. TLC monitored all reactions with silica gel-coated plates. Flash column chromatography was performed using 200-300 mesh silica gel. ^{1}H- and ^{13}C-NMR spectra were recorded at ambient temperature on Bruker 400 instruments. All spectra were referenced to $CDCl_3$ (^{1}H δ 7.26 ppm

and ^{13}C-NMR δ 77.00 ppm). HRMS were obtained on Waters Xevo Q-TOF MS with ESI resource. Melting points were measured on a RY-I apparatus and are reported uncorrected.

General procedure for the synthesis of 3

To a stirred solution of **1** (0.50 mmol) in $CHCl_3$ (6 mL), **2a** (180.8 mg, 0.75 mmol) and Cs_2CO_3 (325.8 mg, 1 mmol) were added under argon atmosphere, and the reaction mixture was stirred for 1-4 h at 0 ºC. After the reaction complete (monitored by TLC), the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL), extracted with CH_2Cl_2 (10 mL×3). The organic phase was combined and dried with Na_2SO_4. The solvent was evaporated and the residue was purified by silica-gel column chromatography (AcOEt : petroleum ether = 1 : 5) to give **3** as white solid.

Methyl 2,8-diphenyl-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3a): 3a was obtained according to the general procedure in 80% yield (145.4 mg), white solid; mp 135-136 ºC; IR (KBr): 3058, 1706, 1660, 1597, 1548, 1500, 1454, 1421, 1394, 1261, 1243, 1123, 1069 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.82 – 7.89 (m, 2H), 7.36 – 7.44 (m, 5H), 7.28 – 7.34 (m, 2H), 7.17 – 7.25 (m, 2H), 5.53 (s, 1H), 4.92 (dd, *J* = 15.2, 6.4 Hz, 1H), 4.68 (dd, *J* = 15.2, 5.6 Hz, 1H), 3.81 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.61, 162.17, 160.06, 142.41, 137.25, 135.91, 133.06, 130.10, 128.81, 128.66, 127.36, 127.04, 125.67, 111.66, 65.29, 52.58, 39.94 ppm; ESI-HRMS calcd. for $C_{21}H_{17}NO_3S$+H 364.1002, found 364.1016.

Methyl 2-phenyl-8-(*p*-tolyl)-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3b): 3b was obtained according to the general procedure in 83% yield (156.6 mg), white solid; mp 140-141 ºC; IR (KBr): 3019, 1722, 1652, 1548, 1504, 1461, 1431, 1228, 1110, 1059 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.82 – 7.88 (m, 2H), 7.37 – 7.41 (m, 3H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.17 (t, *J* = 6.0 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 5.49 (s, 1H), 4.93 (dd, *J* = 15.1, 6.4 Hz, 1H), 4.68 (dd, *J* = 15.1, 5.6 Hz, 1H), 3.80 (s, 3H), 2.31 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.64, 162.06, 160.02, 139.51, 137.34, 136.74, 135.76, 133.11, 130.05, 129.34, 128.80, 127.25, 125.67, 112.04, 65.34, 52.53, 39.72, 20.94 ppm; ESI-HRMS calcd. for $C_{22}H_{19}NO_3S$+H 378.1158, found 378.1168.

Methyl 8-(4-methoxyphenyl)-2-phenyl-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3c): 3c was obtained according to the general procedure in 90% yield (177.1 mg), white solid; mp 122-123 ºC; IR (KBr): 3019, 1720, 1655, 1609, 1549, 1510, 1462, 1433, 1256, 1234, 1125, 1030 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.81 – 7.89 (m, 2H), 7.36 – 7.42 (m, 3H), 7.29 – 7.34 (m, 2H), 7.16 (t, *J* = 6.0 Hz, 1H), 6.80 – 6.86 (m, 2H), 5.46 (s, 1H), 4.93 (dd, *J* = 15.2, 6.4 Hz, 1H), 4.69 (dd, *J* = 15.2, 5.6 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.65, 162.03, 159.93, 158.55, 137.19, 135.68, 134.56, 133.05, 130.06, 128.80, 128.45, 125.63, 113.99, 112.45, 65.43, 55.21, 52.55, 39.35 ppm; ESI-HRMS calcd. for $C_{22}H_{19}NO_4S$+H 394.1108, found 394.1121.

Methyl 8-(4-chlorophenyl)-2-phenyl-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3d): 3d was obtained according to the general procedure in 84% yield (167.1 mg), white solid; mp 124-125 ºC; IR (KBr): 3024, 1715, 1655, 1548, 1503, 1489, 1461, 1256 1228, 1120, 1014 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.79 – 7.91 (m, 2H), 7.37 – 7.45 (m, 3H), 7.32 – 7.37 (m, 2H), 7.26 – 7.30 (m, 2H), 7.19 (t, *J* = 5.8 Hz, 1H), 5.46 (s, 1H), 4.90 (dd, *J* = 15.4, 6.2 Hz, 1H), 4.72 (dd, *J* = 15.4, 5.4 Hz, 1H), 3.80 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.48, 162.45, 160.12, 140.93, 136.44, 136.30, 132.98, 132.96, 130.24, 128.86, 128.82, 128.80, 125.70, 112.00, 65.63, 52.67, 39.52 ppm; ESI-HRMS calcd. for $C_{21}H_{16}NO_3SCl$+H 398.0612, found 398.0626.

Methyl 8-(4-bromophenyl)-2-phenyl-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3e): 3e was obtained according to the general procedure in 63% yield (139.3 mg), white solid; mp 136-137 ºC; IR (KBr): 3021, 1751, 1655, 1548, 1503, 1485, 1435, 1404, 1256, 1241, 1120, 1070 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.81 – 7.89 (m, 2H), 7.37 – 7.44 (m, 5H), 7.27 – 7.31 (m, 2H), 7.18 (dd, *J* = 6.2, 5.4 Hz, 1H), 5.44 (s, 1H), 4.89 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.72 (dd, *J* = 15.6, 5.2 Hz, 1H), 3.80 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.46, 162.46, 160.12, 141.45, 136.48, 136.19, 132.93, 131.75, 130.24, 129.18, 128.86, 125.69, 121.08, 111.89, 65.62, 52.67, 39.57 ppm; ESI-HRMS calcd. for $C_{21}H_{16}NO_3SBr$+H 442.0107, found 442.0118.

Methyl 8-(4-fluorophenyl)-2-phenyl-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3f): 3f was obtained according to the general procedure in 76% yield (144.9 mg), white solid; mp 115-116 ºC; IR (KBr): 3067, 1716, 1659, 1602, 1550, 1505, 1461, 1436, 1390, 1240, 1122, 1065 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.81 – 7.90 (m, 2H), 7.34 – 7.44 (m, 5H), 7.18 (t, *J* = 5.6 Hz, 1H), 6.95 – 7.04 (m, 2H), 5.48 (s, 1H), 4.91 (dd, *J* = 15.5, 6.2 Hz, 1H), 4.72 (dd, *J* = 15.5, 5.2 Hz, 1H), 3.80 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.53, 162.34, 161.78 (d, *J* = 244.5 Hz), 160.04, 138.17 (d, *J* = 3.1 Hz), 136.54, 136.23, 132.98, 130.20, 129.04 (d, *J* = 8.0 Hz), 128.85, 125.68, 115.48 (d, *J* = 21.3 Hz), 112.38, 65.62, 52.63, 39.41 ppm; ESI-HRMS calcd. for $C_{21}H_{16}NO_3SF$+H 382.0908, found 382.0917.

Methyl 8-(4-cyanophenyl)-2-phenyl-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3g): 3g was obtained according to the general procedure in 73% yield (141.8 mg), white solid; mp 73-74 ºC; IR (KBr): 3050, 1712, 1662, 1605, 1554, 1504, 1465, 1436, 1395, 1240, 1119, 1063 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.81 – 7.88 (m, 2H), 7.58 – 7.63 (m, 2H), 7.52 – 7.57 (m, 2H), 7.38 – 7.43 (m, 3H), 7.21 – 7.25 (m, 1H), 5.51 (s, 1H), 4.88 (dd, *J* = 16.0, 6.4 Hz, 1H), 4.76 (dd, *J* = 16.0, 4.8 Hz, 1H), 3.80 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.26, 162.86, 160.29, 147.51, 137.42, 134.92, 132.78, 132.51, 130.40, 128.89, 128.29, 125.69, 118.53, 111.81, 111.06, 65.96, 52.77, 40.09 ppm; ESI-HRMS calcd. for $C_{22}H_{16}N_2O_3S$+H 389.0954, found 389.0966.

Methyl 2-phenyl-8-(*m*-tolyl)-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3h): 3h was obtained according to the general procedure in 95% yield (179.3 mg), white solid; mp 151-152 ºC; IR (KBr): 3017,

1712, 1656, 1602, 1550, 1501, 1427, 1392, 1125, 1064 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.81 – 7.90 (m, 2H), 7.36 – 7.44 (m, 3H), 7.14 – 7.23 (m, 4H), 7.01 – 7.07 (m, 1H), 5.50 (s, 1H), 4.93 (dd, *J* = 15.0, 6.4 Hz, 1H), 4.67 (dd, *J* = 15.0, 5.8 Hz, 1H), 3.81 (s, 3H), 2.32 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.63, 162.07, 159.96, 142.32, 138.34, 137.38, 135.76, 133.04, 130.06, 128.80, 128.49, 127.99, 127.82, 125.63, 124.40, 111.53, 65.19, 52.58, 39.79, 21.48 ppm; ESI-HRMS calcd. for $C_{22}H_{19}NO_3S$+H 378.1158, found 378.1148.

Methyl 8-(3-chlorophenyl)-2-phenyl-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3i): 3i was obtained according to the general procedure in 69% yield (137.3 mg), white solid; mp 152-153 ºC; IR (KBr): 3059, 1706, 1657, 1591, 1550, 1501, 1458, 1436, 1390, 1258, 1244, 1124, 1079 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.81 – 7.91 (m, 2H), 7.34 – 7.46 (m, 4H), 7.29 (dt, *J* = 7.2, 2.0 Hz, 1H), 7.18 – 7.26 (m, 3H), 5.47 (s, 1H), 4.90 (dd, *J* = 15.4, 6.4 Hz, 1H), 4.71 (dd, *J* = 15.4, 5.4 Hz, 1H), 3.82 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.41, 162.51, 160.14, 144.32, 136.56, 136.24, 134.54, 132.92, 130.25, 129.88, 128.85, 127.55, 127.32, 125.70, 125.64, 111.36, 65.48, 52.70, 39.58 ppm; ESI-HRMS calcd. for $C_{21}H_{16}NO_3SCl$+H 398.0612, found 398.0621.

Methyl 2-phenyl-8-(o-tolyl)-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3j): 3j was obtained according to the general procedure in 55% yield (103.8 mg), white solid; mp 125-126 ºC; IR (KBr): 3060, 1716, 1660, 1600, 1549, 1504, 1462, 1431, 1390, 1245, 1124, 1063 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.77 – 7.85 (m, 2H), 7.50 – 7.57 (m, 1H), 7.33 – 7.40 (m, 3H), 7.18 – 7.22 (m, 1H), 7.09 – 7.17 (m, 3H), 5.60 (s, 1H), 5.07 (ddd, *J* = 17.3, 5.3, 1.1 Hz, 1H), 4.90 (ddd, *J* = 17.3, 3.7, 1.3 Hz, 1H), 3.69 (s, 3H), 2.60 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.59, 161.60, 160.03, 140.77, 137.61, 134.88, 133.54, 133.08, 130.71, 130.00, 128.77, 127.91, 127.21, 126.61, 125.59, 117.47, 67.79, 52.37, 37.85, 19.83 ppm; ESI-HRMS calcd. for $C_{22}H_{19}NO_3S$+H 378.1158, found 378.1174.

Methyl 8-(2-chlorophenyl)-2-phenyl-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3k): 3k was obtained according to the general procedure in 86% yield (171.1 mg), white solid; mp 144-145 ºC; IR (KBr): 3065, 1721, 1657, 1598, 1543, 1502, 1469, 1435, 1392, 1258, 1118, 1066 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.77 – 7.91 (m, 2H), 7.61 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.31 – 7.45 (m, 4H), 7.26 – 7.30 (m, 1H), 7.21 (td, *J* = 7.5, 1.3 Hz, 1H), 7.15 (td, *J* = 7.6, 1.9 Hz, 1H), 5.91 (s, 1H), 5.05 (ddd, *J* = 17.7, 5.3, 1.1 Hz, 1H), 4.91 (ddd, *J* = 17.7, 2.9, 1.4 Hz, 1H), 3.71 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.29, 162.13, 160.39, 139.49, 139.00, 133.10, 132.80, 132.08, 130.05, 129.72, 128.98, 128.79, 128.50, 127.38, 125.64, 116.56, 67.99, 52.48, 37.83 ppm; ESI-HRMS calcd. for $C_{12}H_{16}NO_3S$+H 398.0612, found 398.0624.

Methyl 8-(2-bromophenyl)-2-phenyl-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3l): 3l was obtained according to the general procedure in 74% yield (163.7 mg), white solid; mp 134-135 ºC; IR (KBr): 3005, 1722, 1656, 1598, 1501, 1462, 1435, 1257, 1113, 1066 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$)

δ = 7.79 – 7.88 (m, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.34 – 7.41 (m, 3H), 7.23 – 7.30 (m, 2H), 7.07 (t, *J* = 7.6 Hz, 1H), 5.90 (s, 1H), 5.06 (dd, *J* = 18.0, 5.2 Hz, 1H), 4.93 (d, *J* = 18.0 Hz, 1H), 3.71 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.34, 162.14, 160.43, 141.26, 139.17, 133.14, 133.05, 131.88, 130.07, 129.18, 128.81, 128.76, 128.11, 125.68, 123.73, 117.14, 68.27, 52.49, 40.77 ppm; ESI-HRMS calcd. for $C_{21}H_{16}NO_3SBr$+H 442.0107, found 442.0108.

Methyl 2-phenyl-8-(thiophen-2-yl)-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3m): 3m was obtained according to the general procedure in 48% yield (88.7 mg), white solid; mp 106-107 °C; IR (KBr): 3068, 1716, 1659, 1602, 1550, 1505, 1461, 1436, 1390, 1255, 1240, 1123, 1066 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.81 – 7.90 (m, 2H), 7.33 – 7.46 (m, 4H), 7.18 (t, *J* = 5.8 Hz, 1H), 6.94 – 7.05 (m, 2H), 5.47 (s, 1H), 4.91 (dd, *J* = 15.5, 6.4 Hz, 1H), 4.72 (dd, *J* = 15.5, 5.4 Hz, 1H), 3.80 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.57, 162.38, 160.07, 138.22, 138.19, 136.58, 136.26, 133.01, 130.23, 129.11, 129.03, 128.88, 125.71, 115.63, 115.41, 112.40, 65.65, 52.67, 39.45 ppm; ESI-HRMS calcd. for $C_{19}H_{15}NO_3S_2$+H 370.0566, found 370.0577.

Methyl 2-phenyl-8-(pyridin-2-yl)-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3n): 3n was obtained according to the general procedure in 31% yield (56.5 mg), white solid; mp 98-99 °C; IR (KBr): 3012, 1707, 1657, 1585, 1546, 1500, 1463, 1430, 1395, 1260, 1240, 1126, 1067 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.52 – 8.59 (m, 1H), 7.82 – 7.89 (m, 2H), 7.64 (td, *J* = 7.7, 1.7 Hz, 1H), 7.36 – 7.42 (m, 4H), 7.33 (t, *J* = 6.2 Hz, 1H), 7.12 – 7.17 (m, 1H), 5.66 (s, 1H), 5.17 (dd, *J* = 14.6, 6.6 Hz, 1H), 4.69 (dd, *J* = 14.6, 6.0 Hz, 1H), 3.80 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.47, 162.28, 160.79, 160.29, 149.67, 136.98, 136.91, 136.58, 133.08, 130.06, 128.79, 125.68, 122.02, 121.57, 110.01, 65.51, 52.60, 43.01 ppm; ESI-HRMS calcd. for $C_{20}H_{16}N_2O_3S$+H 365.0954, found 365.0974.

Methyl 2-(4-chlorophenyl)-8-phenyl-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3o): 3o was obtained according to the general procedure in 72% yield (143.2 mg), white solid; mp 125-126 °C; IR (KBr): 3061, 1723, 1655, 1597, 1548, 1499, 1454, 1431, 1400, 1229, 1094, 1059 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.76 – 7.81 (m, 2H), 7.34 – 7.41 (m, 4H), 7.28 – 7.34 (m, 2H), 7.21 – 7.26 (m, 1H), 7.19 (t, *J* = 6.2 Hz, 1H), 5.52 (s, 1H), 4.92 (dd, *J* = 15.1, 6.4 Hz, 1H), 4.68 (dd, *J* = 15.1, 5.6 Hz, 1H), 3.81 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.53, 160.76, 160.13, 142.26, 137.19, 136.03, 135.83, 131.54, 129.06, 128.68, 127.32, 127.10, 126.85, 112.07, 65.29, 52.61, 39.91 ppm; ESI-HRMS calcd. for $C_{21}H_{16}NO_3SCl$+H 398.0612, found 398.0625.

Methyl 8-(4-bromophenyl)-2-(4-chlorophenyl)-5,8-dihydrooxepino[2,3-*d*]thiazole-7-carboxylate (3p): 3p was obtained according to the general procedure in 90% yield (214.5 mg), white solid; mp 156-157 °C; IR (KBr): 3048, 1717, 1658, 1555, 1592, 1499, 1484, 1432, 1400, 1241, 1120, 1069 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.74 – 7.81 (m, 2H), 7.40 – 7.45 (m, 2H), 7.34 – 7.39 (m, 2H), 7.26 – 7.31 (m, 2H), 7.16 – 7.21 (m, 1H), 5.44 (s, 1H), 4.89 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.71 (dd, *J* = 15.6, 5.2 Hz, 1H),

3.80 (s, 3H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 166.41, 161.11, 160.29, 141.37, 136.39, 136.26, 136.24, 131.84, 131.54, 129.18, 129.15, 126.94, 121.20, 112.43, 65.69, 52.67, 39.68 ppm; ESI-HRMS calcd. for $C_{21}H_{15}NO_3SBrCl$+H 475.9717, found 475.9730.

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10. CCDC 1545832 (**3a**) and 1545833 (**3j**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center.