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Regioselective construction of six-membered fused heterocyclic rings via Pd/C-mediated C–C coupling followed by iodocyclization strategy: a new entry to 2*H*-1,2-benzothiazine-1,1-dioxides☆

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Abstract—We describe a practical and elegant method of constructing a thiazine ring fused with benzene under mild reaction conditions. A variety of 4-iodo-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides were prepared with high regioselectivity via a two-step process involving Pd/C-mediated C–C coupling of *o*-halobenzenesulfonamides with terminal alkynes, followed by iodocyclization of the resulting *o*-(1-alkynyl)-arenesulfonamide using elemental iodine in acetonitrile. The coupling reaction was carried out using 10% Pd/C–PPh_3–CuI as a catalyst system in the presence of Et_3N. The process worked well for bromides and iodides, and a wide array of terminal alkynes containing alkyl and aryl substituents were employed. The iodocyclization step tolerated a variety of functional groups such as hydroxy, chloro, cyano, and methoxy, producing the six-membered heterocyclic ring selectively. The resulting 4-iodo-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides participated in Sonogashira, Heck, and Suzuki reactions producing a wide range of functionally substituted benzothiazines in good yields.

1. Introduction

Transition metal mediated coupling–cyclization processes, of which many rely on palladium catalysis and involve in situ generation of acetylenic compounds bearing a nucleophilic substituent in close proximity to the triple bond, have proven to be an efficient and versatile way of constructing carbocyclic and heterocyclic structures.[1] Generally, the electrophilic cyclization of *ortho*-functionalized aryl (or heteroaryl) alkynes takes place in the same pot in a tandem fashion. However, the efficiency of the cyclization step largely depends on the reaction conditions employed and the nature of the nucleophilic substituent present in the *o*-(1-alkynyl)-aryl (or heteroaryl) derivatives produced. On several occasions, the uncyclized acetylenic compounds have been isolated, and then cyclized separately to afford the desired products.[2] For instance, coupling of *N*-ethyl-2-iodo-4-methyl-benzenesulfonamide with trimethylsilyl acetylene under Sonogashira conditions afforded the corresponding ethynyl substituted product which, on treatment with NaH, yielded benzoisothiazole.[2c] Recently, iodocyclization of C–C triple bond with a wide variety of nucleophiles, including N, O, and S nucleophiles, has been studied extensively[3] and proved to be an efficient method for intramolecular cyclization. This approach is particularly attractive as it offers the advantage of further transformation of the iodide functional group of the resulting compound into other substituents that is not often feasible via organometallic tandem coupling–cyclization method in a single pot. This has been well exemplified by the recent synthesis of a wide array of heterocycles.[4–13] Notably, the nucleophilicity of the sulfonamide nitrogen of the *o*-(1-alkynyl)benzenesulfonamide moiety towards the electrophilic species produced as a result of activation of the triple bond under the conditions of iodocyclization has not been studied well.[13f]

In conjunction with our new drug discovery research, we have had a longstanding interest in the synthesis of acyclic and cyclic derivatives of the benzenesulfonamide class,[14] e.g., 1,1-dioxo-2,3-dihydrobenzo[*d*]isothiazolyl substituted pyrazoles[14b,c] **2** (Fig. 1). In a further continuation of the above investigation, we became interested in the 2*H*-benzo[*e*][1,2]-thiazine-1,1-dioxide ring system (**3**, Fig. 1), a common structural subunit prevalent in numerous pharmaceutically important anti-inflammatory agents,[15,16] particularly oxicams. Earlier syntheses of 2*H*-benzo[*e*][1,2]thiazines, represented by structure **3**, involve heteroannulation of 2-iodobenzenesulfonamide with ketone enolates under photostimulated

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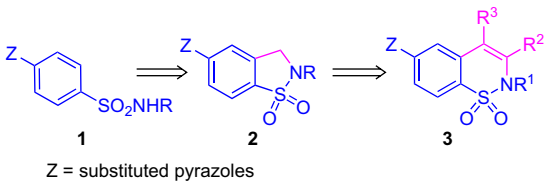
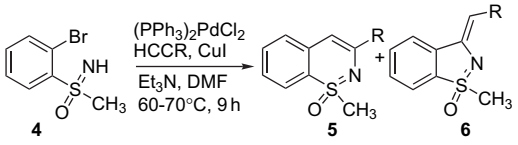


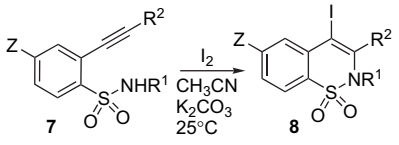
Figure 1. Design of 2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides derived from the benzenesulfonamide class of compounds.

$S_{RN}1$ conditions[17] or multistep syntheses.[18] Recently, inspired by the work of Lane and Snieckus,[2c] a new Pd-mediated one-step synthesis of benzothiazines has been developed by Harmata et al.[19] (Scheme 1).



Scheme 1. Pd-mediated one-step synthesis of benzothiazines.[19]

While this methodology, involving Sonogashira coupling of bromosulfoximine **4** with terminal alkynes, afforded 1,2-benzothiazines **5** in 16–70% yields, a substantial quantity of 1,2-benzoisothiazoles **6** (13–81% yields) were isolated as side products (or as major products in some cases) depending on the nature of alkynes used. Moreover, this methodology is applicable for the synthesis of 3-substituted benzoisothiazines only, and an attempt towards the possible synthesis of 3,4-disubstituted derivative by using an internal alkyne remained inconclusive.[19] Based on the observation of Snieckus and Lane, and in search of an alternative and selective, but more general and versatile process for the synthesis of 1,2-benzothiazines, we decided to explore[20] the use of a coupling–iodocyclization strategy. In this article, we describe the first successful synthesis of 4-iodo-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide derivatives using the chemistry represented in Scheme 2. To the best of our knowledge, synthesis of 2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide ring using a similar strategy and a further structural elaboration of this framework has not been disclosed earlier.



Scheme 2.

2. Results and discussion

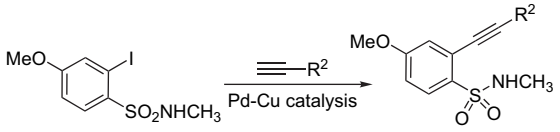
A two-step process to 4-iodo benzothiazines was examined. This involved (i) Pd/C-mediated coupling[21a–c] of *o*-halobenzenesulfonamide **9** with terminal alkynes and (ii) iodocyclization. The required sulfonamide **9** was prepared from the corresponding sulfonyl chloride and alkylamines, followed by treatment with BuLi and elemental iodine according to the procedure reported in the literature.[2c,21d]

2.1. Optimization and scope of the Pd-mediated coupling of *o*-halobenzenesulfonamide with terminal alkynes

For assessing the generality of the overall approach, it was necessary to examine the scope of the Pd-mediated coupling of compound **9** with terminal alkynes. Moreover, a detailed study was required to establish the optimum reaction conditions for the preparation of iodocyclization precursor **7**. Thus, coupling of **9b** with 3-butynol was examined under various reaction conditions (Table 1). After assessing a number of Pd-catalysts, e.g., $Pd(PPh_3)_2Cl_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, 10% Pd/C, etc., and solvents such as DMF, ethanol, 1,4-dioxane, and acetonitrile, it was observed that the use of 10% Pd/C–PPh_3–CuI as a catalyst system in the presence of Et_3N in acetonitrile afforded the best yield of **7b** (Table 1, entry 8). We therefore used this methodology for the preparation of alkynes **7** (Table 2). Importantly, the use of Pd/C–CuI–PPh_3 as catalyst system for efficient Sonogashira coupling has attracted much attention recently, since Pd/C-based methods have an economic advantage especially in large or industrial scale preparations.[22]

Generally, *o*-halobenzenesulfonamides showed high reactivity toward Pd/C-mediated Sonogashira coupling when all the reactions were carried out using a 1:4:2 ratio of Pd/C–PPh_3–CuI at 80 °C for 8–24 h. This allowed the preparation of a variety of functionalized *o*-(1-alkynyl)benzenesulfonamides (Table 2). Both bromo (**9a**) and iodo derivatives (**9b**–**d**) reacted well with terminal alkynes bearing various substituents such as alkyl, hydroxyalkyl, chloroalkyl, cyanoalkyl, aryl, and heterocyclic groups. Good to excellent yields (85–97%) were obtained in all the cases, irrespective of the nature of the substituents present in the halides as well as alkynes. Except in case of arylalkynes no significant dimerization (homocoupling)[23] of the terminal alkynes was observed as a side reaction under the conditions employed.[23f] All the *o*-(1-alkynyl)benzenesulfonamides (**7**) synthesized were characterized by the appearance of the sulfonamide (–SO_2NH–) moiety in the region of δ 5–6 in the ^1H NMR and an alkyne absorption band at 2200–2300 cm^{-1} in the IR spectra.

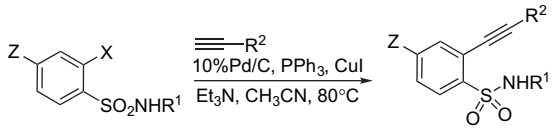
Table 1. Effect of catalyst, base, and solvent on the Pd-mediated coupling of **9b** with 3-butynol[a]



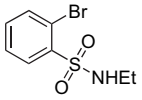
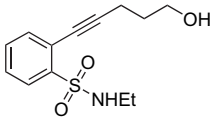
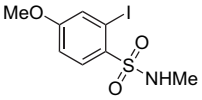
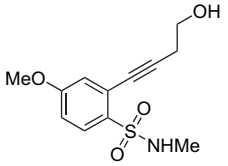
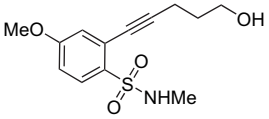
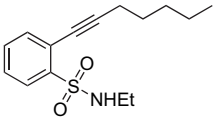
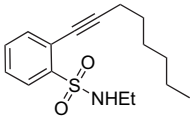
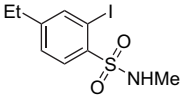
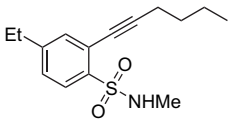
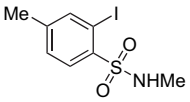
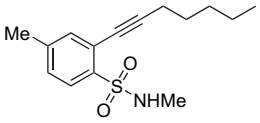
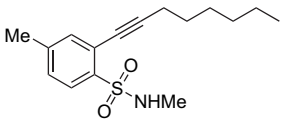
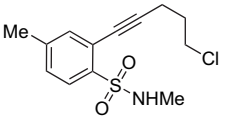
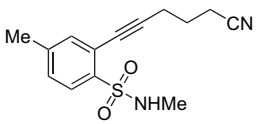
Entry	Pd catalyst	Solvent; base	Temp (°C); time (h)	Yield[b] (%)
1	$Pd(PPh_3)_2Cl_2$	DMF; Et_3N	70; 18	65
2	$Pd(PPh_3)_2Cl_2$	DMF; 2-aminoethanol	70; 18	70
3	$Pd(PPh_3)_2Cl_2$	EtOH; Et_3N	70; 18	75
4	$Pd(PPh_3)_2Cl_2$	1,4-Dioxane; Et_3N	70; 12	70
5	$Pd(OAc)_2$	DMF; Et_3N	80; 24	65
6	$Pd(PPh_3)_4$	DMF; Et_3N	80; 24	70
7[c]	10% Pd/C–PPh_3	EtOH; Et_3N	70; 18	68
8[c]	10% Pd/C–PPh_3	Acetonitrile; Et_3N	70; 18	97
9[c]	10% Pd/C–PPh_3	DMF; Et_3N	70; 18	71

[a] Reaction conditions: **9b** (1.0 equiv), 4-butynol (3.0 equiv), Pd catalyst (0.03 equiv), CuI (0.04 equiv), base (3 equiv) in a solvent under N_2.
[b] Isolated yields.
[c] The reaction was carried out using a 1:4:2 ratio of Pd/C–PPh_3–CuI.

Table 2. Pd/C-mediated synthesis of 2-alkynyl-*N*-methyl-benzenesulfonamide[a] (**7**)

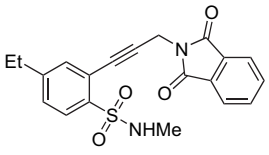
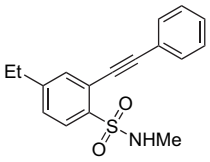
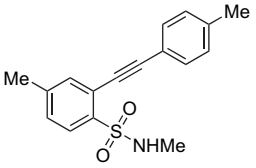
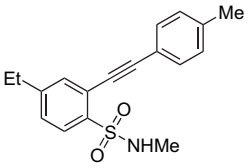
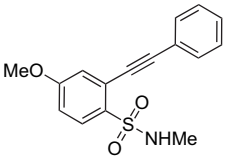


9 **7**

Entry	Aryl halide	Arylalkyne		Reaction time (h)	Yield[b] (%)
1	 **9a**		**7a**	18	85
2	 **9b**		**7b**	18	97
3	**9b**		**7c**	18	94
4	**9a**		**7d**	8	89
5	**9a**		**7e**	10	87
6	 **9c**		**7f**	8	90
7	 **9d**		**7g**	12	87
8	**9d**		**7h**	8	87
9	**9d**		**7i**	12	87
10	**9d**		**7j**	24	94

(*continued*)

Table 2. (*continued*)

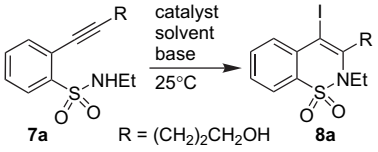
Entry	Aryl halide	Arylalkyne		Reaction time (h)	Yield[b] (%)
11	**9c**		**7k**	24	98
12	**9c**		**7l**	12	94
13	**9d**		**7m**	8	90
14	**9c**		**7n**	10	89
15	**9b**		**7o**	8	90

[a] All the reactions were carried out using 1:4:2 ratio of Pd/C–PPh_3–CuI.
[b] Isolated yields.

2.2. Optimization and scope of the iodocyclization of *o*-(1-alkynyl)benzenesulfonamides

We have observed that *o*-(1-alkynyl)benzenesulfonamide (**7**) undergoes smooth iodocyclization to afford 4-iodo-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides (**8**). Initially, we examined the reaction of *N*-ethyl-2-(5-hydroxy-pent-1-ynyl)-benzenesulfonamide (**7a**) with 2.5 equiv of iodine at room temperature, by changing a number of factors such as solvent, base, and time (Table 3, entries 1–6). After assessing a number of solvents (e.g., ethanol, 1,4-dioxane, dichloromethane, and acetonitrile) and bases (e.g., triethylamine, $NaHCO_3$, Na_2CO_3, and K_2CO_3), a combination of acetonitrile–K_2CO_3 was found to be optimum with respect to the yield of product isolated (Table 3, entry 3). Under these conditions, the reaction proceeded smoothly, and the best yield of **8a** (76%) was achieved when the reaction was carried out for 16 h. However, the reaction time varied from 6 to 24 h depending on the type of alkynyl derivatives **7** used (vide infra). Notably, iodocyclization of **7a** was observed even in the absence of a base (Table 3, entry 7) affording **8a**, albeit in low yield. Presumably, deprotonation of the intermediate generated after cyclization leading to **8a** was facilitated in the presence of a base (see later for a discussion on mechanism). While the use of other electrophiles such as ICl, NBS, etc. was investigated (Table 3, entries 8 and 9), these reagents were found to be less efficient under the conditions studied. Thus, iodine was found to be the best electrophile in this intramolecular cyclization reaction and was chosen for further study. The structure of **8a** was confirmed by its ^{13}C and ^{1}H NMR, IR, and MS spectra, and was further supported by the molecular structure of **8m** determined

Table 3. Effect of electrophile, base, and solvent on the cyclization of **7a**[a]



Entry	Catalyst	Solvent; base	Time (h)	Yield[b] (%)
1	I_2	1,4-Dioxane; Et_3N	24	40
2	I_2	Ethanol; Et_3N	24	35
3	I_2	Acetonitrile; K_2CO_3	16	76
4	I_2	CH_2Cl_2; K_2CO_3	24	50
5	I_2	Acetonitrile; Na_2CO_3	24	60
6	I_2	Acetonitrile; $NaHCO_3$	18	55
7	I_2	Acetonitrile; No base	48	25
8	ICl	Acetonitrile; K_2CO_3	24	55
9	NBS	Acetonitrile; K_2CO_3	24	27

[a] All the reactions were carried out at room temperature using a catalyst (2.5 equiv) and a base (3 equiv).
[b] Isolated yield.

unambiguously by X-ray crystallographic analysis (Fig. 2).[24] Unlike the earlier synthesis of benzothiazines[19] (Scheme 1), no five-membered-ring product was detected in the present study.

Using the optimized reaction conditions for iodocyclization as described above (Table 3, entry 3), a variety of other alkynes **7** were tested in acetonitrile at room temperature, and the results are summarized in Table 4. As indicated, iodocyclization of **7** was efficient in most cases affording a number of corresponding 4-iodo-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides **8** in good to excellent yields (62–87%). Substituents such as methyl (Table 4, entries 7–10 and 13), ethyl (Table 4, entries 6, 11, 12, and 14), and methoxy groups (Table 4, entries 2, 3, and 15) on the benzene ring, and alkyl (Table 4, entries 4–8), chloroalkyl (Table 4, entry 9), cyanoalkyl (Table 4, entry 10), heterocyclyl alkyl (Table 4, entry 11), and aryl groups (Table 4, entries 12–15) at the acetylenic end were well tolerated. In general, simple alkyl and aryl substituents on the triple bond of compound **7** cyclized more rapidly (e.g., 6–12 h) than others (12–24 h), where various groups such as hydroxy, chloro or cyano were present at the distal end of the alkyl side chain. In a separate study, we coupled **9a** and trimethylsilyl acetylene under Pd/C–PPh_3–CuI catalysis, and the resulting alkyne was examined for iodocyclization. In our hands, the cyclization did not proceed, perhaps due to the unfavorable steric crowding caused by the bulky trimethylsilyl group.

The present iodocyclization of **7** showed very high selectivity for six-membered ring formed as a result of '6-*endo-dig*' ring closure. No isomeric five-membered ring products were detected under the conditions employed,[25] nor the product involving the simple addition of iodine to the triple bond of **7**. More importantly, these reactions produced only water-soluble (KI) by-products, thus rendering work-up procedures very simple. However, the use of 2.5 equiv of iodine could be a disadvantage in a relatively large-scale preparation, therefore we attempted to conduct coupling and cyclization step in a single pot. Accordingly, iodine and K_2CO_3 were added to the reaction mixture of **9b** and 4-pentynol at the end of the coupling reaction (Table 1, entry 8), and **8b** was isolated in 25% yield after stirring for 24 h at 25 °C. We then repeated the same reaction sequence by passing the reaction mixture through Celite after completion of the coupling reaction, then carried out iodocyclization in the same pot. Encouragingly, **8b** was isolated in 75% yield demonstrating the potential of this process to be utilized for the preparation of 4-iodo-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides without isolating the intermediates.

2.3. Proposed reaction mechanism

Mechanistically, the Pd/C-mediated coupling of **9** with terminal alkynes follows a typical Sonogashira pathway.[21b] The high reactivity shown by **9** could be due to the coordination of the sulfonamide moiety to palladium in the presumed intermediate, thereby stabilizing the arylpalladium intermediate as shown in Figure 3. A plausible mechanism for the formation of 4-iodo-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides **8** via iodocyclization is shown in Scheme 3. The reaction proceeds via (i) activation of the triple bond of **7** by coordination to I^+ followed by (ii) intramolecular nucleophilic attack by the nitrogen of the sulfonamide group in an '*endo-dig*' fashion. A '5-*exo-dig*' cyclization, although feasible in the presence of a strong base,[2c] was not observed in the present case. In an alternative pathway, the reaction may proceed via deprotonation of the NH of the sulfonamide moiety, followed by intramolecular nucleophilic attack of the resulting anion on the vinylic cation. This anionic sulfonamide moiety now can react either via nitrogen or oxygen producing two regioisomeric products. Since the isomeric (4-iodo-1-oxo-1*H*-1λ^6-benzo[*c*][1,2]oxathiin-1-ylidene)-methylamine derivative was never isolated from the reaction mixture even in trace quantity we believe that this cyclization follows the former pathway.[26] This is further supported by the fact that iodocyclization can proceed in the absence of a base (Table 1, entry 7). In a separate experiment, iodocyclization of 2-(5-hydroxy-pent-1-ynyl)benzenesulfonamide (*N*-de ethyl analogue of **7a**) was attempted under the condition described above (Table 3, entry 3) where no formation of cyclized product was observed. Thus, the iodocyclization seems to be facilitated by several factors. (1) The alkyl group enhances the nucleophilicity of the nitrogen of sulfonamide

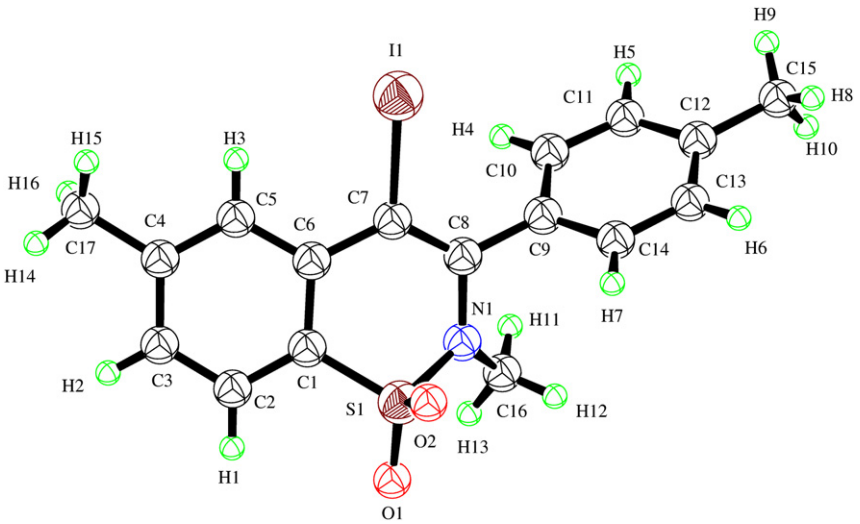
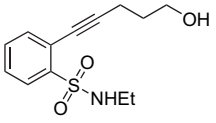
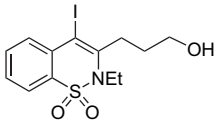
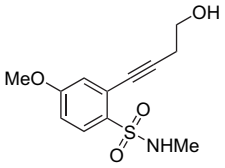
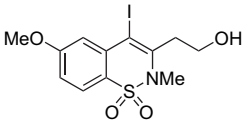
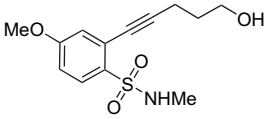
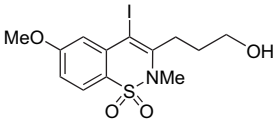
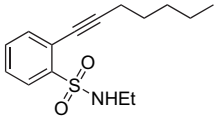
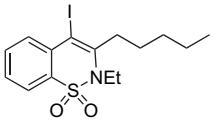
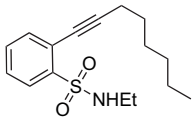
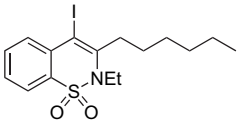
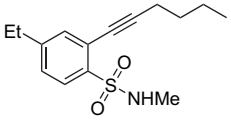
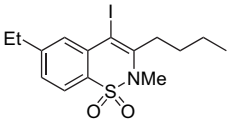
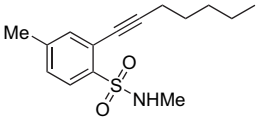
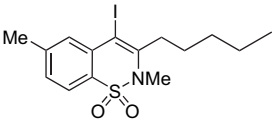
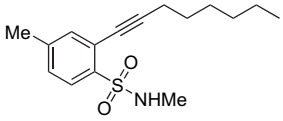
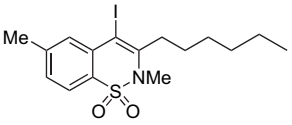
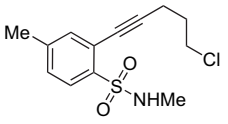
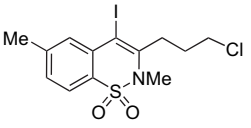
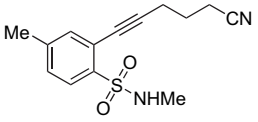
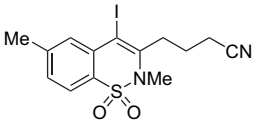
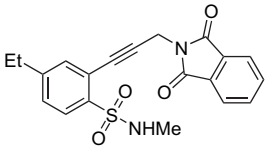
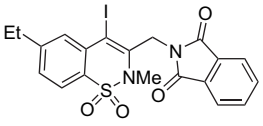


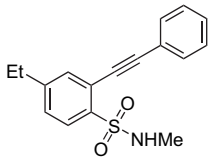
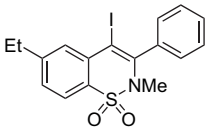
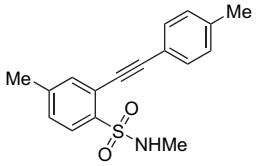
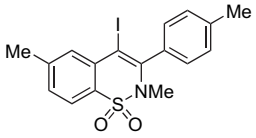
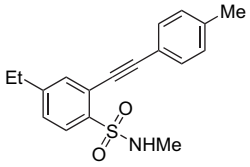
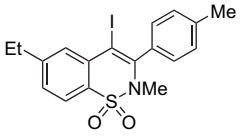
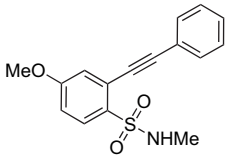
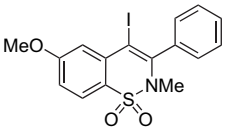
Figure 2. X-ray crystal structure of **8m** (ORTEP diagram).

Table 4. Synthesis of 2*H*-1,2-benzothiazine-1,1-dioxides via iodocyclization[a]

Entry	Alkyne		Time (h)	Product		Yield[b] (%)
1		**7a**	16		**8a**	76
2		**7b**	12		**8b**	80
3		**7c**	18		**8c**	74
4		**7d**	8		**8d**	70
5		**7e**	10		**8e**	62
6		**7f**	8		**8f**	67
7		**7g**	12		**8g**	74
8		**7h**	6		**8h**	70
9		**7i**	16		**8i**	69
10		**7j**	12		**8j**	80
11		**7k**	24		**8k**	85

(*continued*)

Table 4. (*continued*)

Entry	Alkyne		Time (h)	Product		Yield[b] (%)
12		**7l**	8		**8l**	87
13		**7m**	8		**8m**	80
14		**7n**	8		**8n**	87
15		**7o**	8		**8o**	82

[a] All the reactions were carried out at room temperature using 2.5 equiv of I_2 and 3 equiv of K_2CO_3 in acetonitrile.
[b] Isolated yields.

moiety. (2) The electron withdrawing effect of the sulfonamide moiety makes the vinylic cation susceptible for nucleophilic attack leading to the formation of six-membered ring. (3) The presence of a base facilitates the efficient N–H bond cleavage as cyclization proceeds.

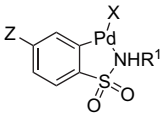
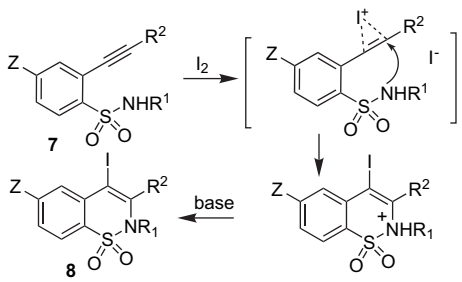


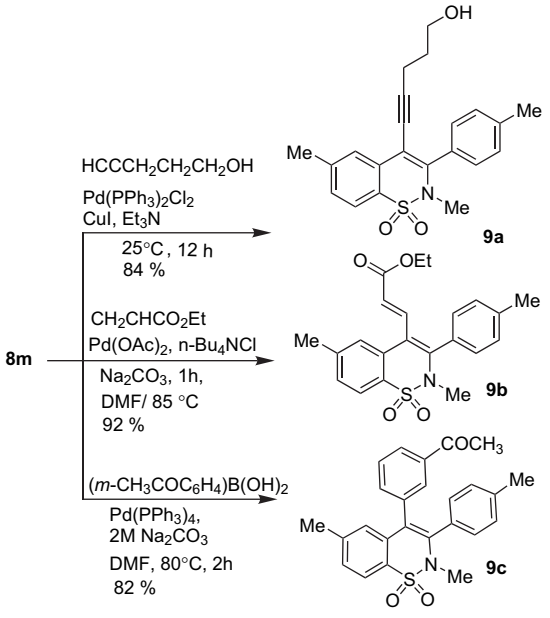
Figure 3. Sulfonamide stabilized arylpalladium intermediate.



Scheme 3. Plausible mechanism of iodocyclization of **7**.

2.4. Structural elaboration of the benzothiazine ring

The presence of the iodo group at the C-4 position of the benzothiazine ring allows further structural elaboration through conversion of the iodide functionality into other substituents. For example, when compound **8m** was exposed to Sonogashira, Heck, and Suzuki coupling conditions in the presence of a terminal alkyne, olefin or aryl boronic acid individually, the corresponding products formed via C–C bond forming reactions were isolated in 82–92% yields (Scheme 4). Notably, 3,4-diaryl substituted 2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides are of pharmacological interest,[27] and can now be easily accessed via Suzuki coupling, as described above. Compound **8n** was de-iodinated in the presence of a Pd(0)-catalyst and sodium formate in DMF to afford the



Scheme 4.

corresponding 3-aryl-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide in 78% yield. It is therefore possible to generate a variety of either 3,4-disubstituted or only 3-substituted 2*H*-benzo-[*e*][1,2]thiazine-1,1-dioxides using the iodo compounds **8** and known palladium catalyzed reactions.

3. Conclusions

A novel two-step strategy has been devised for the synthesis of 2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides that proceeds with high regioselectivity. The process involves (i) Pd/C-mediated facile synthesis of *o*-(1-alkynyl)arenesulfonamide via C–C coupling followed by (ii) the construction of the six-membered ring via efficient iodocyclization with elemental iodine under mild conditions. The coupling reaction worked well for bromides and iodides, which can be readily prepared according to the known methods. This is the first time Pd/C has been employed as a catalyst in a coupling–iodocyclization sequence. The second step of the present synthesis is also the first example of iodocyclization involving intramolecular attack of a $-SO_2NH-$ moiety to a C–C triple bond leading to the formation of benzothiazine ring. Overall, this two-step process tolerates a variety of functional groups such as hydroxy, chloro, cyano, and methoxy, and is generally free from producing any significant side products, e.g., homocoupled products from the terminal alkynes (except in the case of arylalkynes) in the first step or regioisomeric products of benzothiazines in the second step. The process is simple, easy to handle and does not involve the use of expensive reagents or catalysts. The presence of the iodo group on the resulting 4-iodo-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides makes them useful substrates for derivatization by conversion to a wide range of functionally substituted benzothiazines via various Pd-catalyzed transformations. Thus we believe that the present Pd/C-mediated coupling–iodocyclization followed by Pd-catalyzed substitution not only opens up a new path, but also provides a powerful tool for the preparation of diversely substituted benzothiazines. The provision of a wide array of these substances may represent the bottleneck for further studies and development in medicinal chemistry. Further work is in progress to extend the scope of this methodology for the synthesis of more complex structures.

4. Experimental

4.1. General methods

Unless stated otherwise, reactions were performed under a nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F_{254}), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (60–120 mesh) using distilled petroleum ether and ethyl acetate. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ solution on 200 and 400 and 50 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ=0.00) as internal standard and expressed in parts per million. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet) as well as b (broad). Coupling constants (*J*) are given in hertz. Infrared spectra were recorded on a FTIR spectrometer. Melting points were determined by using melting point apparatus and are uncorrected. Thermal analysis data [differential scanning calorimetry (DSC)] were generated with the help of DSC-50 detector. MS spectra were obtained on a mass spectrometer. Chromatographic purity by HPLC was determined by using area normalization method and the condition specified in each case: column, mobile phase (range used), flow rate, detection wavelength, and retention times. All the terminal alkynes used are commercially available except 2-prop-2-ynyl isoindole-1,3-dione that was prepared according to a known procedure.[28] All the *o*-halobenzenesulfonamides were either prepared according to the literature procedure or according to the method described below.

4.2. Preparation of *N*-ethyl-2-bromobenzenesulfonamide (9a)

To a stirred solution of 2-bromobenzenesulfonyl chloride (2 g, 7.82 mmol) in chloroform at 0 °C was added 40% aq solution of ethylamine (1.05 g, 1.45 mL) dropwise. The resulting mixture was refluxed for about 4 h. After completion of the reaction, the solvent was removed under vacuum. The residue was dissolved in chloroform and washed with dil HCl followed by brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to afford a white solid (1.18 g, 57% yield) as a desired product; mp 100–102 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.16 (d, *J*=8.2 Hz, 1H), 7.75 (d, *J*=8.2 Hz, 1H), 7.52–7.26 (m, 2H), 5.07 (br s, NH, 1H), 3.05 (q, *J*=5.7 Hz, 2H), 1.10 (t, *J*=5.6 Hz, 3H); Mass (*m*/*z*) 265 (M+1, 100%); IR (cm^{-1}, KBr) 3292, 1430, 1323; Elemental analysis found C, 36.50; H, 3.80; N, 5.23; $C_8H_{10}BrNO_2S$ requires C, 36.38; H, 3.82; N, 5.30.

4.3. Preparation of *N*-methyl-2-iodo-4-ethylbenzenesulfonamide (9c)

A solution of *N*-methyl-4-ethylbenzenesulfonamide (2 g, 10.05 mmol) in THF (20 mL) was cooled to 0 °C under nitrogen atmosphere and treated with a solution of *n*-BuLi in hexane (12 mL, 21.05 mmol) dropwise. The mixture was stirred at 0 °C for 15 min and then warmed to room temperature with stirring. After stirring for 1 h at room temperature, the resulting bright yellow solution was cooled to −78 °C and stirred for 15 min. A solution of iodine (2.79 g, 11.05 mmol) in THF (15 mL) was added and the resulting mixture was then stirred at −78 °C for 1 h, quenched with a saturated aq solution of NH_4Cl (15 mL), treated with a saturated aq solution of $Na_2S_2O_3$ (50 mL), and was extracted with ethyl acetate. The organic layers were collected, combined, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was then purified by column chromatography using EtOAc–petroleum ether to give the desired product as a white solid (2.8 g, 86% yield); mp 90–92 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.07 (d, *J*=8.2 Hz, 1H), 7.90 (s, 1H), 7.32 (d, *J*=8.2 Hz, 1H), 5.12 (br s, NH, 1H), 2.69 (q, *J*=8.0 Hz, 2H), 2.59 (d, *J*=8.1 Hz, 3H), 1.29 (t, *J*=8.0 Hz, 3H); Mass (*m*/*z*) 326 (M+1, 100%); IR (cm^{-1}, KBr) 3317, 1321, 1163; HPLC 97.62%, Symmetry shield RP18 (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: CH_3CN, gradient (T/% B): 0/30, 2/30, 14/80, 20/80, 21/30, 22/30, flow rate 1.5 mL/min, UV 210 nm, retention time 7.84 min;

Elemental analysis found C, 33.06; H, 3.75; N, 4.37; $C_9H_{12}INO_2S$ requires C, 33.24; H, 3.72; N, 4.31.

4.4. Preparation of *N*-methyl-2-iodo-4-methyl-benzenesulfonamide (9d)

This compound was prepared in 75% yield via iodination of *N*-methyl-4-methyl-benzenesulfonamide using *n*-BuLi in THF followed by treatment with iodine according to the procedure as described above; mp 65–67 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.05 (d, J=8.1 Hz, 1H), 7.89 (s, 1H), 7.28 (d, J=8.1 Hz, 1H), 5.12 (br s, NH, 1H), 2.58 (d, J=8.5 Hz, 3H), 2.37 (s, 3H); Mass (*m*/*z*) 311 (M^++1, 100%); IR (cm^{-1}, KBr) 3296, 1312, 1156; HPLC 98.62%, Symmetry shield RP18 (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: CH_3CN, gradient (T/% B): 0/30, 2/30, 14/80, 20/80, 21/30, 22/30, flow rate 1.5 mL/min, UV 210 nm, retention time 7.84 min; Elemental analysis found C, 30.97; H, 3.22; N, 4.42; $C_8H_{10}INO_2S$ requires C, 30.88; H, 3.24; N, 4.50.

4.5. Preparation of *N*-methyl-2-iodo-4-methoxy-benzenesulfonamide (9b)

This compound was prepared in 66% yield via iodination of *N*-methyl-4-methoxybenzenesulfonamide using *n*-BuLi in THF followed by treatment with iodine according to the procedure as described above; mp 86–88 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.48 (d, J=8.5 Hz, 1H), 7.55 (s, 1H), 6.95 (d, J=8.5 Hz, 1H), 5.12 (br s, NH, 1H), 3.86 (s, 3H), 2.58 (d, J=5.2 Hz, 3H); Mass (*m*/*z*) 326 (M+1, 100%); IR (cm^{-1}, KBr) 3317, 1400, 1321, 1163; Elemental analysis found C, 30.48; H, 3.06; N, 4.19; $C_8H_{10}INO_3S$ requires C, 29.37; H, 3.08; N, 4.28.

4.6. Preparation of *o*-(1-alkynyl)benzenesulfonamides (7)

4.6.1. Typical procedure for the preparation of 7n. A mixture of 4-ethyl-2-iodo-*N*-methyl-benzenesulfonamide **9c** (0.3 g, 0.925 mmol), 10% Pd/C (0.027 g, 0.029 mmol), PPh_3 (0.029 g, 0.11 mmol), CuI (0.010 g, 0.05 mmol), and triethylamine (0.279 g, 0.385 mL, 2.77 mmol) in acetonitrile (15 mL) was stirred at 25 °C for 30 min under nitrogen. To this mixture was added 1-ethynyl-4-methylbenzene (0.321 g, 2.77 mmol) slowly with stirring. The reaction mixture was then stirred at 80 °C for 10 h, cooled to room temperature, diluted with EtOAc (50 mL), and filtered through Celite. The filtrate was collected and concentrated under vacuum. The residue was purified by column chromatography to afford the desired product as brown gum (0.26 g, 89% yield).

4.6.2. *N*-Ethyl-2-(5-hydroxy-pent-1-ynyl)-benzenesulfonamide (7a). Low melting brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.02 (d, J=7.0 Hz, 1H), 7.56 (d, J=6.5 Hz, 1H), 7.42 (t, J=7.0 Hz, 1H), 7.38 (t, J=6.5 Hz, 1H), 5.65 (br s, NH, 1H), 3.67 (t, J=7.1 Hz, 2H), 2.96–2.91 (m, 2H), 2.68 (t, J=7.0 Hz, 2H), 2.42 (q, J=7.0 Hz, 2H), 1.54 (br s, 1H, D_2O exchangeable, –OH), 1.08 (t, J=7.5 Hz, 3H); IR (cm^{-1}, KBr) 3354, 2231, 1433, 1162; *m*/*z* (ES Mass) 268 (M+1, 100); Elemental analysis found C, 58.49; H, 6.43; N, 5.03; $C_{13}H_{17}NO_3S$ requires C, 58.40; H, 6.41; N, 5.24.

4.6.3. 2-(4-Hydroxy-but-1-ynyl)-4-methoxy-*N*-methyl-benzenesulfonamide (7b). Low melting brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.89 (d, J=8.3 Hz, 1H), 7.39 (s, 1H), 7.20 (d, J=8.3 Hz, 1H), 5.50 (br s, NH, 1H), 3.88 (s, 3H), 3.86 (t, J=7.0 Hz, 2H), 3.78 (t, J=7.0 Hz, 2H), 2.54 (d, J=6.8 Hz, 3H), 1.50 (br s, 1H, –OH); IR (cm^{-1}, KBr) 3348, 2211, 1412, 1132; *m*/*z* (ES Mass) 270 (M+1, 100%); Elemental analysis found C, 53.39; H, 5.54; N, 5.29; $C_{12}H_{15}NO_4S$ requires C, 53.52; H, 5.61; N, 5.20.

4.6.4. 2-(5-Hydroxy-pent-1-ynyl)-4-methoxy-*N*-methyl-benzenesulfonamide (7c). Low melting yellow solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.89 (d, J=7.8 Hz, 1H), 7.39 (s, 1H), 7.20 (d, J=7.8 Hz, 1H), 5.50 (br s, NH, 1H), 3.88 (s, 3H), 3.86 (t, J=6.0 Hz, 2H), 3.76 (t, J=6.0 Hz, 2H), 2.54 (d, J=6.5 Hz, 3H), 1.89–1.87 (m, 2H), 1.52 (br s, 1H, –OH); IR (cm^{-1}, neat) 3357, 2228, 1362, 1160; *m*/*z* (ES Mass) 284 (M+1, 100%); Elemental analysis found C, 55.23; H, 6.07; N, 4.64; $C_{13}H_{17}NO_4S$ requires C, 55.11; H, 6.05; N, 4.94.

4.6.5. *N*-Ethyl-2-hept-1-ynyl-benzenesulfonamide (7d). Low melting yellow solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.16 (d, J=7.0 Hz, 1H), 8.01 (d, J=7.2 Hz, 1H), 7.55 (t, J=7.2 Hz, 1H), 7.46 (t, J=7.0 Hz, 1H), 5.06 (br s, NH, 1H), 3.70 (t, J=7.5 Hz, 2H), 2.98–2.90 (m, 4H), 2.51 (t, J=7.0 Hz, 3H), 1.66 (q, J=5.0 Hz, 2H), 1.46–1.40 (m, 2H), 0.94 (t, J=5.0 Hz, 3H); IR (cm^{-1}, neat) 3331, 2227, 1469, 1125; *m*/*z* (ES Mass) 280 (M+1, 100%); Elemental analysis found C, 64.62; H, 7.50; N, 4.68; $C_{15}H_{21}NO_2S$ requires C, 64.48; H, 7.58; N, 5.01.

4.6.6. *N*-Ethyl-2-oct-1-ynyl-benzenesulfonamide (7e). Low melting yellow solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.03 (t, J=7.3 Hz, 1H), 7.55 (d, J=7.3 Hz, 1H), 7.47 (t, J=8.0 Hz, 1H), 7.39 (d, J=8.0 Hz, 1H), 5.14 (br s, NH, 1H), 2.93 (q, J=6.9 Hz, 2H), 2.54 (t, J=7.0 Hz, 3H), 1.70–1.56 (m, 4H), 1.35–1.28 (m, 4H), 1.25 (t, 7.0 Hz, 2H), 1.28 (t, J=7.1 Hz, 3H); IR (cm^{-1}, neat) 3332, 2220, 1462, 1125; *m*/*z* (ES Mass) 294 (M+1, 100%); Elemental analysis found C, 65.58; H, 7.88; N, 4.75; $C_{16}H_{23}NO_2S$ requires C, 65.49; H, 7.90; N, 4.77.

4.6.7. 4-Ethyl-2-hex-1-ynyl-*N*-methyl-benzenesulfonamide (7f). Low melting brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.91 (d, J=8.2 Hz, 1H), 7.40 (s, 1H), 7.22 (d, J=8.2 Hz, 1H), 5.12 (br s, NH, 1H), 2.69 (q, J=7.0 Hz, 2H), 2.58 (d, J=7.9 Hz, 3H), 2.52 (t, J=7.0 Hz, 2H), 1.66–1.64 (m, 2H), 1.40–1.47 (m, 2H), 1.28 (t, J=7.0 Hz, 3H), 0.98 (t, J=7.1 Hz, 3H); IR (cm^{-1}, neat) 3346, 2227, 1332, 1160; *m*/*z* (ES Mass) 280 (M+1, 100%); Elemental analysis found C, 64.39; H, 7.59; N, 5.21; $C_{15}H_{21}NO_2S$ requires C, 64.48; H, 7.58; N, 5.01.

4.6.8. 2-Hept-1-ynyl-4,*N*-dimethyl-benzenesulfonamide (7g). Low melting yellow solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.89 (d, J=8.1 Hz, 1H), 7.38 (s, 1H), 7.21 (d, J=8.1 Hz, 1H), 5.12 (br s, NH, 1H), 2.49 (d, J=7.0 Hz, 3H), 2.47 (t, J=6.5 Hz, 2H), 2.38 (s, 3H), 1.69–1.60 (m, 2H), 1.44 (m, 4H), 0.94 (t, J=6.5 Hz, 3H); IR (cm^{-1}, neat) 3344, 2227, 1325, 1164; *m*/*z* (ES Mass) 280 (M+1, 100%); Elemental analysis found C, 64.51; H, 7.55; N, 4.95; $C_{15}H_{21}NO_2S$ requires C, 64.48; H, 7.58; N, 5.01.

4.6.9. 4,*N*-Dimethyl-2-oct-1-ynyl-benzenesulfonamide (7h). Low melting brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.90 (d, J=8.2 Hz, 1H), 7.23 (s, 1H), 7.19 (d, J=8.2 Hz, 1H), 5.08 (br s, NH, 1H), 2.55 (d, J=6.0 Hz, 3H), 2.46 (t, J=7.0 Hz, 2H), 2.38 (s, 3H), 2.72–1.61 (m, 2H), 1.58–1.41 (m, 2H), 1.39–1.21 (m, 4H), 0.93 (t, J=7.0 Hz, 3H); IR (cm^{-1}, KBr) 3348, 2226, 1332, 1163; *m*/*z* (ES Mass) 294 (M+1, 100%); Elemental analysis found C, 65.75; H, 7.88; N, 4.72; $C_{16}H_{23}NO_2S$ requires C, 65.49; H, 7.90; N, 4.77.

4.6.10. 2-(5-Chloro-pent-1-ynyl)-4,*N*-dimethyl-benzenesulfonamide (7i). Low melting yellow solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.05 (d, J=8.0 Hz, 1H), 7.39 (s, 1H), 7.23 (d, J=8.0 Hz, 1H), 5.03 (br s, NH, 1H), 3.80 (t, J=7.0 Hz, 2H), 2.72 (t, J=7.0 Hz, 2H), 2.56 (d, J=7.8 Hz, 3H), 2.38 (s, 3H), 2.12–1.06 (m 2H); IR (cm^{-1}, neat) 3345, 2228, 1326, 1162; *m*/*z* (ES Mass) 287 (M+1, 100%); Elemental analysis found C, 54.71; H, 5.60; N, 4.98; $C_{13}H_{16}ClNO_2S$ requires C, 54.63; H, 5.64; N, 4.90.

4.6.11. 2-(5-Cyano-pent-1-ynyl)-4,*N*-dimethyl-benzenesulfonamide (7j). Low melting yellow solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.90 (d, J=8.5 Hz, 1H), 7.38 (s, 1H), 7.19 (d, J=8.5 Hz, 1H), 5.23 (br s, NH, 1H), 2.57 (d, J=6.5 Hz, 3H), 2.38 (s, 3H), 2.38–2.27 (m, 4H), 1.29 (t, J=7.0 Hz, 2H); IR (cm^{-1}, neat) 3345, 2226, 1326, 1160; *m*/*z* (ES Mass) 277 (M+1, 100%); Elemental analysis found C, 60.74; H, 5.85; N, 10.27; $C_{14}H_{16}N_2O_2S$ requires C, 60.85; H, 5.84; N, 10.14.

4.6.12. 2-[3-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-prop-1-ynyl]-4-ethyl-*N*-methyl-benzenesulfonamide (7k). Low melting yellow solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.07–7.90 (m, 4H), 7.94–7.84 (m, 2H), 7.40 (s, 1H), 5.88 (br s, NH, 1H), 4.73 (s, 2H), 2.69 (q, J=8.0 Hz, 2H), 2.60 (d, J=6.5 Hz, 3H), 1.25 (t, J=8.0 Hz, 3H); IR (cm^{-1}, neat) 3322, 2228, 1719, 1391, 1160; *m*/*z* (ES Mass) 383 (M+1, 100%); Elemental analysis found C, 62.60; H, 4.79; N, 7.21; $C_{20}H_{18}N_2O_4S$ requires C, 62.81; H, 4.74; N, 7.33.

4.6.13. 4-Ethyl-*N*-methyl-2-phenylethynyl-benzenesulfonamide (7l). Low melting brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.99 (s, 1H), 7.58–7.41 (m, 2H), 7.39–7.32 (m, 3H), 7.27 (d, J=7.8 Hz, 2H), 5.04 (br s, NH, 1H), 2.74 (q, J=8.0 Hz, 2H), 2.61 (d, J=6.5 Hz, 3H), 1.25 (t, J=8.0 Hz, 3H); IR (cm^{-1}, KBr) 3348, 2208, 1331, 1166; *m*/*z* (ES Mass) 300 (M+1, 100%); Elemental analysis found C, 68.09; H, 5.73; N, 4.70; $C_{17}H_{17}NO_2S$ requires C, 68.20; H, 5.72; N, 4.68.

4.6.14. 4,*N*-Dimethyl-2-*p*-tolylethynyl-benzenesulfonamide (7m). Low melting brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.95 (d, J=8.1 Hz, 1H), 7.45 (d, J=8.1 Hz, 1H), 7.21 (s, 1H), 7.15–7.10 (m, 4H), 5.05 (br s, NH, 1H,) 2.60 (d, J=6.5 Hz, 3H), 2.42 (s, 3H), 2.39 (s, 3H); IR (cm^{-1}, KBr) 3323, 2205, 1323, 1144; *m*/*z* (ES Mass) 300 (M+1, 100%); Elemental analysis found C, 68.54; H, 5.70; N, 4.38; $C_{17}H_{17}NO_2S$ requires C, 68.20; H, 5.72; N, 4.68.

4.6.15. 4-Ethyl-*N*-methyl-2-*p*-tolylethynyl-benzenesulfonamide (7n). Low melting brown solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.95 (d, J=8.2 Hz, 1H), 7.45 (d, J=8.2 Hz, 1H), 7.21 (s, 1H), 7.15–7.10 (m, 4H), 5.02 (br s, NH, 1H), 2.60 (d, J=6.0 Hz, 3H), 2.42 (s, 3H), 2.39 (q, J=7.9 Hz, 2H), 0.98 (t, J=8.0 Hz, 3H); IR (cm^{-1}, KBr) 3346, 2210, 1330, 1113; *m*/*z* (ES Mass) 314 (M+1, 100%); Elemental analysis found C, 68.76; H, 6.15; N, 4.58; $C_{18}H_{19}NO_2S$ requires C, 68.98; H, 6.11; N, 4.47.

4.6.16. 2-(5-Chloro-pent-1-ynyl)-4,*N*-dimethyl-benzenesulfonamide (7o). Low melting yellow solid; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.01 (d, J=8.3 Hz, 1H), 7.96 (s, 1H), 7.40 (d, J=8.3 Hz, 2H), 7.18 (d, J=8.3 Hz, 1H), 6.99–6.94 (m, 3H), 5.08 (br s, NH, 1H), 3.85 (s, 3H), 2.60 (d, J=6.5 Hz, 3H); IR (cm^{-1}, neat) 3344, 2224, 1426, 1162; *m*/*z* (ES Mass) 302 (M+1, 100%); Elemental analysis found C, 64.85; H, 4.97; N, 4.49; $C_{16}H_{15}NO_3S$ requires C, 63.77; H, 5.02; N, 4.65.

4.7. Preparation of 4-iodo-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxides (8)

4.7.1. Typical procedure for the preparation of 8n. To a stirred mixture of **7n** (0.20 g, 0.638 mmol) and K_2CO_3 (0.264 g, 1.194 mmol) in acetonitrile (5 mL) was added 2.5 equiv of I_2 (0.405 g, 1.59 mmol) dissolved in acetonitrile (2 mL). The reaction mixture was stirred at room temperature (25 °C) for 8 h. After completion of the reaction (indicated by TLC), the mixture was diluted with cold water (10 mL), washed with a saturated solution of $Na_2S_2O_3$ (15 mL), and extracted with ethyl acetate (50 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether to afford the desired product as a white solid (0.245 g, 87%).

4.7.2. 3-(2-Ethyl-4-iodo-1,1-dioxo-1,2-dihydro-1λ^6-benzo[*e*][1,2]thiazin-3-yl)propan-1-ol (8a). Low melting yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.11 (d, J=7.6 Hz, 1H), 7.86 (d, J=7.0 Hz, 1H), 7.77 (t, J=7.6 Hz, 1H), 7.70 (t, J=7.0 Hz, 1H), 3.50 (q, J=7.5 Hz, 2H), 3.52–3.37 (m, 2H), 2.94–2.87 (m, 1H), 2.57–2.39 (m, 1H), 2.22–2.13 (m, 2H), 1.14 (t, J=7.5 Hz, 3H); IR (cm^{-1}, neat) 3428, 1337, 1146; *m*/*z* (ES Mass) 394 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 155.0, 137.0, 131.9, 131.6, 128.0, 126.5, 125.4, 63.1 (CH_2), 58.9 (C–I), 34.8 (NCH_2), 27.5 (CH_2), 26.1 (CH_2), 12.7 (CH_3); HPLC 99.73%, column Inertsil ODS 3V (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: acetonitrile, gradient (T/% B): 0/40, 2/40, 12/80, 20/80, 21/40, 22/40, flow rate: 1.0 mL/min, UV 210 nm, retention time 9.98 min; Elemental analysis found C, 39.59; H, 4.12; N, 3.67; $C_{13}H_{16}INO_3S$ requires C, 39.71; H, 4.10; N, 3.56.

4.7.3. 2-(4-Iodo-6-methoxy-2-methyl-1,1-dioxo-1,2-dihydro-1λ^6-benzo[*e*][1,2]thiazin-3-yl)-ethanol (8b). Low melting brown solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J=8.4 Hz, 1H), 7.37 (s, 1H), 7.01 (d, J=8.4 Hz, 1H), 4.04–3.92 (m, 2H), 3.91 (s, 3H), 3.11 (s, 3H), 3.10–3.03 (m, 2H), 2.16 (br s, –OH, 1H); IR (cm^{-1}, KBr) 3545, 1331, 1140; *m*/*z* (ES Mass) 396 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 162.7, 144.5, 135.9, 124.5, 122.9, 117.7, 116.4, 61.6 (CH_2), 60.8 (OCH_3), 55.9 (C–I), 40.6 (NCH_3), 34.2 (CH_2); HPLC 98.94%, Hichrom RPB

(250×4.6) mm, mobile phase A: 0.01 M KH_2PO_4 (pH 6.5 with KOH), mobile phase B: acetonitrile, gradient (T/% B): 0/60, 5/60, 15/80, 30/80, 34/60, 35/60, flow rate: 1.0 mL/min, UV 210 nm, retention time 17.16 min; Elemental analysis found C, 36.38; H, 3.55; N, 3.63; $C_{12}H_{14}INO_4S$ requires C, 36.47; H, 3.57; N, 3.54.

4.7.4. 3-(4-Iodo-6-methoxy-2-methyl-1,1-dioxo-1,2-dihydro-1-λ⁶-benzo[*e*][1,2]thiazin-3-yl)-propan-1-ol (8c). White solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (s, 1H), 7.63 (d, J=7.1 Hz, 1H), 7.30 (d, J=7.1 Hz, 1H), 3.80 (t, J=7.0 Hz, 2H), 3.16 (s, 3H), 2.96 (t, J=7.1 Hz, 2H), 2.48 (s, 3H), 1.99–1.97 (m, 2H), 1.56 (br s, 1H, –OH); IR (cm^{-1}, KBr) 3545, 1331, 1140; *m/z* (ES Mass) 410 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 149.8, 143.2, 133.9, 132.7, 130.6, 129.6, 122.1, 61.5 (CH_2), 55.8 (OCH_3), 53.6 (C–I), 32.6 (NCH_3), 27.2 (CH_2), 19.2 (CH_2); HPLC 99.42%, Inertsil ODS 3V (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: CH_3CN, gradient (T/% B): 0/40, 2/40, 14/80, 25/80, 29/40, 30/40, flow rate: 1.5 mL/min, UV 210 nm, retention time 13.63 min; Elemental analysis found C, 38.41; H, 3.85; N, 3.23; $C_{13}H_{16}INO_4S$ requires C, 38.15; H, 3.94; N, 3.42.

4.7.5. 2-Ethyl-4-iodo-3-pentyl-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide (8d). Low melting yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80–7.74 (m, 2H), 7.62 (t, J=8.2 Hz, 1H), 7.45 (t, J=8.2 Hz, 1H), 3.44–3.33 (m, 2H), 3.52 (q, J=7.0 Hz, 2H), 2.89–2.73 (m, 2H), 1.74–1.67 (m, 2H), 1.56–1.30 (m, 2H), 1.28 (t, J=7.0 Hz, 3H), 0.95 (t, J=4.0 Hz, 3H); IR (cm^{-1}, neat) 3524, 1432, 1121; *m/z* (ES Mass) 406 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156.6, 144.9, 134.3, 133.2, 132.1, 130.1, 128.6, 86.3, 39.1, 37.8 (CH_2), 32.2 (CH_2), 30.6 (CH_2), 29.2 (CH_2), 29.2 (CH_3), 19.6 (CH_3); HPLC 99.20, Symmetry shield RP8 (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: CH_3CN, gradient (T/% B): 0/50, 2/50, 12/80, 20/80, 21/50, 22/50, flow rate: 1.5 mL/min, UV 210 nm, retention time 9.44 min; Elemental analysis found C, 44.64; H, 4.91; N, 3.26; $C_{15}H_{20}INO_2S$ requires C, 44.45; H, 4.97; N, 3.46.

4.7.6. 2-Ethyl-3-hexyl-4-iodo-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide (8e). Low melting yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.83 (d, J=7.8 Hz, 1H), 7.75 (d, J=7.5 Hz, 1H), 7.61 (t, J=7.8 Hz, 1H), 7.51 (t, J=7.5 Hz, 1H), 3.51 (q, J=7.0 Hz, 2H), 2.93 (t, J=7.1 Hz, 2H), 1.71–1.64 (m, 2H), 1.54–1.41 (m, 2H), 1.37–1.17 (m, 4H), 1.14 (t, J=7.0 Hz, 3H), 0.92 (t, J=7.2 Hz, 3H); IR (cm^{-1}, neat) 3525, 1335, 1182; *m/z* (ES Mass) 420 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 156.6, 144.9, 134.3, 133.2, 132.1, 130.1, 128.6, 77.8, 39.1 (CH_2), 37.8 (CH_2), 32.2 (CH_2), 30.6 (CH_2), 29.2 (CH_2), 19.6 (CH_2), 17.7 (CH_3), 14.8 (CH_3); HPLC 98.39%, Inertsil ODS 3V (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: acetonitrile, gradient (T/% B): 0/40, 2/40, 12/80, 20/80, 21/40, 22/40, flow rate: 1.0 mL/min, UV 210 nm, retention time 7.60 min; Elemental analysis found C, 45.67; H, 5.38; N, 3.65; $C_{16}H_{22}INO_2S$ requires C, 45.83; H, 5.29; N, 3.34.

4.7.7. 3-Butyl-6-ethyl-4-iodo-2-methyl-2*H*-benzo[*e*][1,2]-thiazine-1,1-dioxide (8f). Low melting white solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (s, 1H), 7.65 (d, J=8.1 Hz, 1H), 7.30 (d, J=8.1 Hz, 1H), 3.17 (s, 3H), 2.98–2.71 (m, 4H), 2.81 (q, J=8.5 Hz, 2H), 1.72–1.63 (m, 2H), 1.30 (t, J=8.5 Hz, 3H), 0.95 (t, J=8.0 Hz, 3H); IR (cm^{-1}, KBr) 3545, 1331, 1140; *m/z* (ES Mass) 406 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 149.2, 146.0, 134.0, 131.6 (2C), 130.8, 129.4, 56.0 (C–I), 33.3 (NCH_3), 29.7 (CH_2), 29.1 (CH_2), 23.7 (CH_2), 21.9 (CH_2), 15.4 (CH_3), 15.0 (CH_3); HPLC 98.31%, Hichrom RPB (250×4.6) mm, mobile phase: A: 0.01 M KH_2PO_4 (pH 6.5 with KOH), mobile phase B: acetonitrile, gradient (T/% B): 0/50, 5/50, 20/80, 30/80, 34/50, 35/50, flow rate: 1.0 mL/min, UV: 210 nm, retention time 12.34 min; Elemental analysis found C, 44.45; H, 5.29; N, 3.46; $C_{15}H_{20}INO_2S$ requires C, 44.43; H, 5.28; N, 3.47.

4.7.8. 4-Iodo-2,6-dimethyl-3-pentyl-2*H*-benzo[*e*][1,2]-thiazine-1,1-dioxide (8g). Low melting yellow solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (s, 1H), 7.63 (d, J=7.0 Hz, 1H), 7.28 (d, J=7.0 Hz, 1H), 3.16 (s, 3H), 2.81–2.79 (m, 2H), 2.47 (s, 3H), 1.73–1.65 (m, 2H), 1.54–1.42 (m, 2H), 1.39–1.25 (m, 2H), 0.94–0.90 (t, J=4.5 Hz, 3H); IR (cm^{-1}, neat) 3524, 1432, 1121; *m/z* (ES Mass) 406 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 146.1, 142.9, 133.9, 132.5, 130.7, 128.6, 121.8, 58.0 (C–I), 37.9 (NCH_3), 31.5 (CH_2), 29.9 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 26.9 (CH_3), 14.0 (CH_3); HPLC 99.20%, Symmetry shield RP8 (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: acetonitrile, gradient (T/% B): 0/50, 2/50, 12/80, 20/80, 21/50, 22/50, flow rate: 1.5 mL/min, UV 210 nm, retention time 9.44 min; Elemental analysis found C, 44.75; H, 4.90; N, 3.37; $C_{15}H_{20}INO_2S$ requires C, 44.45; H, 4.97; N, 3.46.

4.7.9. 3-Hexyl-4-iodo-2,6-dimethyl-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide (8h). Low melting yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (s, 1H), 7.63 (d, J=8.1 Hz, 1H), 7.28 (d, J=8.1 Hz, 1H), 3.16 (s, 3H), 2.81–2.79 (m, 2H), 2.47 (s, 3H), 1.73–1.65 (m, 2H), 1.54–1.42 (m, 3H), 1.39–1.25 (m, 3H), 0.94–0.90 (m, 3H); IR (cm^{-1}, neat) 3526, 1335, 1144; *m/z* (ES Mass) 420 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 146.10, 142.9, 133.9, 132.5, 130.7, 128.6, 121.8, 58.2 (C–I), 37.9 (NCH_3), 31.5 (CH_2), 29.9 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 26.9 (CH_2), 22.9 (CH_3), 14.0 (CH_3); HPLC 98.72%, ACE 5 C18 (250×4.0) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: acetonitrile, gradient (T/% B): 0/30, 2/30, 13/80, 26/80, 28/30, 30/30, flow rate: 1.0 mL/min, UV 210 nm, retention time 12.38 min; Elemental analysis found C, 45.99; H, 5.26; N, 3.30; $C_{16}H_{22}INO_2S$ requires C, 45.83; H, 5.29; N, 3.34.

4.7.10. 3-(3-Chloro-propyl)-4-iodo-2,6-dimethyl-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide (8i). Low melting yellow solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (s, 1H), 7.65 (d, J=7.0 Hz, 1H), 7.35 (d, J=7.0 Hz, 1H), 3.71 (t, J=7.0 Hz, 2H), 3.28 (t, J=6.5 Hz, 2H), 3.07 (s, 3H), 2.48 (s, 3H), 2.25–2.19 (m, 2H); IR (cm^{-1}, neat) 3534, 1433, 1112; *m/z* (ES Mass) 412 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.1, 141.0, 134.2, 132.9, 130.9, 125.4 (2C), 58.2 (C–I), 44.1 (CH_2), 33.2 (NCH_3), 29.9 (CH_2), 23.5 (CH_2), 21.8 (CH_3); HPLC 99.23%, Inertsil ODS 3V (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: acetonitrile, gradient (T/% B): 0/40, 2/40, 12/80, 20/80, 21/40, 22/40, flow rate: 1.0 mL/min, UV 210 nm, retention time

9.81 min; Elemental analysis found C, 37.64; H, 3.77; N, 3.48; $C_{13}H_{15}ClINO_2S$ requires C, 37.93; H, 3.67; N, 3.40.

4.7.11. 4-(4-Iodo-2,6-dimethyl-1,1-dioxo-1,2-dihydro-1-benzo[*e*][1,2]thiazin-3-yl)-butyronitrile (8j). Low melting brown solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J=8.2 Hz, 1H), 7.55 (s, 1H), 7.28 (d, J=8.2 Hz, 1H), 3.11–3.00 (m, 1H), 2.99 (s, 3H), 2.98–2.87 (m, 1H), 2.53–2.50 (m, 2H), 2.49 (s, 3H), 2.11 (t, J=6.5 Hz, 2H); IR (cm^{-1}, neat) 3534, 1432, 1133; *m/z* (ES Mass) 403 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 153.7, 144.4, 143.2, 133.6, 132.7, 132.5, 129.8, 122.0, 79.4, 30.1 (NCH_3), 24.0 (CH_2), 23.1 (CH_2), 21.5 (CH_3), 15.9 (CH_2); HPLC 99.20%, Symmetry shield RP8 (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: acetonitrile, gradient (T/% B): 0/50, 2/50, 12/80, 20/80, 21/50, 22/50, flow rate: 1.5 mL/min, UV 210 nm, retention time 10.09 min; Elemental analysis found C, 41.58; H, 3.74; N, 6.99; $C_{14}H_{15}IN_2O_2S$ requires C, 41.80; H, 3.76; N, 6.96.

4.7.12. 2-(6-Ethyl-4-iodo-2-methyl-1,1-dioxo-1,2-dihydro-1λ^6-benzo[*e*][1,2]thiazin-3-ylmethyl)-isoindole-1,3-dione (8k). Off-white solid; mp 198–200 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (t, J=8.0 Hz, 1H), 7.94 (d, J=8.2 Hz, 1H), 7.92 (t, J=8.0 Hz, 1H), 7.76 (d, J=8.0 Hz, 1H), 7.40 (d, J=7.0 Hz, 1H), 7.26 (d, J=7.2 Hz, 1H), 7.95 (s, 1H), 2.68 (q, J=7.5 Hz, 2H), 2.50 (s, 3H), 2.49 (s, 2H), 1.18 (t, J=8.0 Hz, 3H); IR (cm^{-1}, KBr) 3331, 1716 (C═O), 1390, 1160; *m/z* (ES Mass) 509 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 166.9 (2C), 149.2, 145.9, 141.7, 139.0, 134.8 (2C), 133.1, 131.5, 129.2 (2C), 128.3, 123.5, 123.4, 56.7 (C–I), 40.8 (CH_2), 33.6 (NCH_3), 28.9 (CH_2), 15.0 (CH_3); HPLC 98.17%, Inertsil ODS 3V (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: acetonitrile, gradient (T/% B): 0/30, 2/30, 12/80, 18/80, 19/30, 20/30; flow rate: 1.5 mL/min, UV 225 nm, retention time 8.92 min; Elemental analysis found C, 47.57; H, 3.30; N, 5.48; $C_{20}H_{17}IN_2O_4S$ requires C, 47.26; H, 3.37; N, 5.51.

4.7.13. 6-Ethyl-4-iodo-2-methyl-3-phenyl-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide (8l). White solid; mp 98–99 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, J=8.0 Hz, 1H), 7.55–7.51 (m, 2H), 7.49–7.40 (m, 4H), 7.36 (d, J=8.2 Hz, 1H), 2.92 (s, 3H), 2.82 (q, J=7.9 Hz, 2H), 1.32 (t, J=8.0 Hz, 3H); IR (cm^{-1}, KBr) 3549, 1455, 1325; *m/z* (ES Mass) 426 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 149.4, 145.1, 140.1, 137.7, 134.5, 132.5, 130.9, 130.0, 129.9 (2C), 128.8, 128.5, 121.9, 59.2 (C–I), 35.3 (NCH_3), 29.1 (CH_2), 15.4 (CH_3); HPLC 97.08%, Inertsil ODS 3V (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: acetonitrile, gradient (T/% B): 0/50, 2/50, 8/80, 24/80, 25/50, 26/50, flow rate: 1.0 mL/min, UV 210 nm, retention time 13.37 min; Elemental analysis found C, 47.64; H, 3.82; N, 3.38; $C_{17}H_{16}INO_2S$ requires C, 48.01; H, 3.79; N, 3.29.

4.7.14. 4-Iodo-2,6-dimethyl-3-*p*-tolyl-2*H*-benzo[*e*][1,2]-thiazine-1,1-dioxide (8m). White solid; mp 158–160 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (d, J=8.1 Hz, 2H), 7.42 (d, J=8.0 Hz, 2H), 7.34 (d, J=8.2 Hz, 2H), 7.29 (s, 1H), 2.91 (s, 3H), 2.51 (s, 3H), 2.43 (s, 3H); IR (cm^{-1}, KBr) 3545, 1336, 1169; *m/z* (ES Mass) 426 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 145.2, 143.1, 140.1, 134.7, 134.6, 133.4, 133.4, 129.9, 129.7 (2C), 129.2, 123.2, 121.8, 58.3 (C–I), 35.3 (NCH_3), 21.8 (CH_3), 21.5 (CH_3); HPLC 98.95%, Inertsil ODS 3V (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4 (pH 6.5 with KOH), mobile phase B: acetonitrile, gradient (T/% B): 0/60, 2/60, 8/60, 20/80, 24/60, 25/60; flow rate: 1.5 mL/min, UV 210 nm, retention time 9.47 min; Elemental analysis found C, 48.12; H, 3.75; N, 3.20; $C_{17}H_{16}INO_2S$ requires C, 48.01; H, 3.79; N, 3.29.

4.7.15. 6-Ethyl-4-iodo-2-methyl-3-*p*-tolyl-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide (8n). White solid; mp 102–104 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (d, J=8.1 Hz, 1H), 7.73 (d, J=8.2 Hz, 1H), 7.43 (d, J=8.1 Hz, 1H), 7.42 (d, J=8.2 Hz, 1H), 7.38 (d, J=8.0 Hz, 2H), 7.36 (s, 1H), 2.91 (s, 3H), 2.81 (q, J=8.0 Hz, 2H), 2.43 (s, 3H), 1.33 (t, J=8.0 Hz, 3H); IR (cm^{-1}, KBr) 3545, 1342, 1183; *m/z* (ES Mass) 440 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 149.4, 145.2, 140.1, 134.8, 134.6, 132.5 (2C), 129.9 (2C), 129.2, 128.7, 121.9, 121.2, 58.3, 35.3 (NCH_3), 29.1 (CH_2), 21.5 (CH_3), 15.4 (CH_3); HPLC 98.16%, Symmetry shield RP8 (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: acetonitrile, gradient (T/% B): 0/50, 2/50, 12/80, 20/80, 24/50, 25/50, flow rate: 1.5 mL/min, UV 210 nm, retention time 11.03 min; Elemental analysis found C, 49.01; H, 4.18; N, 3.29; $C_{18}H_{18}INO_2S$ requires C, 49.21; H, 4.13; N, 3.19.

4.7.16. 4-Iodo-6-methoxy-2-methyl-3-phenyl-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide (8o). Low melting brown solid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, J=7.0 Hz, 1H), 7.52 (d, J=7.0 Hz, 1H), 7.51–7.50 (m, 2H), 7.49–7.43 (m, 3H), 7.05 (s, 1H), 3.93 (s, 3H), 2.92 (s, 3H); IR (cm^{-1}, KBr) 3543, 1452, 1324, 1170; *m/z* (ES Mass) 428 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 145.1, 142.8, 139.0, 134.0, 132.9, 129.3, 128.4 (2C), 127.7, 126.4, 126.2 (2C), 113.6, 56.7, 55.3, 34.7 (CH_3); HPLC 98.90%, Inertsil ODS 3V (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: acetonitrile, gradient (T/% B): 0/30, 2/30, 12/80, 18/80, 19/30, 20/30, flow rate: 1.0 mL/min, UV 240 nm, retention time 6.79 min; Elemental analysis found C, 44.58; H, 3.32; N, 3.20; $C_{16}H_{14}INO_3S$ requires C, 44.98; H, 3.30; N, 3.28.

4.8. Preparation of 5-(2,6-dimethyl-1,1-dioxo-3-*p*-tolyl-1,2-dihydro-1-benzo[*e*][1,2]thiazin-4-yl)-pent-4-yn-1-ol (9a)

A mixture of compound **8m** (0.2 g, 0.470 mmol), $Pd(PPh_3)Cl_2$ (16 mg, 0.023 mmol), CuI (5 mg, 0.028 mmol), and triethylamine (0.190 g, 0.262 mL, 1.88 mmol) in acetonitrile (8 mL) was stirred at 25 °C for 30 min under nitrogen. 4-Pentyne-1-ol (0.118 g, 0.130 mL, 1.41 mmol) was added slowly to the mixture with stirring. The resulting mixture was then stirred at 25 °C for 12 h, diluted with water (50 mL), and extracted with ethyl acetate (3×20 mL). The organic layers were collected, combined, dried over anhydrous Na_2SO_4, and concentrated under low vacuum. The residue was then purified by column chromatography using petroleum ether–ethyl acetate to give the desired product as a low melting colorless solid (0.150 g, 84% yield); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, J=7.0 Hz, 2H), 7.64 (d, J=8.0 Hz, 2H), 7.34 (d, J=7.0 Hz, 2H), 7.25 (s, 1H), 3.60 (t, J=6.0 Hz, 2H), 2.93

(s, 3H), 2.50 (s, 3H), 2.46 (t, J=7.0 Hz, 2H), 2.42 (s, 3H), 1.75–1.68 (m, 2H), 1.54 (br s, 1H, –OH); IR (cm^{-1}, neat) 3396, 1339, 1170; *m/z* (ES Mass) 382 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 146.5, 142.7, 139.9 (2C), 129.9, 129.9, 128.9, 128.9, 128.9, 128.8, 128.8, 127.7, 121.7, 108.5, 94.8, 77.6, 61.3 (CH_2), 35.3 (NCH_3), 30.9 (CH_2), 21.8 (CH_2), 21.4 (CH_3), 16.0 (CH_3); HPLC 98.42%, Inertsil ODS 3V (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: acetonitrile, gradient (T/% B): 0/40, 2/40, 12/80, 20/80, 21/40, 22/40, flow rate: 1.5 mL/min, UV 210 nm, retention time 8.73 min; Elemental analysis found C, 69.32; H, 6.06; N, 3.61; $C_{22}H_{23}NO_3S$ requires C, 69.26; H, 6.08; N, 3.67.

4.9. Preparation of 3-(2,6-dimethyl-1,1-dioxo-3-*p*-tolyl-1,2-dihydro-1-benzo[*e*][1,2]thiazine-4-yl)-acrylic acid ethyl ester (9b)

To a solution of **8m** (0.175 g, 0.41 mmol) and ethyl acrylate (0.164 g, 1.64 mmol, 4.0 equiv) in DMF (10 mL) were added $Pd(OAc)_2$ (0.005 g, 0.022 mmol), n-Bu_4NCl (0.114 g, 0.41 mmol), and Na_2CO_3 (0.11 g, 1.03 mmol). The mixture was then stirred at 85 °C for 1 h under nitrogen. After completion of the reaction (indicated by TLC), the mixture was cooled to room temperature, diluted with water (80 mL), and extracted with ethyl acetate (3×15 mL). Organic layers were collected, combined, washed with saturated aq NaCl solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate–petroleum ether to afford the desired product (150 mg, 92% yield) as yellow powder; mp 142–144 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, J=8.0 Hz, 1H), 7.72 (s, 1H), 7.60 (d, J=16.1 Hz, 1H), 7.39–7.38 (m, 3H), 7.37 (d, J=7.0 Hz, 2H), 6.17 (d, J=16.8 Hz, 1H), 4.14 (q, J=7.0 Hz, 2H), 2.91 (s, 3H), 2.50 (s, 3H), 1.53 (s, 3H), 1.22 (t, J=7.0 Hz, 3H); IR (cm^{-1}, KBr) 3405, 1718, 1336, 1179; *m/z* (ES Mass) 398 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 167.1 (C═O), 146.2, 142.3, 140.6, 140.4, 132.3, 130.9, 129.9 (2C), 129.8 (2C), 129.5, 129.0, 127.6, 122.2, 120.5, 117.4, 60.3 (OCH_2), 34.2 (NCH_3), 21.9 (CH_2), 21.4 (CH_3), 14.2 (CH_3); HPLC 97.50%, Inertsil ODS 3V (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: acetonitrile, gradient (T/% B): 0/40, 2/40, 12/80, 20/80, 21/40, 22/40, flow rate: 1.5 mL/min, UV 210 nm, retention time 11.20 min; Elemental analysis found C, 66.35; H, 5.81; N, 3.60; $C_{22}H_{23}NO_4S$ requires C, 66.48; H, 5.83; N, 3.52.

4.10. Preparation of 1-[3-(2,6-dimethyl-1,1-dioxo-3-*p*-tolyl-1,2-dihydro-1-benzo[*e*][1,2]thiazine-4-yl)-phenyl]-ethanone (9c)

To a mixture of **8m** (0.2 g, 0.47 mmol) and 3-acetyl bezeneboronic acid (0.083 g, 0.51 mmol) in DMF (10 mL) were added $Pd(PPh_3)_4$ (0.016 g, 0.014 mmol) and 2 M Na_2CO_3 solution (0.4 g, 3.77 mmol in 3.5 mL of water). The mixture was then stirred at 80 °C under for 2 h under nitrogen. After completion of the reaction (indicated by TLC), the mixture was cooled to room temperature, diluted with water (80 mL), and extracted with ethyl acetate (3×20 mL). Organic layers were collected, combined, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography using ethyl acetate–hexane to afford the desired product (160 mg, 82% yield) as white powder; mp 164–165 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, J=8.1 Hz, 1H), 7.81 (s, 1H), 7.80 (d, J=8.1 Hz, 1H), 7.41–7.25 (m, 4H), 7.13 (d, J=7.5 Hz, 1H), 7.00–6.95 (m, 3H), 2.98 (s, 3H), 2.52 (s, 3H), 2.33 (s, 3H), 2.24 (s, 3H); IR (cm^{-1}, KBr) 3423, 1684 (C═O), 1335, 1171; *m/z* (ES Mass) 418 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 182.3 (C═O), 141.5, 138.6, 136.8, 136.0, 133.6, 131.2, 130.9, 129.9, 128.9 (2C), 128.7 (2C), 128.6 (2C), 128.3 (2C), 127.1, 126.9, 122.4, 121.8, 34.1 (NCH_3), 26.6 (CH_3), 21.8 (CH_3), 15.7 (CH_3); HPLC 99.32%, Inertsil ODS 3V (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: acetonitrile, gradient (T/% B): 0/40, 2/40, 12/80, 20/80, 21/40, 22/40, flow rate: 1.0 mL/min, UV 210 nm, retention time 10.30 min; Elemental analysis found C, 71.81; H, 5.57; N, 3.39; $C_{25}H_{23}NO_3S$ requires C, 71.92; H, 5.55; N, 3.35.

4.11. Preparation of 6-ethyl-2-methyl-3-*p*-tolyl-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide (9d)

To a mixture of compound **8m** (0.160 g, 0.364 mmol) and sodium formate (0.042 g, 0.620 mmol) in DMF (2 mL) was added $Pd(PPh_3)_4$ (0.016 g, 0.0145 mmol) and the mixture was stirred at 80 °C for about 3 h under nitrogen. The mixture was then cooled to room temperature, diluted with water (70 mL), washed with saturated NaCl solution (25 mL), and extracted with ethyl acetate (3×10 mL). Organic layers were collected, combined, dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using ethyl acetate–hexane to afford the desired product (90 mg, 78% yield) as white powder; mp 101–102 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.80 (s, 1H), 7.56 (dd, J=7.4 and 2.0 Hz, 2H), 7.33 (dd, J=7.4 and 1.8 Hz, 2H), 7.25 (dd, J=8.0 and 2.0 Hz, 2H), 6.65 (s, 1H), 2.99 (s, 3H), 2.74 (q, J=8.0 Hz, 2H), 2.41 (s, 3H), 1.30 (t, J=7.8 Hz, 3H); IR (cm^{-1}, KBr) 3545, 1332, 1145; *m/z* (ES Mass) 314 (M+1, 100%); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 148.9, 144.7, 139.9, 133.0, 131.9, 129.6, 129.5, 128.9, 127.8, 127.5 (2C), 126.6, 122.5, 96.8 (CH═), 35.7 (NCH_3), 28.9 (CH_2), 21.3 (CH_3), 15.3 (CH_3); HPLC 97.32%, Inertsil ODS 3V (150×4.6) mm, mobile phase A: 0.01 M KH_2PO_4, mobile phase B: acetonitrile, gradient (T/% B): 0/40, 2/40, 12/80, 20/80, 21/40, 22/40, flow rate: 1.0 mL/min, UV 210 nm, retention time 7.92 min; Elemental analysis found C, 66.77; H, 6.13; N, 4.51; $C_{18}H_{19}NO_2S$ requires C, 66.98; H, 6.11; N, 4.47.

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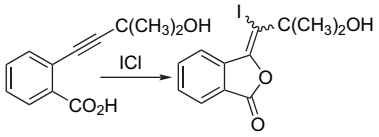
Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.12.040.

References and notes

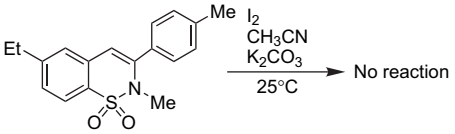
1. For excellent reviews, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079; (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285; (c) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127; (d) Vizer, S. A.; Yerzhanov, K. B.; Al Aziz Al Quntar, A.; Dembitsky, V. M. *Tetrahedron* **2004**, *60*, 5499.
2. (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764; (b) Kundu, N. G.; Khan, M. W. *Tetrahedron* **2000**, *56*, 4777; (c) Lane, C.; Snieckus, V. *Synlett* **2000**, 1294; (d) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Tetrahedron* **2001**, *57*, 8017.
3. Frederickson, M.; Grigg, R. *Org. Prep. Proced. Int.* **1997**, *29*, 33.
4. For benzo[*b*]furans, see: (a) Banwell, M. G.; Flynn, B. L.; Willis, A. C.; Hamel, E. *Aust. J. Chem.* **1999**, *52*, 767; (b) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432; (c) Colobert, F.; Castanet, A.-S.; Abillard, O. *Eur. J. Org. Chem.* **2005**, 3334; (d) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292; For benzo[*b*]thiophenes, see: (e) Yue, D.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 1905; (f) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2003**, *5*, 4377.
5. (a) For furopyridines, see: Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2002**, *4*, 2409; (b) For furoquinolines, see: Aillaud, I.; Bossharth, E.; Conreaux, D.; Desbordes, P.; Monteiro, N.; Balme, G. *Org. Lett.* **2006**, *8*, 1113.
6. For furopyrimidines, see: Rao, M. S.; Esho, N.; Sergeant, C.; Roman, D. *J. Org. Chem.* **2003**, *68*, 6788.
7. For indoles, see: (a) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037; (b) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406; (c) Yao, D.; Yue, D.; Larock, R. C. *J. Comb. Chem.* **2005**, *7*, 809.
8. For isoquinolines and naphthyridines, see: Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437.
9. For isoindolinones, see: Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432.
10. For isochromenes, see: (a) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028; (b) Yue, D.; Della Ca, N.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581.
11. For isocoumarins, see: (a) Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936; (b) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067; (c) For phosphaisocoumarins, see: Peng, A.-Y.; Ding, Y.-X. *Org. Lett.* **2004**, *6*, 1119.
12. For coumestans, see: Yao, T.; Yue, D.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 9985.
13. For other recent examples of iodonium-promoted heterocyclizations of acetylenic compounds, see: (a) Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, *7*, 1769; (b) Liu, Y.; Song, F.; Cong, L. *J. Org. Chem.* **2005**, *70*, 6999; (c) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 7679; (d) Liu, Y.; Zhou, S. *Org. Lett.* **2005**, *7*, 4609; (e) Waldo, J. P.; Larock, R. C. *Org. Lett.* **2005**, *7*, 5203; (f) For iodocyclization of sulfonamide derivatives of *o*-(1-alkynyl)anilines leading to 3-iodoindoles, see: Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539.
14. (a) Pal, M.; Madan, M.; Srinivas, P.; Pattabiraman, V. R.; Kalleda, S. R.; Akhila, V.; Ramesh, M.; Rao Mamidi, N. V. S.; Casturi, S. R.; Malde, A.; Gopalakrishnan, B.; Yeleswarapu, K. R. *J. Med. Chem.* **2003**, *46*, 3975; (b) Pal, M.; Veeramaneni, V. R.; Kumar, S.; Vangoori, A.; Mullangi, R.; Misra, P.; Rajjak, S. A.; Lohray, V. B.; Casturi, S. R.; Yeleswarapu, K. R. *Lett. Drug Des. Discovery* **2005**, *2*, 329; (c) Pal, M.; Veeramaneni, V. R.; Kumar, S.; Lohray, V. B.; Yeleswarapu, K. R. *J. Indian Chem. Soc.* **2003**, *80*, 1095.
15. Lombardino, J. G.; Wiseman, E. H. *Med. Res. Rev.* **1982**, *2*, 127.
16. Lazer, E. S.; Miao, C. K.; Cywin, C. L.; Sorcek, R.; Wong, H.-C.; Meng, Z.; Potocki, I.; Hoermann, M.; Snow, R. J.; Tschantz, M. A.; Kelly, T. A.; McNeil, D. W.; Coutts, S. J.; Churchill, L.; Graham, A. G.; David, E.; Grob, P. M.; Engel, W.; Meier, H.; Trummlitz, G. *J. Med. Chem.* **1997**, *40*, 980 and references cited therein.
17. Layman, W. J., Jr.; Greenwood, T. D.; Downey, A. L.; Wolfe, J. F. *J. Org. Chem.* **2005**, *70*, 9147.
18. (a) Sianesi, E.; Redaelli, R.; Magistretti, M. J.; Massarani, E. *J. Med. Chem.* **1973**, *16*, 1133; (b) Lombardino, J. G.; Wiseman, E. H. *J. Med. Chem.* **1971**, *14*, 973; (c) Catsoulacos, P. *J. Heterocycl. Chem.* **1971**, *8*, 947; (d) Hauser, C. R.; Wantanabe, H.; Mao, C.-L.; Barnish, I. T. *J. Org. Chem.* **1969**, *34*, 919; (e) Takeuchi, Y.; Liu, Z.; Satoh, A.; Shiragami, T.; Shibata, N. *Chem. Pharm. Bull.* **1999**, *47*, 1730; (f) Wells, G. J.; Tao, M.; Josef, K. A.; Bihovsky, R. *J. Med. Chem.* **2001**, *44*, 3488; (g) Vidal, A.; Madelmont, J.-C.; Mounetou, E. *Synthesis* **2006**, 591.
19. Harmata, M.; Rayanil, K.-o.; Gomes, M. G.; Zheng, P.; Calkins, N. L.; Kim, S.-Y.; Fan, Y.; Bumbu, V.; Lee, D. R.; Wacharasindhu, S.; Hong, X. *Org. Lett.* **2005**, *7*, 143.
20. Our interest stems from the fact that in 1992 one of us (MP) observed that iodocyclization of *o*-(1-alkynyl)benzoic acid, generated in situ under Sonogashira conditions, in the presence of ICl afforded the corresponding 3-iodo substituted ylidenephthalide, see: (a) Kundu, N. G.; Pal, M.; Nandi, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 561; (b) Kundu, N. G.; Pal, M. *J. Chem. Soc., Chem. Commun.* **1993**, 86.



21. (a) Batchu, V. R.; Subramanian, V.; Parasuraman, K.; Swamy, N. K.; Kumar, S.; Pal, M. *Tetrahedron* **2005**, *61*, 9869; (b) Subramanian, V.; Batchu, V. R.; Barange, D.; Pal, M. *J. Org. Chem.* **2005**, *70*, 4778; (c) Pal, M.; Batchu, V. R.; Swamy, N. K.; Padakanti, S. *Tetrahedron Lett.* **2006**, *47*, 3923; (d) MacNeil, S. L.; Familoni, O. B.; Snieckus, V. *J. Org. Chem.* **2001**, *66*, 3662.
22. For a review, see: Seki, M. *Synthesis* **2006**, 2975.
23. Dimerization of terminal alkynes (Glaser coupling), a side reaction often observed under the Sonogashira coupling conditions, predominates in the presence of oxygen or other reagents, see for example: (a) Kundu, N. G.; Pal, M.; Chowdhury, C. *J. Chem. Res. Synop.* **1993**, 432; (b) Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 1969; (c) Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 5752; (d) Batsanov, A. S.; Collings, J. C.; Fairlamb, I. J. S.; Holland, J. P.; Howard, J. A. K.; Lin, Z.; Marder, T. B.; Parsons, A. C.; Ward, R. M.; Zhu, J. *J. Org. Chem.* **2005**, *70*, 703; (e) Fairlamb, I. J. S.; Bauerlein, P. S.; Marrison, L. R.; Dickinson, J. M. *Chem. Commun.* **2003**, 632; (f) Formation of 5–10% of dimeric product was observed when arylalkynes were used. CuI in the presence of an amine base is known to

have a significant role in the oxidative homocoupling of terminal acetylenes and arylalkynes perhaps due to their higher reactivity than other alkynes are prone to undergo faster oxidative homocoupling.

24. Single crystals suitable for X-ray diffraction of **8m** were grown from a mixture of methanol, ethyl acetate, and petroleum ether. The compound crystallizes in monoclinic space group *P*21 with cell dimensions a=9.183(1) Å, b=9.118(1) Å, c=10.428(1) Å, β=101.829(5)°, and V=854.6(2) Å^3 with Z=2. The intensity data have been collected on Rigaku AFC-7S diffractometer with Mercury CCD area detector using graphite monochromatic Mo Kα radiation. The structure has been solved with direct methods and refined using least squares procedure using the Crystal Structure software. The present R factors are $R1$=0.034 and Rw=0.42. The number of observed reflections is 3420. Crystallographic data (excluding structure factors) for **8m** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 620161.
25. (a) This behavior, which is not clear at this stage, perhaps could be ascribed to the structural features of the starting sulfonamide, was different from the previously reported cyclizations of the sulfoximine, which invariably led to the mixture of regioisomeric five and six-membered ring products, see Ref. 19; (b) Recently, the intramolecular cyclization of alkynylamides has been studied by Larock et al., which mainly produced isoindolin-1-ones in the presence of iodine, see Ref. 9.
26. The possibility that the formation of **8** may proceed through (i) deprotonation, (ii) cyclization, and (iii) iodination of the resultant 3-substituted benzothiazines is ruled out by the following experiment: 6-ethyl-2-methyl-3-*p*-tolyl-2*H*-benzo[*e*][1,2]thiazine-1,1-dioxide (**9d**) prepared from **8n** was recovered unchanged after treatment with iodine and K_2CO_3 in acetonitrile at 25 °C for 16 h.



27. Pandey, V. K.; Pathak, S. R. *Indian J. Chem., Sect. B* **2002**, *41*, 1749.
28. Lee, K. Y.; Lee, M. J.; Kim, J. N. *Tetrahedron* **2005**, *61*, 8705.