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Preparation of S-2-halophenyl-2,1-benzothiazines

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ABSTRACT

Derivatives of 2,1-benzothiazines are useful synthetic intermediates for a variety of applications. We became interested in developing a one-pot procedure to S-2-halophenyl-2,1-benzothiazines as potential precursors to P,N type ligands for metals. Accordingly, we reacted S-2-halophenyl-S-methylsulfoximines with 2-bromobenzaldehydes using the Buchwald-Hartwig reaction under conditions previously developed in our laboratory. We found that 2-halophenylmethyl sulfoximines show lower reactivity in process than methylphenyl sulfoximine. Among the 2-(*S*)-2-halophenyl-(*S*)-methylsulfoximines tested, S-2-fluorophenyl-S-methyl sulfoximine afforded higher yields of benzothiazines than the bromine- or chlorine-substituted congeners. In the coupling of S-2-halophenyl-S-methylsulfoximines to 2-bromobenzaldehyde, using Ruphos as a ligand gave the best yields.

1. Introduction

2,1-Benzothiazines containing a sulfoximine functional group are a significant class of compounds that find use as chiral ligands [1], building blocks in organic synthesis [2], and fluorophores [3]. Other 2,1-benzothiazines have been developed as potential therapeutic agents [4].

Our interest in benzothiazine chemistry is long-standing [5]. A big leap forward in the synthesis of these compounds took place in 1999 when we published a one-pot procedure for the synthesis of these compounds using sulfoximines and 2-halobenzaldehydes and related compounds in conjunction with the Buchwald-Hartwig reaction (Scheme 1)[6b] using a coupling reaction introduced by Bolm [6a]. Developments since that time have expanded the scope of this process [7].

We envisioned that 2-halophenylbenzothiazines would be potential precursors to functionalized new P,N ligands [8] and thus would expand the chemistry's impact further. Our earlier work had demonstrated that the N-arylation of sulfoximines affords benzothiazines very readily (Scheme 1). We wondered if having a halogen substituent ortho to the sulfoximine group on an S-methyl-S-arylsulfoximine would be problematic, especially since one could imagine such sulfoximines coupling to each other to form dimeric, cyclic bis-sulfoximines.

2. Results/discussion

We began by investigating the reactivity of 2-bromophenyl sulfoximine **4a** with 2-bromobenzaldehyde (**5**) under our standard reaction conditions. While a sulfoximine without a bromine substituent would have reacted to produce the corresponding benzothiazine in high yield, we observed three products, one arising from simple *N*-arylation (**6a**, 10%), a condensation product (**7a**, 52%), and the desired benzothiazine (**8a**, 9%). Starting material was also recovered (**4a**, 28%) (Scheme 2). Since our previous work had suggested that condensation products like **7a** could not be converted to benzothiazines under the reaction conditions, we deemed that the presence of the bromine atom in **4a** slowed coupling, presumably at the ligand exchange stage when the sulfoximine nitrogen becomes bound to the palladium product of oxidative addition to **5**. Alternatively, the result could be interpreted as accelerating the condensation reaction leading to **7a**. In either case, we wondered if we could optimize the reaction to favor the formation of **8a**, and to what extent that might be possible.

We first examined the nature of the ligand as well as the Pd source on the course of the reaction. The results are shown in Table 1. At least under conditions of reflux in toluene, the nature of the ligand did not have a strong impact on the outcome of the reaction.

As the presence of base is also a key factor in the process, the

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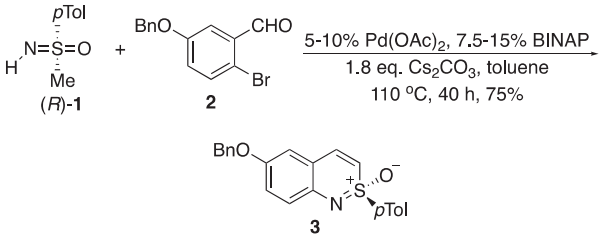
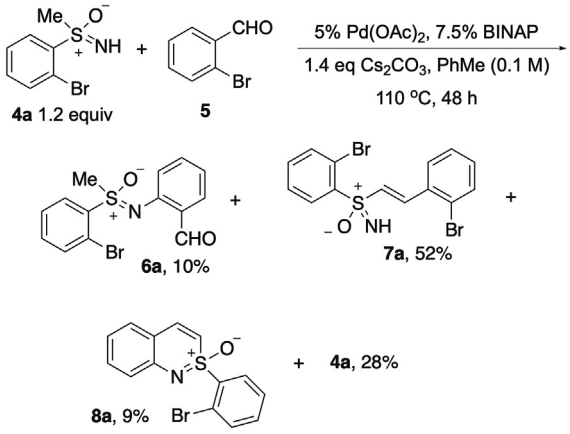
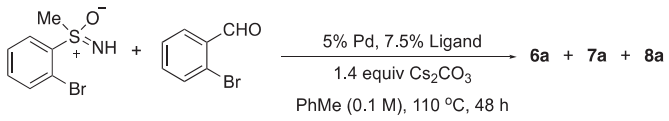


Scheme 1. A one-pot, one operation approach to 2,1-benzothiazines.



Scheme 2. Reaction of S-2-bromophenyl-S-methylsulfoximine (**4a**) with 2-bromobenzaldehyde.

Table 1
Effects of different Pd sources and ligands on the coupling reaction.



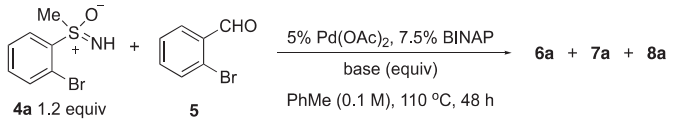
Entry	Pd	Ligand	6a (%)	7a (%)	8a (%)	4a (%)
1	Pd_2dba_3	BINAP	9	40	6	28
2	$Pd(PPh_3)_4$	–	6	39	7	30
3	$Pd(PPh_3)_2Cl_2$	BINAP	14	44	8	25
4	$Pd(OAc)_2$	P (*t*-Bu)$_3$	9	48	11	a
5	$Pd(OAc)_2$	Brettphos	10	49	6	a
6	$Pd(OAc)_2$	RuPhos	7	34	5	32
7	$Pd(OAc)_2$	BINAP	7	37	6	28
8	PEPPSI-I	–	3	30	4	34
9	PEPPSI-II	–	4	43	7	a

[a] Starting material not recovered.

reaction was investigated using different bases (Table 2). Cesium carbonate appeared to perform better than any other bases examined. The use of increasing amounts of base appeared to increase the consumption of **4a** but did not have a substantial impact on the yield of **8a** (Table 2, entries 3–4). The use of 4 Å molecular sieves had no noteworthy effect on the yield of **8a** (Table 2, entry 5).

Given earlier success synthesizing benzothiazines from aryl chlorides and sulfoximine under microwave irradiation [9], we decided to investigate the effect of microwaves on the synthetic problem at hand. The reaction time for these reactions was 1.5 h with freshly distilled toluene used as solvent. In most cases, additional catalyst was added to the reaction mixture and the process heating was continued for another 1.5 h. As summarized in Table 3,

Table 2
Coupling of **4a** and **5** with base variations.



Entry	Base (equiv)	6a (%)	7a (%)	8a (%)	4a (%)
1	CsOAc (1.4)	7	37	6	28
2	NaOt-Bu(1.4)	9	45	12	a
3	Cs_2CO_3(2.8)	12	55	13	a
4	Cs_2CO_3 (5.2)	14	55	12	a
5	Cs_2CO_3 (1.4)[b]	14	46	15	a

[a] Starting material not recovered.
[b] 4 Å MS (20%) were added.

the results were not impressive, certainly no better than conducting the reaction at reflux.

We next decided to investigate a different electrophile in the reaction and chose 2-iodobenzaldehyde. Though the Bolm group had shown that iodoarenes are not good candidates for Buchwald-Hartwig couplings using palladium catalysts, we decided to test the compound [10]. In the event, the reaction proceeded no better than that 2-bromobenzaldehyde.

Concerned that **4a** was undergoing metal-catalyzed processes [11] that, though undetected, were deleterious to benzothiazine formation, we decided to investigate the fluorinated sulfoximine **4b**. This compound was easily prepared using standard methods for the synthesis of sulfoximine (Scheme 3) [12]. As we had developed a procedure for the Pd-catalyzed *N*- arylation of sulfoximines with aryl chlorides in the presence of RuPhos [13], we decided to investigate the coupling of **4b** with **5** using this ligand. Thus, a slight excess of **4b** reacted with **5** in toluene at 120 °C in a sealed tube for 3 days to afford **8b** in 60% yield, along with 20% of the *N*-arylation product **6b** with complete consumption of **4b** (Scheme 4). No special precautions with respect to purging the system with inert gas before beginning the reaction were needed. This result was fortuitously the best result for the coupling of **4b** with **5**. Other examples with various variable changes are shown in Table 4. Only yields of **8b** were recorded. RuPhos and similar ligands perform best in this reaction (Table 4, entries 4, 7–8, 14–16).

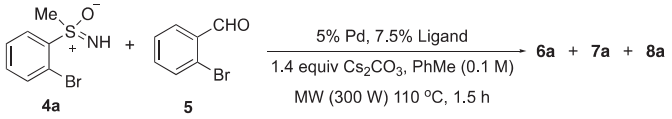
With a procedure that yielded useful amounts of benzothiazine **8b** in place, the scope of the reaction was expanded to other 2-halophenyl sulfoximines and several 2-bromobenzaldehydes. The results are summarized in Table 5. As expected, under these newly developed conditions, **4a** produced only modest yields of the corresponding benzothiazine (Table 5, entries 1, 4, 7,10).

Unreacted **4a** was recovered in all its coupling reaction with different 2-bromobenzaldehydes. The chlorinated sulfoximine **4c** gave moderate yields in its coupling reactions (Table 5, entries 3, 6, 9, 12). As expected, yields were best using **4b** (Table 5, entries 2, 5, 8, 11). While yields of the benzothiazines reported here are lower than from analogous methods involving non-halogenated sulfoximines, this methodology does allow rapid access to halogenated benzothiazines that to date are not accessible by any other method.

3. Conclusion

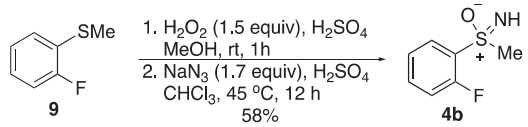
In summary, we have developed a route to *S*-2-halogenophenylbenzothiazines. The process proceeds in moderate yield, and is much slower than the corresponding reaction using an non-halogenated sulfoximine. Whether the direct introduction of a

Table 3
Coupling of **4a** and **5** using microwave irradiation.

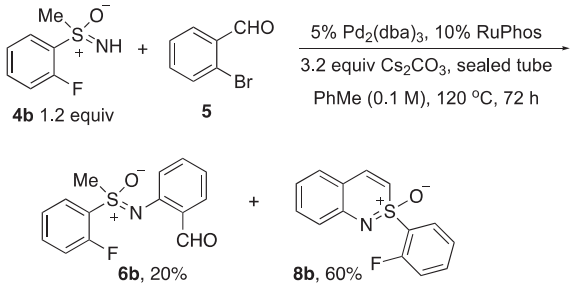


Entry	Pd	Ligand	6a (%)	7a (%)	8a (%)	4a (%)
1[b,c]	$Pd(OAc)_2$	BINAP	6	26	7	38
2[b,d]	$Pd(OAc)_2$	BINAP	16	45	10	a
3[b,e]	$Pd(OAc)_2$	BINAP	18	44	15	a
4[b]	Pd_2dba_3	BINAP	14	35	10	27
5[b]	$Pd(PPh_3)_2Cl_2$	–	7	29	9	28
6	$Pd(OAc)_2$	PCy_3	10	30	14	29

[a] Starting material not recovered.
[b] Two reaction cycles performed.
[c] One equiv of **5** was used.
[d] Three equiv of **5** were used.
[e] Five equiv of **5** were used.



Scheme 3. Synthesis of **4b**.



Scheme 4. Reaction of **4b** with **5**.

halogen onto an existing benzothiazine is a better route to such compounds remains to be seen, though some progress has been made in this area [14].

4. Experimental section

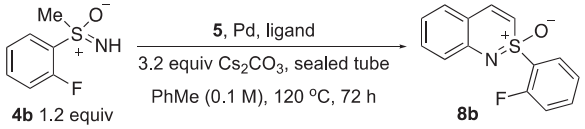
4.1. General

All reactions were carried out under an argon atmosphere in a flame dried sealed tube except where reported otherwise. CuI was used as purchased from Acros Organics. DMSO was purchased from Drysolv® Acros Organics and distilled over CaH_2. Acetonitrile was distilled over CaH_2. Toluene and THF were distilled over sodium metal and oxygen was removed by generation of a benzophenone ketyl. Pd_2dba_3, RuPhos, Cs_2CO_3 were used as purchased from Aldrich® and used as received. The synthesis of **4a**–**d** followed a standard protocol for the synthesis of sulfoximines of this general type [12]. All the reaction yields were reported based on the best result, if not stated otherwise.

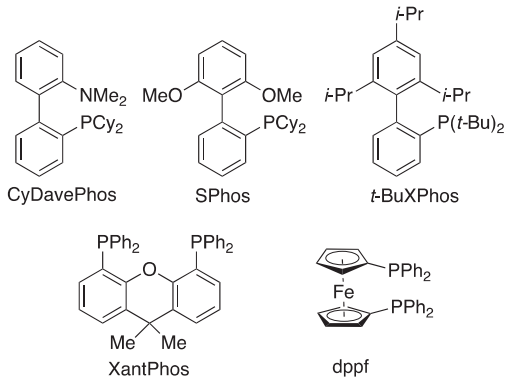
4.2. Synthesis of sulfoximines *4*: general procedure

To a round-bottom flask equipped with a stir bar was added a

Table 4
Optimization studies on the preparation of **8b**.



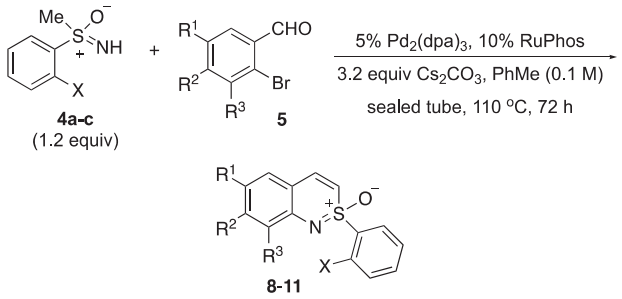
Entry	Pd (mol %)	Ligand (mol %)	Yield (%)
1	$Pd(OAc)_2$ (5)	RuPhos (10)	38
2	$Pd(PPh_3)_4$ (5)	RuPhos (10)	33
3	Pd_2 (dba)$_3$ (5)	BINAP (10)	23
4	Pd_2 (dba)$_3$ (5)	RuPhos (10)	60
5	$Pd(PPh_3)_4$ (5)	–	35
6	Pd_2 (dba)$_3$ (5)	CyDavePhos (10)	35
7	Pd_2 (dba)$_3$ (5)	SPhos (10)	55
8	Pd_2 (dba)$_3$ (5)	BrettPhos (10)	50
9	Pd_2 (dba)$_3$ (5)	*t*-BuXPhos (10)	20
10	Pd_2 (dba)$_3$ (5)	XantPhos (10)	16
11	Pd_2 (dba)$_3$ (5)	dppf (10)	12
12	Pd_2 (dba)$_3$ (2.5)	RuPhos (10)	42
13	Pd_2 (dba)$_3$ (5)	RuPhos (5)	35
14	Pd_2 (dba)$_3$ (7.5)	RuPhos (10)	53
15	Pd_2 (dba)$_3$ (5)	RuPhos (15)	53
16	Pd_2 (dba)3 (7.5)	RuPhos (15)	57



mixture of sulfide (43.93 mmol) and H_2SO_4/2-propanol (10 mL, 4.4 M, 4.4% w/w H_2SO_4/2-propanol), MeOH (125 mL, 0.4 M). 30% H_2O_2 (5.5 mL, 53.8 mmol, 1.2 equiv) was added. The reaction mixture was stirred for 4 h at rt. Water (500 mL) was added to the mixture. The aqueous layer was saturated with sodium chloride and extracted with chloroform (3 × 150 mL). The combined organic extracts were dried over magnesium sulfate and evaporated to give the pure sulfoxide for the next reaction. A round-bottom flask equipped with a condenser, a stir bar, a thermometer, and an addition funnel, was charged with a mixture of the sulfoxide, sodium azide (75.2 mmol, 1.71 equiv), and 100 mL of chloroform (0.5 M) and cooled in an ice bath. To this slurry, concentrated sulfuric acid (13.44 mL, 3.2 M) was added over 15 min. The mixture was then carefully warmed up to 45 °C. The mixture was heated further at 45 °C for 12 h. After cooling, 100 mL of ice water was added. After all the salts were dissolved, the chloroform layer was separated, and the aqueous layer was reextracted with 100 mL of chloroform. The aqueous layer was made slightly alkaline with a 20% sodium hydroxide solution and extracted twice with 3 × 100 mL of chloroform. The combined organic extracts were dried over magnesium sulfate, filtered, and the solvent was removed to afford product.

S-(2-Bromophenyl)-S-methyl sulfoximine (**4a**) and S-(2-chlorophenyl)-S-methyl sulfoximine (**4c**) were prepared based on the above procedure and displayed ^{1}H NMR and ^{13}C NMR spectra as

Table 5
Synthesis of halogenated benzothiazines.



Entry	X	R [1]	R [2]	R [3]	Product	Yield (%)
1	Br	H	H	H	**8a**	35
2	F	H	H	H	**8b**	60
3	Cl	H	H	H	**8c**	45
4	Br	-OBn	H	H	**9a**	45
5	F	-OBn	H	H	**9b**	55
6	Cl	-OBn	H	H	**9c**	50
7	Br	H	H	-OMe	**10a**	40
8	F	H	H	-OMe	**10b**	65
9	Cl	H	H	-OMe	**10c**	60
10	Br	H	F	H	**11a**	28
11	F	H	F	H	**11b**	45
12	Cl	H	F	H	**11c**	42

reported in the literature [5a].

*4.2.1. S-2-(Fluorophenyl)-S-methyl sulfoximine (**4b**)*

58% yield in two steps following the above procedure from commercially available S-(2-flurophenyl)-S-methyl sulfide. $R_f = 0.2$ (50% ethyl acetate/hexanes); dull white solid, mp 78–80 °C; IR ($CHCl_3$) 3250, 3140, 2925, 1598, 1472, 1226, 1016, 999, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (dt, $J = 7.5$, 1.5 Hz, 1H), 7.63–7.58 (m, 1H), 7.32 (dt, $J = 7.5$, 1.5 Hz, 1H), 7.22 (dt, J = 7.5, 1.0 Hz, 1H), 3.28 (s, 3H), 3.00 (b, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1(d, $J = 2.5$ Hz), 135.2 (d, $J = 8.75$ Hz), 131.4 (d, $J = 2.5$ Hz), 129.6, 124.5 (d, $J = 3.75$ Hz), 117.2 (d, $J = 21.25$ Hz), 44.78 (d, $J = 2.5$ Hz); HRMS calculated for $(C_7H_8FNOS)Na^+$: 196.0202, found: 196.0189.

*4.3. General procedure for the preparation of S-2-halophenylbenzothiazines. 2-(2-Fluorophenyl) benzo[c][1,2] thiazine-2-oxide (**8b**) (procedure A)*

2-Bromobenzaldehyde **5** (0.220 g, 1.19 mmol), sulfoximine **4b** (0.25 g, 1.43 mmol), Pd_2dba_3 (0.05459 g, 0.0595 mmol), Cs_2CO_3 (1.240 g, 3.808 mmol), and Ruphos (0.0554 g, 0.119 mmol) were combined in a sealed tube under open air conditions. Toluene (11.9 mL, 0.1 M) was introduced. The sealed tube was capped and heated to 120 °C in an oil bath for 72 h. After cooling to rt, the reaction mixture was diluted in dichloromethane and filtered through a plug of Celite. The filtrate was concentrated in vacuo, and the resulting brownish semisolid was purified by flash chromatography (SiO_2) with 20–30% ethyl acetate/hexanes to afford 0.184 g of **8b** (60% yield) as pale brown solid; $R_f = 0.4$ (30% ethyl acetate/hexanes); 60% yield; mp 117–119 °C; IR ($CHCl_3$) 3059, 2928, 2918, 1607, 1520, 1450, 1286, 1047, 998, 884, 784, 727, 684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (dt, $J = 8.0$, 1.5 Hz, 1H), δ 7.70 (d, $J = 10.0$ Hz, 1H), δ 7.62–7.60 (m, 1H), 7.46 (t, $J = 7.0$ Hz, 1H), 7.33–7.35 (m, 2H), 7.29 (d, $J = 7.5$ Hz, 1H), 7.20 (t, $J = 9.5$ Hz, 1H),7.02 (t, $J = 9.5$ Hz, 1H), 6.39 (d, $J = 9.5$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 158.5, 145.1, 140.6, 136.0, 135.9, 132.3, 129.8, 129.7, 129.6, 129.4, 124.37 124.34, 123.9, 120.3, 117.6, 117.4, 116.1, 108.9, 108.8; HRMS calculated for $(C_{14}H_{10}FNOS)Na^+$: 282.0359; found: 282.0361.

*4.3.1. 2-(((2-Fluorophenyl) (methyl) (oxo)-λ6-sulfaneylidene) amino) benzaldehyde (**6b**)*

Purified by column chromatography (SiO_2) using 30% ethyl acetate/hexanes, $R_f = 0.35$ (30% ethyl acetate/hexanes); pale yellow crystals from 50% ethyl acetate/hexanes; 20% yield; mp 83–85 °C; IR ($CHCl_3$) 3030, 2960, 2849, 1683, 1660, 1595, 1473, 1384, 1216, 1286, 1075, 1024, 998, 884, 784, 727, 684 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.6 (s, 1H), 8.02 (dt, $J = 8.5$, 1.5 Hz, 1H), δ 7.76 (dd, $J = 7.5$, 1.5 Hz, 1H), 7.60 (m, 1H), 7.33 (t, $J = 7.5$ Hz, 1H), 7.27–7.20 (m, 2H), 7.17 (t, $J = 9.5$ Hz, 1H), 7.11 (d, $J = 8.0$ Hz, 1H), 6.94 (t, $J = 7.5$ Hz, 1H), 3.48 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 159.8 (d, $J = 253.75$ Hz) 148.2, 136.1 (d, $J = 8.75$ Hz), 134.7, 131.7, 129.6, 127.7, 126.4 (d, $J = 13.75$ Hz), 124.9 (d, $J = 3.75$ Hz), 122.9, 122.7, 117.5 (d, $J = 21.25$ Hz), 45.29 (d, $J = 2.5$ Hz); HRMS calculated for $(C_{14}H_{12}FNO_2S)Na^+$: 300.0464; found: 300.0467.

*4.3.1.1. Crystal structure of compound **6b**.* $C_{14}H_{12}FNO_2S$, M = 277.31; a block crystal (0.50 × 0.45 × 0.35 mm), T = 173 (2) K, λ = 0.71073 Å, orthorhombic, space group: P21/n, a = 14.2559 (12) Å, b = 11.0583 (9) Å, c = 16.5580 (14) Å, V = 2610.3 (4) A^3, 22 369 total reflections, 17 735 unique, $R_{int} = 0.0279$ R1 = 0.0345 (I > 2s), w*R2* = 0.0865, Flack parameter: 0.44 (6).

*4.3.2. 2-(2-Chlorophenyl)benzo[c][1,2]thiazine-2-oxide (**8c**)*

Purified by column chromatography (SiO_2) using 30% ethyl acetate/hexanes; pale yellow solid, $R_f = 0.4$ (30% ethyl acetate/hexanes), 45% yield; mp 178–180 °C; IR ($CHCl_3$) 3059, 2928, 2918, 1607, 1520, 1450, 1215, 1170, 1047, 998, 884, 784, 727, 684 629 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, $J = 7.0$, 2.0 Hz, 1H), δ 7.78 (d, $J = 9.5$ Hz, 1H), δ 7.57–7.55 (m, 4H), 7.53 (t, $J = 7.0$ Hz, 1H), 7.48 (d, $J = 8.0$ Hz, 1H), 7.29 (t, $J = 7.0$ Hz, 1H), 7.07 (t, $J = 7.0$ Hz, 1H), 6.39 (d, $J = 9.5$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 141.6, 138.0, 135.7, 134.5, 132.4, 132.3, 130.4, 129.8, 127.0, 124.0, 120.2, 116.3, 107.3; HRMS calculated for $(C_{14}H_{10}ClNOS)Na^+$: 298.0063, found: 298.0068.

*4.3.3. 6-(Benzyloxy)-2-(2-bromophenyl) benzo[c][1,2]thiazine 2-oxide (**9a**)*

Purified by column chromatography (SiO_2) using 30% ethyl acetate/hexanes, greenish yellow liquid; 45% yield; IR ($CHCl_3$) 3067, 2925, 2824, 1733, 1652, 1539, 1496, 1286, 1215, 1041, 990, 829, 749, 668 cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 8.24 (dd, $J = 8.5$, 1.5 Hz, 1H), 7.74 (dd, $J = 8.0$, 1.0 Hz, 1H), 7.70 (d, $J = 10.0$ Hz, 1H), 7.55 (dt, $J = 7.5$, 1.0 Hz, 1H), 7.45–7.42 (m, 3H), 7.38–7.35 (m, 2H), 7.35–7.33 (m, 1H), 7.20 (d, $J = 1.5$ Hz, 2H), 6.99 (d, $J = 1.5$ Hz, 1H), 6.33 (d, $J = 10.0$ Hz, 1H). 5.07 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 141.1, 140.1, 139.0, 136.9, 135.8, 134.4, 130.9, 128.6, 128.0, 127.5, 125.2, 124.8, 122.3, 116.2, 107.1, 70.7; HRMS calculated for $(C_{21}H_{16}BrNO_2S)Na^+$: 447.9977, found: 447.9977.

*4.3.4. 6-(benzyloxy)-2-(2-fluorophenyl) benzo[c][1,2]thiazine 2-oxide (**9b**)*

Purified by column chromatography (SiO_2) using 30% ethyl acetate/hexanes; yellow sticky liquid; 55% yield; IR ($CHCl_3$) 3067, 2929, 2863, 1673, 1590, 1472, 1226, 1016, 990, 829, 749, 668 cm-1; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (dt, $J = 7.5$, 1.5 Hz, 1H), 7.64 (d, $J = 10$ Hz, 1H), 7.64–7.62 (m, 2H), 7.44–7.43 (m, 2H), 7.34–7.33 (m, 2H), 7.25–7.23 (m, 1H), 7.19–7.18 (m, 2H), 6.89 (d, $J = 3.0$ Hz, 1H), 6.52 (d, $J = 10.0$ Hz, 1H). 5.07 (s, 2H); $_{13}C$ NMR (125 MHz, $CDCl_3$) δ 160.5 (d, $J = 256.25$ Hz), 152.4, 139.9 (d, $J = 25$ Hz), 136.9, 135.9 (d, $J = 7.5$ Hz), 129.5 (d, $J = 11.25$ Hz), 128.6, 128.0, 127.5 (d, $J = 12.5$ Hz), 125.0, 124.3 (d, $J = 5$ Hz), 122.1, 117.5 (d, $J = 21.25$ Hz), 116.1, 112.6, 109.0, 70.71; HRMS calculated for $(C_{21}H_{16}FNO_2S)Na^+$: 388.0777;

found: 388.0775.

*4.3.5. 6-(Benzyloxy)-2-(2-chlorophenyl) benzo[c][1,2]thiazine 2-oxide (**9c**)*

Purified by column chromatography (SiO_2) using 30% ethyl acetate/hexanes; pale yellow oil; 50% yield; IR ($CHCl_3$) 3067, 2925, 1652, 1590, 1472, 1215, 1170, 1023, 990, 829, 749, 668 593 cm-1; 1H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, $J = 8.0$ Hz, 1H), 7.69 (d, $J = 10.0$ Hz, 1H), 7.53–7.50 (m, 3H), 7.44–7.38 (m, 2H), 7.40 (t, $J = 7.5$ Hz, 2H), 7.20–7.19 (m, 1H), 6.90 (d, $J = 2$ Hz, 1H), 6.37 (d, $J = 10$ Hz, 1H), 5.07 (s, 2H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 140.9, 140.0, 138.0, 137.0, 135.7, 134.5, 132.2, 130.5, 128.6, 128.0, 127.5, 125.0, 125.1, 122.2, 116.0, 112.6, 107.5, 70.7; HRMS calculated for $(C_{21}H_{16}ClNO_2S)Na^+$: 404.0482, found: 404.0490.

*4.3.6. 2-(2-Bromophenyl)-8-methoxybenzo [c][1,2]thiazine 2-oxide (**10a**)*

Purified by column chromatography (SiO_2) using 30% ethyl acetate/hexanes; pale yellow solid; 40% yield; mp 173–175 °C; IR ($CHCl_3$) 3057, 2992, 2937, 2836, 1601, 1599, 1429, 1372, 1175, 1080, 997, 807, 720, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (dt, $J = 7.5$, 1.5 Hz, 1H), 7.77 (d, $J = 10.0$ Hz, 1H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.53 (t, $J = 7.5$ Hz, 1H), 7.42 (dt, $J = 7.5$, 6.0 Hz, 1H), 7.02–6.97 (m, 3H), 6.31 (d, $J = 10.0$ Hz, 1H). 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 141.6, 138.9, 135.8, 135.6, 134.3, 131.0, 127.3, 125.2, 121.7, 119.6, 116.7, 112.5, 107.0, 56.1; HRMS calculated for $(C_{15}H_{12}BrNO_2S)Na^+$: 371.9664, found: 371.9662.

*4.3.7. 2-(2-Fluorophenyl)-8-methoxybenzo [c][1,2]thiazine 2-oxide (**10b**)*

Purified by column chromatography (SiO_2) using 30% ethyl acetate/hexanes; pale yellow solid recrystallized from ethyl acetate/hexane, 65% yield; mp 168–170 °C; IR ($CHCl_3$) 3064, 2986, 2937, 2837, 1599, 1547, 1472, 1289, 1257, 1000, 997, 828, 720, 682, 593 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dt, $J = 7.5$, 1.5 Hz, 1H), 7.72 (d, $J = 10.0$ Hz, 1H), 7.60–7.59 (m, 2H), 7.35 (t, $J = 7.5$ Hz, 1H), 7.16 (dt, $J = 9.5$, 8.5 Hz, 1H), 7.01–6.97 (m, 3H), 6.50 (d, $J = 10$ Hz, 1H). 3.94 (s, 3H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, (d, $J = 256.25$ Hz), 151.9, 140.5, 136.1 (d, $J = 8.75$ Hz), 135.5, 135.9 (d, $J = 7.5$ Hz), 129.9, 129.5 (d, $J = 11.25$ Hz), 124.17 (d, $J = 3.75$ Hz), 121.7, 119.7, 117.5 (d, $J = 20$ Hz), 116.6, 112.6, 109.0, 56.1; HRMS calculated for $(C_{15}H_{12}FNO_2S)Na^+$: 312.0464, found: 312.0463.

*4.3.7.1. Crystal structure of compound **10b**.* $C_{14}H_{12}FNO_2S$, M = 289.32; a block crystal (0.55 × 0.14 × 0.10 mm), T = 173 (2) K, λ = 0.71073 Å, trigonal, space group: P21/n, a = 30.100 (13) Å, b = 30.100 (13) Å, c = 7.609 (3)Å, V = 5970 (4) A^3, 22 369 total reflections, 3049 unique, R int = 0.0279 R1 = 0.0255(I > 2s), w*R*2 = 0.0628, Flack parameter: 0.00 (5).

*4.3.8. 2-(2-Chlorophenyl)-8-methoxybenzo [c][1,2]thiazine 2-oxide (**10c**)*

Purified by column chromatography (SiO_2) using 30% ethyl acetate/hexanes; pale yellow solid recrystallized from ethyl acetate/hexane; 60% yield; mp 185–187 °C; IR ($CHCl_3$) 3057, 2992, 2937, 2836, 1601, 1599, 1429, 1372, 1215, 1170, 1080, 997, 807, 720, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (dt, $J = 7.5$, 1.5 Hz, 1H), 7.77 (d, $J = 10$ Hz, 1H), 7.70 (d, $J = 8.0$ Hz, 1H), 7.53 (t, $J = 7.5$ Hz, 1H), 7.42 (dt, $J = 7.5$, 6.0 Hz, 1H), 7.02–6.97 (m, 3H), 6.31 (d, $J = 10.0$ Hz, 1H). 3.92 (s, 3H) ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 141.6, 138.9, 135.8, 135.6, 134.3, 131.0, 127.3, 125.2, 121.7, 119.6, 116.7, 112.5, 107.0, 56.1; HRMS calculated for $(C_{15}H_{12}ClNO_2S)Na^+$: 328.0169, found: 328.0172.

*4.3.9. 2-(2-Bromophenyl)-7-fluorobenzo [c][1,2]thiazine 2-oxide (**11a**)*

Purified by column chromatography (SiO_2) using 30% ethyl acetate/hexanes, yellow sticky liquid, $R_f = 0.4$ (30% ethyl acetate/hexanes), 28% yield; IR ($CHCl_3$) 3072, 3035, 2928, 1605, 1539, 1496, 1286, 1215, 1041, 907, 884, 784, 727, 676, 569, cm-1; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (dd, $J = 7.0$, 1.0 Hz, 1H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.74 (d, $J = 10.0$ Hz, 1H), 7.59 (t, $J = 7.5$ Hz, 1H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.34 (dd, $J = 6.5$, 2.5 Hz, 1H), 6.93 (dt, $J = 10.5$, 2.0 Hz, 1H), 6.76 (dt, $J = 8.0$, 2.0 Hz, 1H), 6.28 (d, $J = 10.0$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3 (d, $J = 250$ Hz), 147.6 (d, $J = 13.75$ Hz), 141.2, 138.7, 135.9, 134.6, 131.8 (d, $J = 11.25$ Hz), 130.8, 129.1, 128.7, 127.7, 124.7, 113.2, 109.7 (d, $J = 22.5$ Hz), 109.1 (d, $J = 23.75$ Hz), 105.8 (d, $J = 2.5$ Hz); HRMS calculated for $(C_{14}H_9BrFNOS)Na^+$: 359.9564, found: 359.9474.

*4.3.10. 7-Fluoro-2-(2-fluorophenyl) benzo[c] [1,2]thiazine 2-oxide (**11b**)*

Purified by column chromatography (SiO_2) using 30% ethyl acetate/hexanes, sticky liquid, $R_f = 0.4$ (30% ethyl acetate/hexanes); 45% yield; IR ($CHCl_3$) 3040, 2918, 1607, 1520, 1450, 1286, 1047, 998, 890, 784, 727, 626 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (dt, $J = 8.0$, 1.5 Hz, 1H), 7.68 (d, $J = 10.0$ Hz, 1H), 7.64–7.63 (m, 1H), 7.36 (t, $J = 8.0$ Hz, 1H), 7.35 (m, 1H), 7.19 (t, $J = 9.0$ Hz, 1H), 6.93 (dd, $J = 11.0$, 2.5 Hz, 1H), 6.77 (dt, $J = 8.0$, 2.5 Hz, 1H), 6.46 (d, $J = 10.0$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3 (d, $J = 250$ Hz), 160.6 (d, $J = 255$ Hz), 147.2 (d, $J = 13.75$ Hz), 140.1, 136.2 (d, $J = 8.75$ Hz), 131.7 (d, $J = 11.25$ Hz), 129.4 (d, $J = 12.5$ Hz), 124.4 (d, $J = 3.75$ Hz), 117.6 (d, $J = 21.25$ Hz), 113.01 (d, $J = 1.25$ Hz), 109.6 (d, $J = 22.5$ Hz), 109.1 (d, $J = 23.75$ Hz), 107.6; HRMS calculated for $(C_{14}H_9F_2NOS)Na^+$: 300.0265, found: 300.0270.

*4.3.11. 2-(2-Chlorophenyl)-7-fluorobenzo [c][1,2]thiazine 2-oxide (**11c**)*

Purified by column chromatography (SiO_2) using 30% ethyl acetate/hexanes; sticky liquid; $R_f = 0.4$ (30% ethyl acetate/hexanes); 42% yield; IR ($CHCl_3$) 3040, 2908, 1616, 1512, 1450, 1215, 1170 1046, 978, 854, 727, 684 646 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, $J = 6.0$, 1.5 Hz, 1H), 7.72 (d, $J = 10.0$ Hz, 1H), 7.54–7.53 (m, 3H), 7.35 (dd, J = 6.5, 2.0 Hz, 1H), 6.93 (dd, $J = 11.0$, 2.5 Hz, 1H), 6.76 (dt, $J = 2.5$, 0.5 Hz, 1H), 6.39 (d, $J = 10.0$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3 (d, $J = 250$ Hz), 147.5 (d, $J = 13.75$ Hz), 141.0, 137.7, 135.7, 134.7, 132.3, 131.8 (d, $J = 11.25$ Hz), 130.4, 127.1, 113.0, 109.6 (d, $J = 22.5$ Hz), 109.0 (d, $J = 23.75$ Hz), 106.2 (d, $J = 2.5$ Hz); HRMS calculated for $(C_{14}H_9ClFNOS)Na^+$: 315.9969, found: 315.9976.

*4.4. Typical procedure for the coupling reaction of 2-bromophenyl sulfoximine **4a** with **5** (procedure B)*

2-Bromobenzaldehyde **5** (0.164 g, 0.89 mmol), sulfoximine **4a** (0.25 g, 1.06 mmol), $Pd(OAc)_2$ (0.0100 g, 0.0443 mmol), Cs_2CO_3 (0.405 g, 1.24 mmol), BINAP (0.0415 g, 0.0667 mmol) were added together in a sealed tube with toluene (8.9 mL, 0.1 M) inside a glove bag filled with nitrogen and capped. The mixture was degassed by bubbling with argon for 15 min with stirring at rt and heated to 110 °C for 48 h. After cooling to rt, the reaction mixture was diluted in dichloromethane and filtered through a plug of Celite. After concentrated in vacuo, the brownish semisolid was purified by flash chromatography (SiO_2) with 20–30% ethyl acetate/hexanes to afford 0.113 g of **7a** (37%) as pale yellow solid, 0.016 g of **6a** (7%), 0.018 g of **8a** (6%) and 0.07 g of **4a** (28%) were recovered.

*4.4.1. 2-(((2-Bromophenyl) (methyl) (oxo)-λ6-sulfaneylidene) amino)benzaldehyde (**6a**)*

Purified by column chromatography (SiO_2) using 30% ethyl

acetate/hexanes, pale yellow solid, mp 129–131 °C; R_f = 0.35 (30% ethyl acetate/hexanes); 7% yield; IR ($CHCl_3$) 3024,2963, 2927, 2849, 1681, 1657, 1593, 1571, 1474, 1451, 1320, 1216, 1102, 1075, 1013, 960, 831, 784, 727, 684 530 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.36 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.79 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.69 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.19 (dt, *J* = 6.5, 0.5 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 3.55 (s, 3H); $_{13}C$ NMR (125 MHz, $CDCl_3$) δ 192.6, 148.1, 137.7, 135.9, 134.7, 134.7, 133.4, 129.2, 128.2, 127.8, 122.0, 121.8, 120.3, 43.8; HRMS calculated for $(C_{14}H_{12}BrNO_2S)Na^+$: 359.9664, found: 359.9673.

4.4.2. (E)-(2-Bromophenyl) (2-bromostyryl) (imino)-λ6-sulfanone (**7a**)

Purified by column chromatography (SiO_2) using 50% ethyl acetate/hexanes, pale yellow solid crystallized in 50% ethyl acetate/hexanes, R_f = 0.35 (50% ethyl acetate/hexanes); 37% yield; mp 124–127 °C; IR ($CHCl_3$) 3329, 3264, 3062, 2929, 1609, 1439, 1239, 1215, 1112, 1027, 969, 851, 814, 752, 667, 699, 644, 554 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 8.0 Hz, 1H), 8.15 (d, *J* = 15.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.27–7.26 (m, 1H), 7.18 (d, *J* = 15 Hz, 1H), 3.17 (s, br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 142.0, 135.6, 133.9, 133.6, 132.8, 131.9, 130.9, 129.4, 128.4, 128.0, 127.8, 125.6, 120; HRMS calculated for $(C_{14}H_{11}Br_2NOS)Na^+$: 421.8820, found: 421.8820.

4.4.2.1. Crystal structure of compound ***7a***. $C_{14}H_{11}Br_2NOS$, M = 400.11; a block crystal (0.50 × 0.50 × 0.20 mm), T = 173 (2) K, λ = 0.71073 Å, monoclinic, space group: P21/n, a = 14.7558 (16) Å, b = 14.6322 (16) Å, c = 14.9319 (17) Å, V = 2896.3 (6) A^3, 20 085 total reflections, 6367 unique, Rint = 0.0563 R1 = 0.0655 (I > 2s), w*R*2 = 0.1709.

4.4.3. 2-(2-bromophenyl) benzo[c][1,2]thiazine-2-oxide(**8a**)

Purified by column chromatography (SiO_2) using 30% ethyl acetate/hexanes, pale yellow solid recrystallized from 50% ethyl acetate/hexanes, mp 189–191 °C; R_f = 0.4 (30% ethyl acetate/hexanes); 35% yield; IR ($CHCl_3$) 3052, 3013, 2928, 1605, 1527, 1450, 1178, 1047, 995, 884, 784, 727, 676, 569, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.78 (d, *J* = 10.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.56 (t, J = 7.5, Hz, 1H), 7.46 (dd, J = 7.5, 1.0 Hz, 2H), 7.38 (d, *J* = 7.0 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.34 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 141.8, 139.1, 135.8, 134.5, 132.4, 130.8, 129.8, 127.6, 124.7, 124.1, 120.2, 116.3, 107.0; HRMS calculated for $(C_{14}H_{10}BrNOS)Na^+$: 341.9558, found: 341.9566.

4.4.3.1. Crystal structure of compound ***8a***. $C_{14}H_{10}BrNOS$, M = 320.20; a block crystal (0.50 × 0.15 × 0.15 mm), T = 173 (2) K, λ = 0.71073 Å, Orthorhombic, space group: P 21 21 21, a = 6.1056 (3) Å, b = 9.9557 (5) Å, c = 20.7650 (11) Å, V = 1262.21 (11) A^3, 9063 total reflections, 2771 unique, Rint = 0.0305 R1 = 0.0266 (I > 2s), w*R*2 = 0.0539, Flack parameter: 0.492 (8).

4.5. General procedure for the coupling reaction of S-(2-bromophenyl)-S-methyl sulfoximine **4a** with **5** under microwave irradiation. (Procedure C)

In a microwave tube kept inside a glove bag filled with nitrogen, 2-bromobenzaldehyde **5** (0.164 g, 0.89 mmol), sulfoximine **4a** (0.25 g, 1.06 mmol), $Pd(OAc)_2$ (10 mg, 0.0443 mmol), Cs_2CO_3 (0.405 g, 1.24 mmol), BINAP (0.0415 g, 0.0667 mmol) were added. Toluene (8.9 mL, 0.1 M) was introduced and the tube was capped. The microwave tube was taken out of the glove bag and the reaction mixture was degassed by bubbling with argon for 15 min with stirring at rt. The reaction was heated to 110 °C in a microwave reactor for 1.5 h. After cooling to room temperature, $Pd(OAc)_2$ (0.0100 g, 0.0443 mmol), Cs_2CO_3 (0.405 g, 1.24 mmol), BINAP (0.0415 g, 0.0667 mmol) were added again and the reaction was heated to 110 °C for another 1.5 h. After cooling to room temperature, the reaction mixture was diluted in dichloromethane and filtered through a plug of Celite. The filtrate was concentrated in vacuo, the resulting brown semisolid was purified by flash chromatography (SiO_2) with 20–30% ethyl acetate/hexanes to afford 0.092 g of **7a** (26%), 0.017 g of **6a** (6%), 0.019 g of **8a** (7%) and 0.095 g of **4a** (38% recovered).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.131991.

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