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SYNTHESIS OF IODINATED THIAZOLO[2,3-*a*]ISOQUINOLINIUM SALTS AND THEIR CRYSTAL STRUCTURES WITH/WITHOUT HALOGEN BOND

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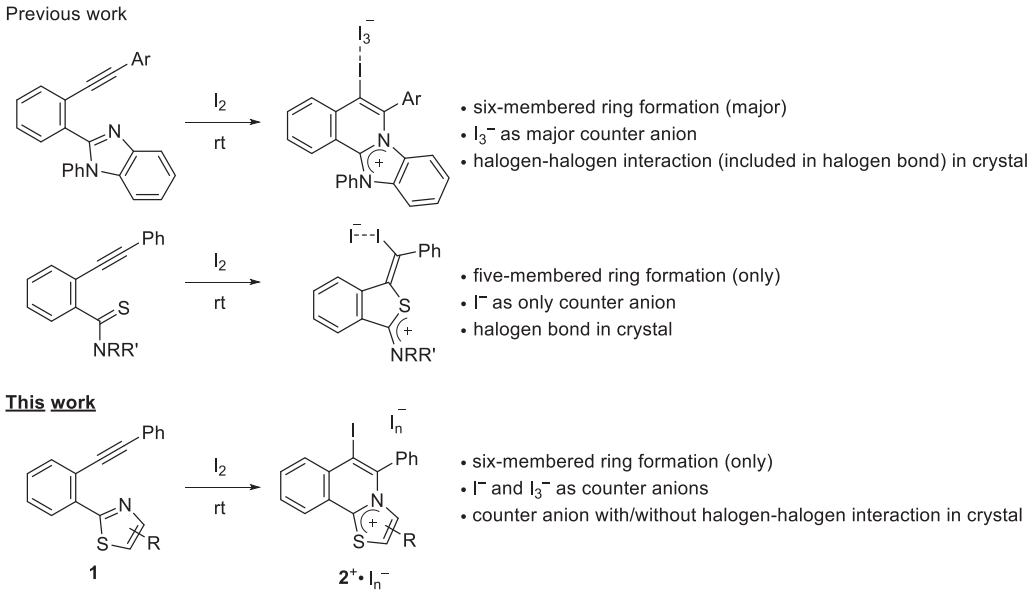
Abstract – We investigated the cyclization reaction of 2-(2-(phenylethynyl)-phenyl)thiazoles with I_2. A six-membered ring was formed to produce the corresponding thiazolo[2,3-*a*]isoquinolin-7-ium salts. The counter anions (I^- and I_3^-) varied based on the structure of the thiazole moiety. We also revealed the single-crystal X-ray structures of those thiazolo[2,3-*a*]isoquinolin-7-ium salts. We discovered that various structures with and without halogen bonds existed, although they were the prospective structures to make "charge-assisted halogen bonds".

INTRODUCTION

Iodine-induced cyclization reaction is one of the most powerful methods for constructing heterocyclic compounds. This method results in iodinated compounds, whose functional group can be utilized in further conversions to other functional groups. Recently, the iodine atom in organic compounds is focused on as a halogen donor in halogen bonds, which is utilized in the field of crystal engineering,[1] pharmaceutical applications,[2] functional materials,[3] and organic catalysts.[4] Especially, the iodine atom bearing cationic moiety produces the strong halogen bond called the "charge-assisted halogen bond".[5] Controlling the counter anion and the halogen bond is important in utilizing such interaction. We have reported the construction of six-membered rings by the reaction of 2-(2-(arylethynyl)phenyl)benzimidazoles with I_2 to result in benz[4,5]imidazo[2,1-*a*]isoquinolin-7-ium compounds (Scheme 1).[6] Also, benz[4,5]imidazo[2,1-*a*]isoindol-10-ium compounds, which were obtained from five-membered-ring formations, were observed as a minor component. They were obtained as the compounds with triiodide (I_3^-) as a major counter anion at room temperature. Those results were contrast

This paper is dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th birthday.

to the reaction of 2-(phenylethynyl)benzothioamide with I_2 to produce the fused five-membered-ring compound, benzo[*c*]thiophen-1-aminium, which possessed iodide (I^-) as a counter anion,[7] and all of their crystal structures showed the I···I interaction, including the halogen bond. We were interested in the compound (**1**) bearing the thiazole moiety which possessed the structural features both in imidazole as a nitrogen containing heteroaromatic and in thioamide as a resonance structure between S–C–N bonds. We herein report the reaction of 2-(2-(phenylethynyl)phenyl)thiazole derivatives with I_2 to construct six-membered rings. The counter anion was varied in the substrates, but the compounds with I_3^- were mainly obtained in the case of the compounds bearing substituents on thiazole ring. We also found that in some cases there was no interaction between iodine atoms in the X-ray crystal structure analysis.

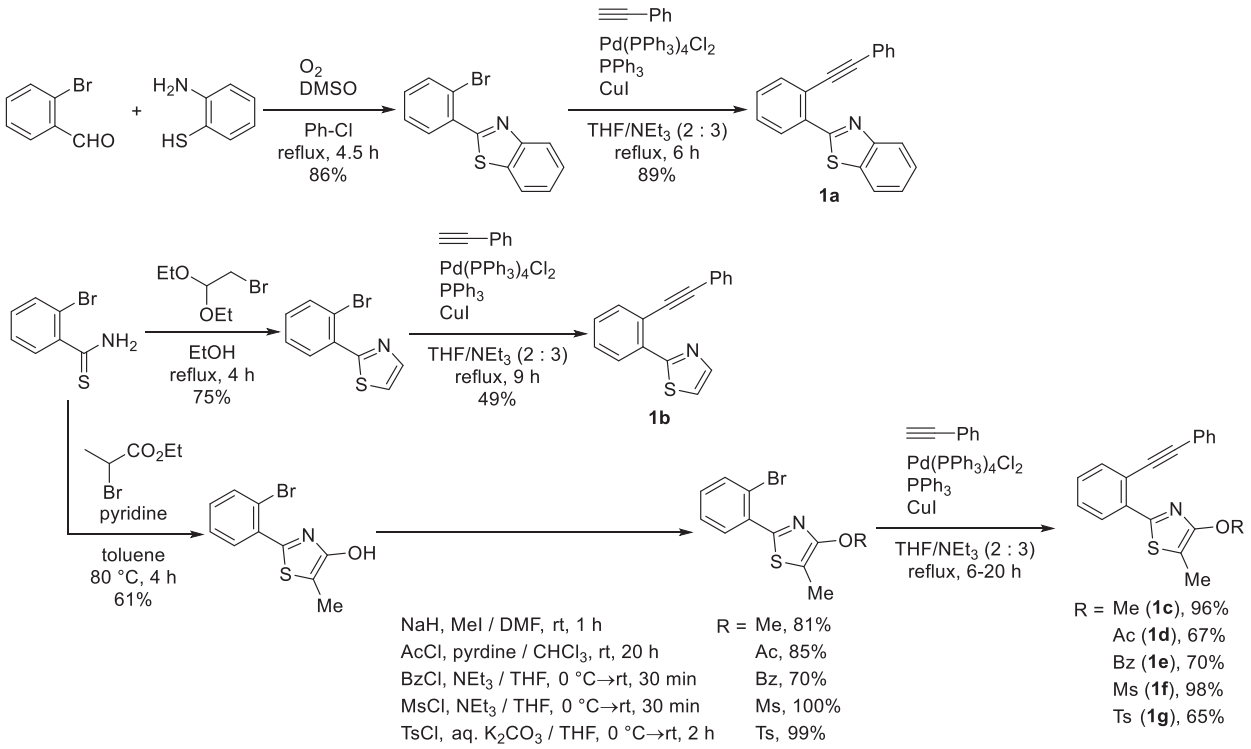


Scheme 1. Features of compounds by the reaction of substrates with iodine

RESULT AND DISCUSSION

PREPARATION OF 2-(2-(PHENYLETHYNYL)PHENYL)THIAZOLES

The substrates were synthesized by the thiazole-ring formation followed by the Sonogashira coupling reaction to introduce the triple bond moiety. The benzothiazole ring for **1a** was constructed by the condensation reaction of 2-bromobenzaldehyde with 2-aminobenzenethiol (Scheme 2).[8] Sonogashira coupling was successful in the conditions utilized for the coupling reaction of nitrogen containing aromatic rings.[9] The thiazole ring for **1b** was obtained by the condensation reaction of 2-bromobenzothioamide with 2-bromo-1,1-diethoxyethane.[10] The compounds (**1c-g**) bearing substituents on the thiazole ring were obtained through the transformation of the hydroxyl group of 2-(2-bromophenyl)-5-methylthiazol-4-ol, which was produced by the reaction of 2-bromobenzothioamide with ethyl 2-bromopropanoate.[11]



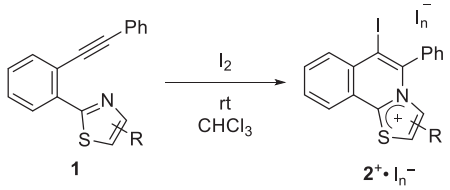
Scheme 2. Preparation of the substrates (**1a-g**)

REACTION OF 2-(2-(PHENYLETHYNYL)PHENYL)THIAZOLES WITH I_2

We examined the reaction with I_2 in $CHCl_3$. When **1a** was treated with 1 mol-equiv. of I_2 at room temperature, a precipitate was observed while the reaction was in progress. After being stirred for 1 d, the precipitate was collected and the filtrate was subjected to column chromatography to obtain the recovered substrate (41%) (Table 1, entry 1). From ^{1}H NMR analysis of the precipitate, a single organic component was observed, which contrasts with the reaction of 2-(2-(arylethynyl)phenyl)benzimidazoles.[6] Based on the X-ray crystallographic analysis (vide infra), we found that the compound formed a six-membered ring (**2a**$^+$), 5-iodo-6-phenylbenzo[4,5]thiazolo[2,3-*a*]isoquinolin-7-ium, was produced. However, the elemental analysis of the precipitate did not demonstrate the agreement of the compound with a single counter anion (calculation for **2a**$^+$•I^- with C, 44.63%; H, 2.32%; N, 2.48%, calculation for **2a**$^+$•I_3^- with C, 30.80%; H, 1.60%; N, 1.71%, and experimental data with C, 33.99%; H, 1.61%; N, 1.80%). This margin would be attributed to the mixing of the counter anions. When two counter anions (I^- and I_3^-) were included, the ratio of **2a**$^+$•I^- and **2a**$^+$•I_3^- was calculated for 28 : 72. As for the result, we estimated that the yields of **2a**$^+$•I^- and **2a**$^+$•I_3^- were 15% and 38%, respectively. The prolonged reaction time resulted in a slight increase in the yield of the cyclization in keeping with the ratio of **2a**$^+$•I^- and **2a**$^+$•I_3^- (entry 2). When increasing the amount of I_2, an exchange of the ratio of **2a**$^+$•I^- and **2a**$^+$•I_3^- was observed with a reduction in the total yield of products and the recovery of **1** (entry 3). We could not give a clear explanation of this result. But one possibility can be proposed. The reaction could proceed under the

equilibrium between the solution and the precipitate. When the larger amount of solutes such as excess amounts of I_2 exist, the solubility of the precipitated **2a**$^+$•I^- is decreased. Also, the amount of **2a**$^+$•I^- in the solution is decreased to give lower yields of **2a**$^+$•I_3^- formed by the reaction **2a**$^+$•I^- with I_2. There was no tendency of the selectivity of the counter anions between the reaction of **1a** and **1b**. In the case of the reaction of **1b** without fused benzene ring, the ratio of **2b**$^+$•I^- was increased in the case of 1 mol-equiv. of I_2 (**2b**$^+$•I^- and **2b**$^+$•I_3^- = 62 : 38) (entry 4). By increasing the amount of I_2, **2b**$^+$•I_3^- was obtained as a major product (entry 5).

Table 1. Reaction of **1** with I_2[a]



Entry	Substrate	Mol-equiv. of I_2	Time (d)	Yield of **2**$^+$•I^- (%)	Yield of **2**$^+$•I_3^- (%)	Recovery of **1** (%)
1	**1a**	1.0	1	15[b]	38[b]	41
2	**1a**	1.0	3	16[b]	42[b]	36
3	**1a**	2.0	3	38[b]	13[b]	31
4	**1b**	1.0	3	45[b]	27[b]	16
5	**1b**	2.0	3	4[b]	89[b]	0
6	**1c**	1.0	1	0	49	51
7	**1c**	1.0	3	0	50	35
8	**1c**	2.0	3	0	74	2
9	**1d**	1.0	3	0	48	51
10	**1d**	2.0	3	0	94	6
11	**1e**	1.0	3	0	49	49
12	**1e**	2.0	3	0	79	18
13	**1f**	1.0	3	0	49	42
14	**1f**	2.0	3	0	86	13
15	**1g**	1.0	3	0	50	45
16	**1g**	2.0	3	0	95	trace

[a] Reaction conditions: **1** (0.3 mmol), $CHCl_3$ (3 mL), room temperature. [b] Yields were determined by the estimation with weight of the precipitate and the elemental analysis.

Complete selectivity of **2**$^+$•I_3^- was observed in the case of the compounds with substituted thiazole rings (**1c-g**). When we treated **1c** with 1mol-equiv. of I_2, the precipitate was produced with a 51% recovery of

1c. The component of the precipitate was in accordance with the corresponding cyclic cation and I_3^- estimated from the elemental analysis (calculation for **2c**$^+$•I_3^- with C, 28.07%; H, 1.86%; N, 1.72%, and experimental data with C, 28.07%; H, 1.75%; N, 1.55%). The yield of the product (**2c**$^+$•I_3^-) was determined to be 49% (entry 6). A prolonged reaction time produced the same yield of **2c**$^+$•I_3^- (entry 7). We obtained **2c**$^+$•I_3^- in a 74% yield by increasing the amount of I_2 (entry 8). Other substrates bearing various oxygen functional substituents (**1d**, **1e**, **1f**, and **1g**) gave the same results. The yields of the cyclized product were not in excess of 50% in the case of the reaction with 1 mol-equiv. of I_2 (entries 9, 11, 13 and 15). Thus, the complete selectivity of **2**$^+$•I_3^- in **1d-g** occurred. The products were obtained in good to excellent yields by using 2 mol-equiv. of I_2 (entries 10, 12, 14 and 16). The reason for the complete selectivity of **1c-g** was unclear. It seems that the solubility of the precipitate was affected because **2**$^+$•I_3^- was selectively formed from the compounds having substituents which would be increased by the solubility of **2**$^+$•I^- in organic solvents.

SINGLE-CRYSTAL STRUCTURES OF IODINATED THIAZOLO[2,3-*A*]ISOQUINOLINIUM

To reveal the halogen bond interaction, we examined single-crystal X-ray analysis. We obtained good crystals to measure the single-crystal X-ray structures of **2a**$^+$•I^-, **2c**$^+$•I_3^-, **2d**$^+$•I_3^-, **2e**$^+$•I_3^-, **2f**$^+$•I_3^-, and **2g**$^+$•I_3^-. The single **2a**$^+$•I^- crystals with DMSO were obtained from the mixture of counter anions by the recrystallization from DMSO by the diffusion of hexane vapor. The single crystals of **2c**$^+$•I_3^-, **2d**$^+$•I_3^-, **2e**$^+$•I_3^-, **2f**$^+$•I_3^-, and **2g**$^+$•I_3^- were produced by the recrystallization from $CHCl_3$ by the diffusion of hexane vapor. The crystal structures were summarized in Figure 1 and Table 2. A halogen bond between two iodine atoms was observed in **2a**$^+$•I^-•DMSO with a distance of 3.570 Å, which is a 90% distance of the sum of van der Waals (vdW) radii [3.96 Å = 1.98 Å (I) + 1.98 Å (I)] (Figure 1a).[12] The I···I–C angle with 167.2° was slightly deviated from the ideal angle (180°). In the crystals of **2**$^+$•I_3^-, the same motif was found in the interaction between thiazolo[2,3-*a*]isoquinolin-7-ium cation and I_3^- in **2c**$^+$•I_3^-, **2d**$^+$•I_3^-, and **2f**$^+$•I_3^- (Figure 1b, c, and e). Two types of I_3^- were found in the crystal structures. One of two types of I_3^- interacted with iodine atom on thiazolo[2,3-*a*]isoquinolin-7-ium cation with 93~95% distances of the sum of vdW radii (3.666 Å for **2c**$^+$•I_3^-, 3.772 Å for **2d**$^+$•I_3^-, and 3.681 Å for **2f**$^+$•I_3^-) (Figure 1b, c, and e). A halogen bond was found on both sides of I_3^-. Another I_3^- was freed from the interaction with a halogen bond, and approximated hydrogen atom on the benzene ring, although the distances were not shorter than the sum of vdW radii [2.98 Å = 1.98 Å (I) + 1.00 Å (H(arom.))] (3.177 Å (C···I: 4.124 Å) for **2c**$^+$•I_3^-, 3.089 Å (C···I: 4.023 Å) for **2d**$^+$•I_3^-, and 3.098 Å (C···I: 4.305 Å) for **2f**$^+$•I_3^-). The center iodine atom in I_3^- was located near sulfur atoms on thiazolium rings with near equal or a shorter distance compared with the sum of vdW radii [3.78 Å = 1.98 Å (I) + 1.80 Å (S)] (3.814 Å for **2c**$^+$•I_3^-, 3.732 Å for **2d**$^+$•I_3^-, and 3.825 Å for **2f**$^+$•I_3^-). **2e**$^+$•I_3^- produced a crystal structure without a halogen bond (Figure 1d). I_3^- was

located near the iodine atom on the thiazolo[2,3-*a*]isoquinolin-7-ium cation. But the distance between two iodine atoms (4.019 Å) were longer than the sum of vdW radii. Contact between iodine and hydrogen atoms was also found, but the distance (3.127 Å (C···I: 4.034 Å)) was too long to judge it to be a hydrogen bond. In the crystal structure of **2g**$^{+}$•I_3^{-}, there were two conformers (conformer A and B) (Figure 1f). Both structures possessed a halogen bond with the distance of 3.644 Å and 3.732 Å between two iodine atoms, which were shorter than the sum of vdW radii. But another side of I_3^{-} showed no interaction to nearby molecules. To discuss the halogen bond in **2**$^{+}$•I_3^{-}, the difference between the two angles of I···I–C and I···I–I ($\Delta\theta$) was also important because that difference showed 90° in an ideal halogen bond. Summarized in Table 1, all of $\Delta\theta$ in **2**$^{+}$•I_3^{-} was observed within 35–105°. This type of halogen-halogen interaction was categorized as type II, which is actually a halogen bond.[13] However, large deviations from 90° were found in **2e**$^{+}$•I_3^{-} and **2g**$^{+}$•I_3^{-} (conformer A) with $\Delta\theta$ of 51.7° and 50.3°, respectively. Thus, the charge-assisted halogen bond in the cationic part was preferentially obtained in **2a**$^{+}$•I^{-}, **2c**$^{+}$•I_3^{-}, **2d**$^{+}$•I_3^{-}, **2f**$^{+}$•I_3^{-}, and **2g**$^{+}$•I_3^{-} (conformer B). From those results, the interaction with halogen bonds in the crystals was influenced in the bulkiness of substituent on the thiazole ring: the compounds with bulkier substituent such as **2e**$^{+}$•I_3^{-} and **2g**$^{+}$•I_3^{-} formed little to no halogen bonds.

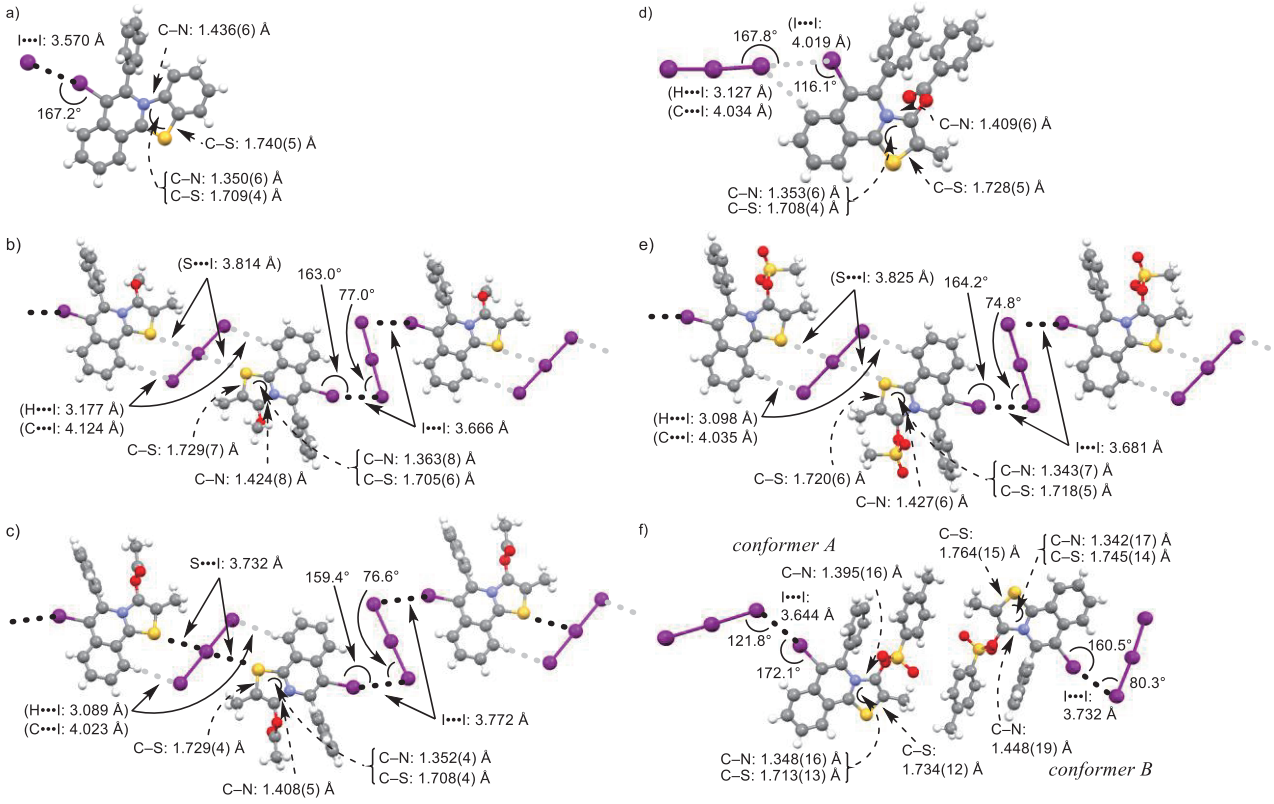
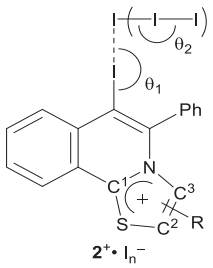


Figure 1. Single-crystal X-ray structure of a) **2a**$^{+}$•I^{-}•DMSO, b) **2c**$^{+}$•I_3^{-}, c) **2d**$^{+}$•I_3^{-}, d) **2e**$^{+}$•I_3^{-}, e) **2f**$^{+}$•I_3^{-}, and f) **2g**$^{+}$•I_3^{-} with selected distances and angles. DMSO molecule was omitted in a) to clarify the thiazolo[2,3-*a*]isoquinolinium structure and halogen bond.

Table 2. Selected Distances and Angles of Single-crystal X-ray Structure and Existence of Electrostatic Interaction



Crystal	I···I (Å)[a]	$\Delta\theta$ (°)[b]	C^1–S (Å)	C^1–N (Å)	C^2–S (Å)	C^3–N (Å)	Electrostatic interaction[c]
2a$^+$•I^-•DMSO	3.570 [90.2]	–	1.709(4)	1.350(6)	1.740(5)	1.436(6)	○ [DMSO]
2c$^+$•I_3^-	3.666 [92.6]	84.0	1.705(6)	1.363(8)	1.729(7)	1.424(8)	×
2d$^+$•I_3^-	3.772 [95.3]	82.8	1.708(4)	1.352(4)	1.729(4)	1.408(5)	○ [I_3^-]
2e$^+$•I_3^-	4.019 [101.5]	51.7	1.708(4)	1.353(6)	1.728(5)	1.409(6)	×
2f$^+$•I_3^-	3.681 [93.0]	89.4	1.718(5)	1.343(7)	1.720(6)	1.427(6)	○ [I_3^-]
2g$^+$•I_3^- (conformer A)	3.644 [92.0]	50.3	1.713(13)	1.348(16)	1.734(12)	1.395(16)	○ [SO_2Me]
2g$^+$•I_3^- (conformer B)	3.732 [94.2]	80.2	1.745(14)	1.342(17)	1.764(15)	1.448(19)	×

[a] Value in square bracket was percentage of the sum of vdW radii (distance I···I / 3.96 (sum of vdW radii of iodine). [b] $\Delta\theta = |\theta_1 - \theta_2|$. [c] Structure in square bracket was represented the interaction partner of N–C–S resonant cation.

Focusing on the cationic part, the resonance structure in N–C–S was observed. The distances of C^1–S and C^1–N were shorter than that of the C–S single bond (C (sp^2)–S: 1.75 Å) and that of the C–N single bond with conjugation (N (planar)–C (sp^2): 1.36 Å) and longer than those of C=S and C=N double bonds (C–S: 1.68 Å (thiourea), and N (planar)–C (sp^2): 1.28 Å) (Table 2).[14] The shorter distances of the C^1–N bond along with the elongation of the C^1–S bond were found in **2f**$^+$•I_3^- and **2g**$^+$•I_3^-, whose compounds possessed the stronger electron-withdrawing substituents (OMs and OTs, respectively). Thus, the resonance structure was affected by the substituent on thiazolium ring. The distance of the C^2–S bond was consistent with the value of benzo[*d*]thiazole and oxalic acid complex (CCDC-845393) (1.7222(13) Å).[15] On the contrary, the distance of C^3–N was shown to be longer than that of benzo[*d*]thiazole and oxalic acid complex (CCDC-845393) (1.2979(15) Å). This could be a reason for the steric repulsion between the substituent on the thiazolium ring and phenyl group of the triple bond in **1**.

In **2a**$^+$•I^-•DMSO, **2d**$^+$•I_3^-, **2f**$^+$•I_3^-, and **2g**$^+$•I_3^- (conformer A), the electrostatic interaction on the thiazolium ring was observed (Table 2 and Figure 2). The DMSO molecule in **2a**$^+$•I^- interacted with the carbon on the N–C–S resonance structure with 2.928 Å, whose value was shorter than the sum of vdW radii [3.29 Å = 1.52 Å (O) + 1.77 Å (C(arom.))] (Figure 2a). CH–π interaction with the distance of 2.727

Å (C···C: 3.609 Å) was also observed in-between benzene rings of benzo[*d*]thiazole moiety and the methyl group of DMSO. The electrostatic interactions between the N–C–S resonance structure and the edge of iodine(s) of I_3^- were found in the crystal structures of **2d**$^+$•I_3^- and **2f**$^+$•I_3^-. There was close contact between carbon and iodine (3.652 Å) in **2d**$^+$•I_3^- [the sum of vdW radii: 3.75 Å = 1.98 Å (I) + 1.77 Å (C(arom.))] (Figure 2b). The two interactions with 3.503 Å (C···I) and 3.522 Å (N···I) [the sum of vdW radii: 3.53 Å = 1.98 Å (I) + 1.55 Å (N(sp^2))] was found in **2f**$^+$•I_3^- (Figure 2c). Such contacts in **2d**$^+$•I_3^- and **2f**$^+$•I_3^- were observed at the edge of both I_3^- bearing a halogen bond. **2g**$^+$•I_3^- (conformer A) formed the interaction between the thiazolium ring and oxygen of sulfonyl moiety with a distance of 2.936 Å (Figure 2d); but **2g**$^+$•I_3^- (conformer B) had no electrostatic interaction whereas the close contact between hydrogen on the phenyl ring and centered iodine atom of I_3^- belonged to the conformer A was observed with 2.971 Å compared with the sum of vdW radii [2.98 Å = 1.98 Å (I) + 1.00 Å (H(arom.))]. Represented in Table 2, there were crystal structures without the electrostatic interaction whereas the halogen bond was formed. Especially, there was no interaction with the halogen bond and the electrostatic interaction in **2e**$^+$•I_3^-. Thus, the halogen bond could be formed with preference of the electrostatic interaction.

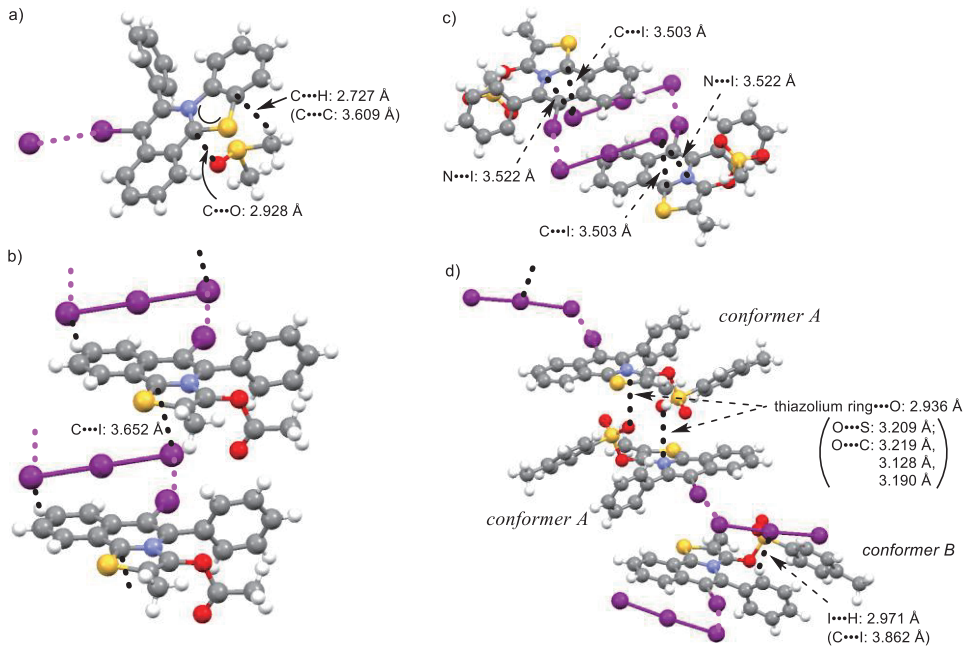


Figure 2. Electrostatic interaction in a) **2a**$^+$•I$^-$•DMSO, b) **2d**$^+$•I_3^-, c) **2f**$^+$•I_3^-, and d) **2g**$^+$•I_3^- with selected distances. Purple dotted line represented I···I interaction.

From the packing structure, the unique features were observed in those crystals. We found the alignment of the thiazolo[2,3-*a*]isoquinolin-7-ium π-plane in all obtained crystals. The sheet structure along the thiazolo[2,3-*a*]isoquinolin-7-ium π-plane was revealed in **2a**$^+$•I$^-$•DMSO and **2e**$^+$•I_3^- (Figure 3). The

molecules of **2a**$^{+}$•I^{-} in the sheet were located at a distance of 3.011 Å (C···I: 3.839 Å) and 2.966 Å (C···I: 3.800 Å) at the iodide atom and hydrogen on benzene ring (shown as **B** and **C** in Figure 3a), which were nearly equal to the sum of the vdW radii [2.98 Å = 1.98 Å (I) + 1.00 Å (H(arom.))]. The molecules were also in contact with DMSO by CH–π (between methyl group of DMSO and benzene ring) and CH–O (between hydrogen on benzene ring and oxygen of DMSO) interactions with the distance of 2.805 Å (C···C: 3.689 Å) and 2.473 Å (O···C: 3.266 Å) depicted as **D** and **E** in Figure 3a, respectively (refer to the sum of vdW radii for CH–π [2.97 Å = 1.20 Å (H) +1.77 Å (C(sp^2))] and for CH–O [2.70 Å = 1.20 Å (H) + 1.50 Å (O(sp^2))]). Interactions between layers were also observed (Figure 3b). In addition to the electrostatic interaction and CH–π interaction shown in Figure 2a (also shown in Figure 3b with **A** and **B**), the interaction between sulfur atoms on thiazolo[2,3-*a*]isoquinolin-7-ium structure were found with a distance of 3.370 Å, depicted as **C** in Figure 3b, which was shorter than that of the sum of vdW radii [3.60 Å = 1.80 Å (S) + 1.80 Å (S)]. From the crystal structure of **2e**$^{+}$•I_3^{-}, the sheet-like structure was found, although there was no interaction between the molecules (Figure 3c). Each sheet had contact between carbonyl oxygen and aromatic hydrogen atoms with 2.586 Å (C···O: 3.428 Å) and 2.553 Å (C···O: 3.401 Å), which were slightly longer than the sum of vdW radii [2.50 Å = 1.50 Å (O(sp^2) + 1.00 Å (H(arom.))] (depicted as **A** and **A'** in Figure 3d).

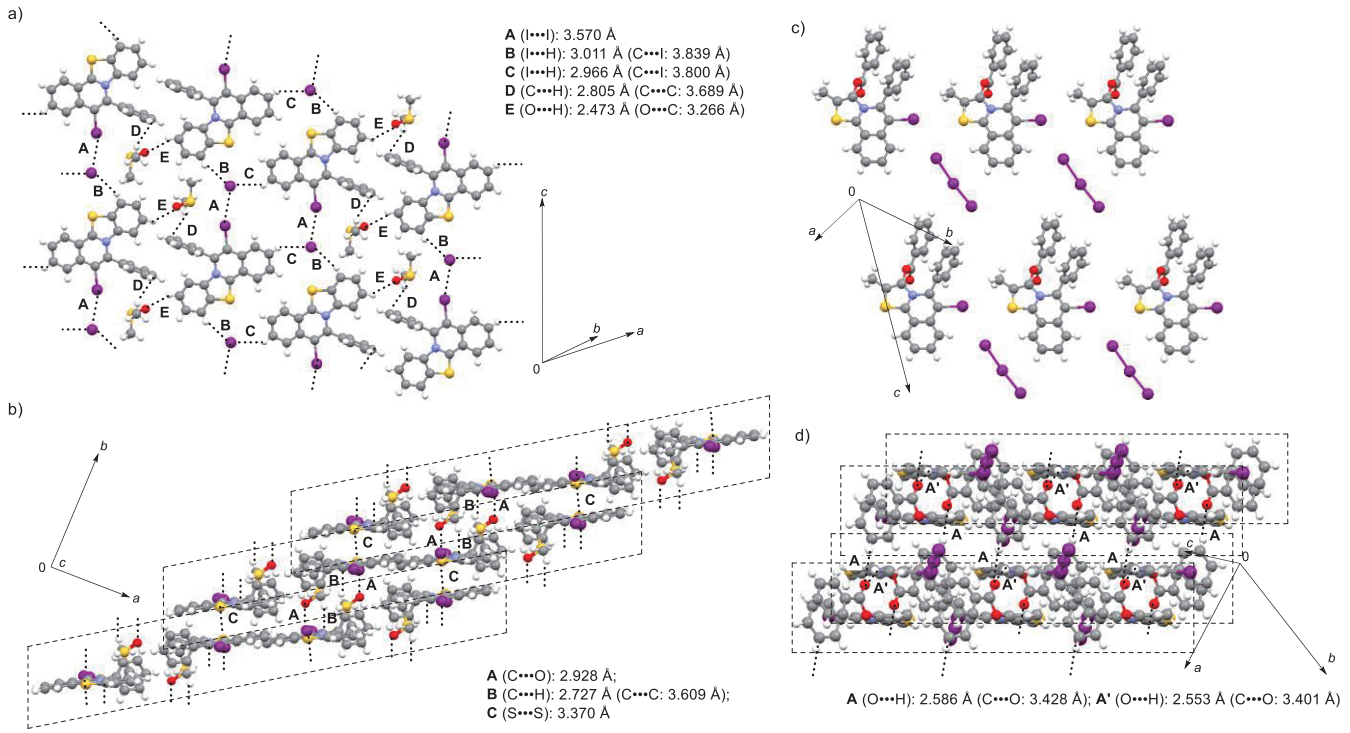


Figure 3. Sheet structures of a) **2a**$^{+}$•I^{-}•DMSO and c) **2e**$^{+}$•I_3^{-} and the interactions between the layers of b) **2a**$^{+}$•I^{-}•DMSO and d) **2e**$^{+}$•I_3^{-} with selected distances. One sheet was shown with frame in b) and d).

The sheet-like structures along the thiazolo[2,3-*a*]isoquinolin-7-ium π-plane were also found in **2c**$^+$•I_3^-, **2d**$^+$•I_3^-, and **2f**$^+$•I_3^- which had the same motif shown in Figure 1b, c, and e (Figure 4a, b, and c). Each sheet was packed with the aid of electrostatic interaction and other contacts. In the crystal structure of **2c**$^+$•I_3^-, the close contact between the benzene ring and the centered iodine of I_3^- with the distance (3.654 Å) was observed cut in the sum of vdW radii [3.75 Å = 1.98 Å (I) + 1.77 Å (C(arom.))] (depicted as **A** in Figure 4d). The CH–π interaction was also observed with a distance of 2.891 Å (C···I: 3.867 Å) by using hydrogen of methyl group on thiazolium moiety (depicted by **B** in Figure 4d). Only the electrostatic interaction shown in Figure 2b was observed as the interaction between the bands in **2d**$^+$•I_3^- (depicted as **A** in Figure 4e). In the case of **2f**$^+$•I_3^-, in addition to the electrostatic interaction represented in Figure 2c, the CH–π interaction was also observed with the distance of 2.831 Å (C···C: 3.341 Å) by using hydrogen of the mesyl group (depicted as **B** in Figure 4f).

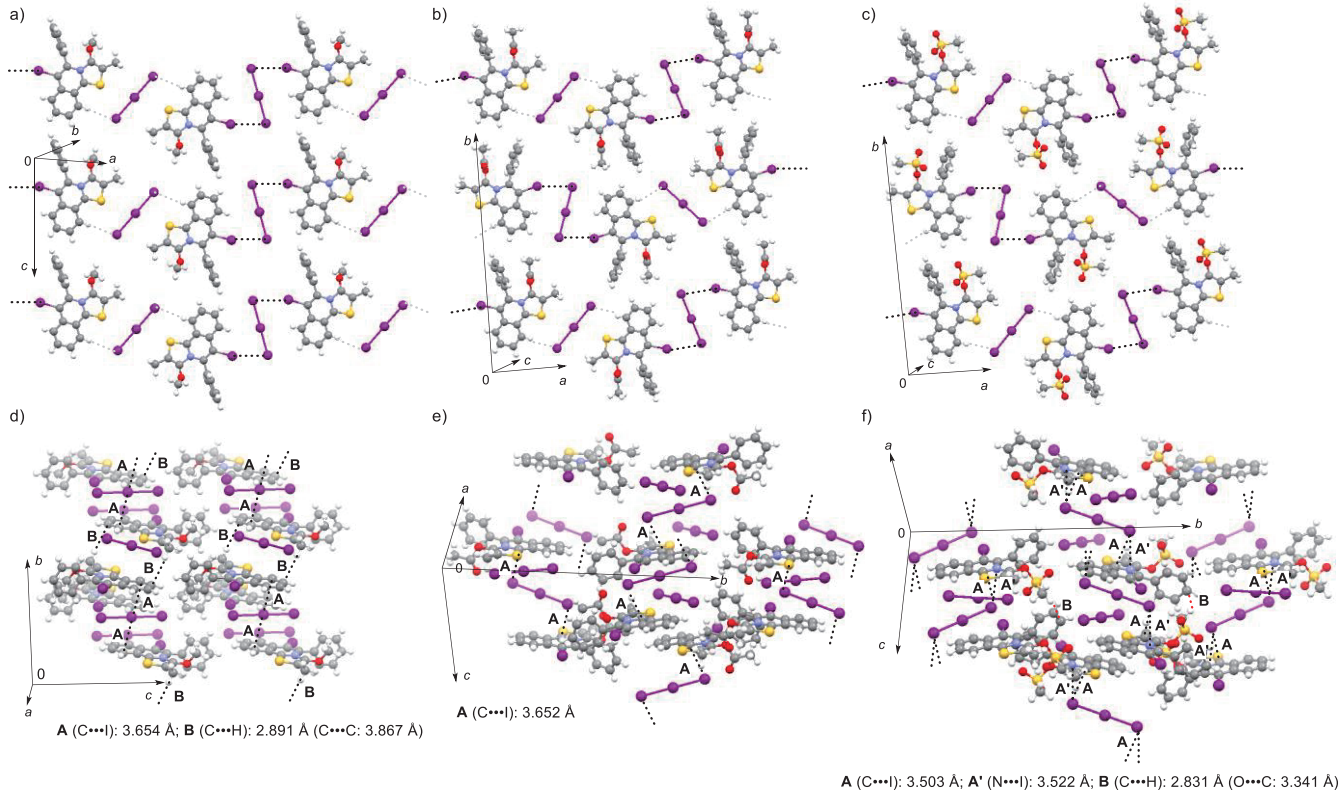


Figure 4. Sheet structures and interaction between the layers of a), d) **2c**$^+$•I_3^-, b), e) **2d**$^+$•I_3^-, and c), f) **2f**$^+$•I_3^- with selected distances.

From the crystal structure of **2g**$^+$•I_3^-, The band-like structure along the thiazolo[2,3-*a*]isoquinolin-7-ium π-plane was found. This band consisted of two lines of conformer A and conformer B (Figure 5a). The interactions of I···S with 3.734 Å and I···H with 2.870 Å (C···I: 3.742 Å) were found in conformer A with short distances against the sum of vdW radii [3.78 Å = 1.98 Å (I) + 1.80 Å (S) and 2.98 Å = 1.98 Å

(I) + 1.00 Å (H(arom.))] (depicted as **A** and **B** in Figure 5a). The interaction of I···S with 3.709 Å was obtained in conformer B (depicted as **A'** in Figure 5a). These band-like structures were stacked with the interactions represented in Figure 2d (Figure 1e).

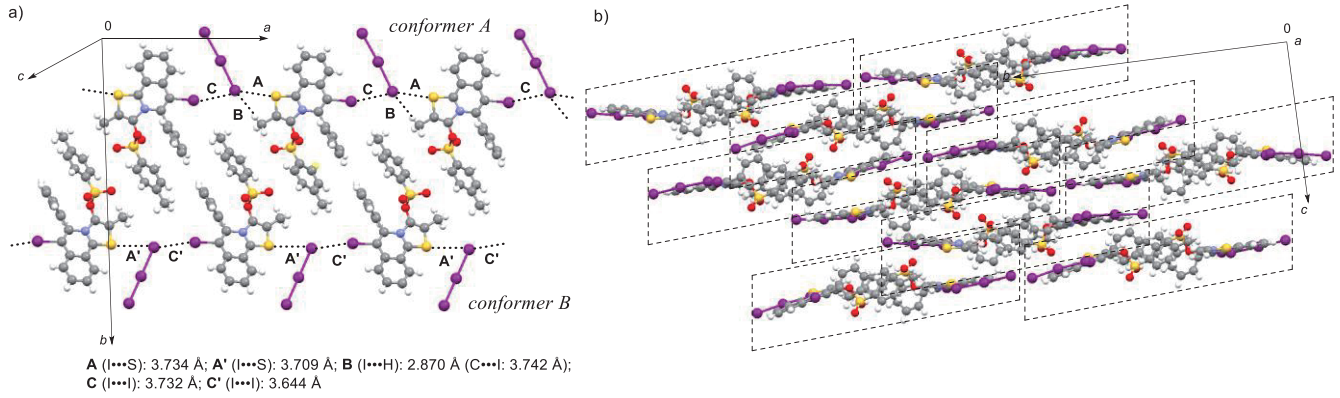


Figure 5. a) The band-like structure and b) the packing of **2g**$^{+}$•I_3^{-} with selected distances. The band-like structure was shown with frame in b).

CONCLUSION

In conclusion, we synthesized thiazolo[2,3-*a*]isoquinolin-7-ium salts from 2-(2-(phenylethynyl)phenyl)thiazoles by the iodine-induced cyclization reaction. The reaction efficiently proceeded at room temperature to produce the six-membered cyclic compounds. The counter anions (I^- and I_3^-) varied based on the structure of thiazole moiety. In the case of the substituted thiazole derivatives, the selectivity of I_3^- was very high and the compound with I_3^- was only obtained even in the reaction with half the amount of I_2 corresponding to their formation. We also revealed that the compounds with or without a halogen bond were obtained in their crystal structures. The compounds bearing bulkier substituents on thiazole moiety show the preference to make the crystal structure without the halogen bond, although "charge-assisted halogen bond" formation would promote the halogen bond. Furthermore, one of them (**2e**$^{+}$•I_3^{-}) showed no halogen-halogen interaction. It is a clear contrast against the benz[4,5]imidazo[2,1-*a*]isoquinolin-7-ium compounds which gave the halogen-halogen interaction in all reported crystals.[6] We also found the unique alignment of the thiazolo[2,3-*a*]isoquinolin-7-ium π-plane. These results could serve as useful information for designing crystal structures with halogen bonds.

EXPERIMENTAL

Melting points were determined with Yanaco MP-J3 and values were uncorrected. NMR spectra were recorded at 300 MHz (proton) (75 MHz (carbon-13)) on Varian Mercury plus spectrometer or Bruker DPX-300 and at 400 MHz (proton) (100 MHz (carbon-13)) on Bruker AVANCE III-400M. Chemical

shifts (δ) of ^{1}H NMR were expressed in parts per million downfield or upfield from tetramethylsilane in $CDCl_3$ (δ = 0), DMSO-d_5 (δ = 2.49), or acetone-d_5 (δ = 2.04) as an internal standard. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), m (multiplet), bs (broadened singlet), and coupling constants (*J*) are reported in hertz units. Chemical shifts (δ) of ^{13}C NMR are expressed in parts per million downfield or upfield from $CDCl_3$ (δ = 77.0), DMSO-d_6 (δ = 39.6), or acetone-d_6 (δ = 28.1) as an internal standard. Elemental analyses (EA) were carried out on Exeter Analytical, Inc. CE-440F in Center for Analytical Instrumentation of Chiba University. Mass spectra were carried out on THERMO FisherExactive in Center for Analytical Instrumentation of Chiba University. Anhydrous THF was distilled from sodium benzophenone ketyl immediately prior to use. Anhydrous toluene was distilled from sodium hydride and was stored with MS 4 Å. Anhydrous DMF was distilled from P_2O_5 under reduced pressure and was stored with MS 4 Å. Anhydrous $CHCl_3$ was distilled from $CaCl_2$ after washing with aq. NaOH, and was stored with MS 4 Å. The reactions were performed under nitrogen atmosphere otherwise noted.

Synthesis of 2-(2-Bromophenyl)benzo[*d*]thiazole: A solution of 2-bromobenzaldehyde (0.559 g, 3.02 mmol), 2-aminobenzenethiol (0.666 g, 5.32 mmol) and DMSO (0.478 g, 6.11 mmol) in chlorobenzene (10 mL) was refluxed for 4.5 h under O_2 atmosphere. After evaporation in vacuo, the residual mixture was subjected to column chromatography on silica-gel (hexane : EtOAc = 5 : 1) to give 2-(2-bromophenyl)benzo[*d*]thiazole (0.754 g, 2.60 mmol, 86%) as purple solid: mp = 63–64 °C ($CHCl_3$) [lit.:[16] 63.3–65.1 °C]; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.31 (dt, *J* = 1.6 and 8.0 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.52 (t, *J* = 7.1 Hz, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.99 (dd, *J* = 1.6 and 7.7 Hz, 1H), 8.14 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 121.4, 122.1, 123.6, 125.5, 126.3, 127.5, 131.2, 132.2, 134.1, 134.5, 136.1, 152.7, 165.6.[16]

Synthesis of 2-(2-Bromophenyl)thiazole: To a solution of 2-bromobenzothioamide (0.360 g, 1.67 mmol) in EtOH (2 mL) was added 2-bromo-1,1-diethoxyethane (0.38 mL, 2.53 mmol). After being stirred for 4 h under reflux, the reaction mixture was cooled to room temperature. After addition of H_2O (5 mL), the mixture was extracted with EtOAc (10 mL × 4). The combined organic layer was washed with brine (5 mL) and dried over $MgSO_4$. After evaporation in vacuo, the residual mixture was subjected to column chromatography on silica-gel (hexane : EtOAc = 15 : 1 to 2 : 1) to give 2-(2-bromophenyl)thiazole (0.304 g, 1.26mmol, 75%) as yellow oil:^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25 (dt, *J* = 1.8 and 7.4 Hz, 1H), 7.39 (dt, *J* = 1.2 and 7.7 Hz, 1H), 7.47 (d, *J* = 3.3 Hz, 1H), 7.69 (dd, *J* = 1.2 and 8.0 Hz, 1H), 7.94 (d, *J* = 3.3 Hz, 1H), 8.02 (dd, *J* = 1.7 and 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 120.5, 121.6, 127.5, 130.5, 131.6, 134.0, 134.1, 142.6, 165.0; IR (neat): ν = 3112, 3077, 296, 1930, 1730, 1560, 1463, 1433, 1264, 1155, 1062, 1026, 973, 876, 758, 717, 636, 545, 447 cm^{-1}. HRMS (ESI) calcd for C_9H_7BrNS ($[M+H]^+$): 239.9477, found: *m*/*z* 239.9479.

Synthesis of 2-(2-Bromophenyl)-5-methylthiazol-4-ol: To a solution of 2-bromobenzothiazole (0.864 g, 4.00 mmol) and pyridine (1.266 g, 16.0mmol) in toluene (12 mL) was dropwise added ethyl 2-bromopropanoate (1.086 g, 6.00 mmol). After being stirred at 80 °C for 4 h, the reaction mixture was cooled to room temperature. After evaporation in vacuo, the residual mixture was subjected to column chromatography on silica-gel (hexane : EtOAc = 4 : 1) to give 2-(2-bromophenyl)-5-methylthiazol-4-ol (0.624 g, 2.43 mmol, 61%) as white solid: mp 126–127 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.30 (s, 3H), 7.24 (dt, *J* = 1.7 and 7.9 Hz, 1H), 7.41 (dt, *J* = 1.2 and 7.7 Hz, 1H), 7.68 (dd, *J* = 1.2 and 8.0 Hz, 1H), 7.80 (dd, *J* = 1.7 and 7.8 Hz, 1H), 11.26 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 9.2, 105.9, 121.4, 127.7, 130.3, 131.2, 133.3, 134.1, 157.5, 157.9; IR (KBr): ν = 3067, 2916, 2737, 2669, 1594, 1411, 1235, 1134, 982, 741 cm^{-1}. HRMS (ESI) calcd for $C_{10}H_9BrNOS$ ([M+H]$^+$): 269.9583, found: *m*/*z* 269.9582.

Synthesis of 2-(2-Bromophenyl)-4-methoxy-5-methylthiazole: To a solution of 2-(2-bromophenyl)-5-methylthiazol-4-ol (0.307 g, 1.14 mmol) in DMF (5 mL) was added NaH (60 wt% oil dispersion) (48.0 mg, 1.20 mmol) at room temperature, and the mixture was stirred for 1 h at that temperature. To the reaction mixture was added MeI (0.170 g, 1.20 mmol). After being stirred for 30 min, to the reaction mixture was added H_2O (10 mL). After being extracted with EtOAc (10 mL × 3), the organic layer was dried with $MgSO_4$. After evaporation in vacuo, the residual mixture was subjected to column chromatography on silica-gel (hexane : EtOAc = 20 : 1) to give 2-(2-bromophenyl)-4-methoxy-5-methylthiazole (0.262 g, 0.921 mmol, 81%) as white solid: mp = 44–46 °C ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.32 (s, 3H), 4.06 (s, 3H), 7.21 (dt, *J* = 1.7 and 7.3 Hz, 1H), 7.38 (dt, *J* = 1.2 and 7.3 Hz, 1H), 7.66 (dd, *J* = 1.0 and 8.0 Hz, 1H), 8.07 (dd, *J* =1.8 and 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 9.0, 57.7, 108.2, 120.8, 127.4, 129.7, 130.7, 134.0, 134.1, 156.0, 159.8; IR (KBr): ν = 3008, 2973, 2923, 2853, 1966, 1553, 1355, 1151, 1023, 755, 633, 442 cm^{-1}. HRMS (ESI) calcd for $C_{11}H_{11}BrNOS$ ([M+H]$^+$): 283.9727, found: *m*/*z* 283.9739.

Synthesis of 4-Acetoxy-2-(2-bromophenyl)-5-methylthiazole: To a solution of 2-(2-bromophenyl)-5-methylthiazol-4-ol (2.469 g, 9.14 mmol) in $CHCl_3$ (30 mL) was added pyridine (1.084 g, 13.7 mmol) and acetyl chloride (0.717 g, 9.14 mmol) at room temperature. The mixture was stirred for 20 h at that temperature. After concentration in vacuo, the residual mixture was subjected to column chromatography on silica-gel (hexane : EtOAc = 6 : 1) to give 4-acetoxy-2-(2-bromophenyl)-5-methylthiazole (2.420g, 7.75 mmol, 85%) as colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.31 (s, 3H), 2.36 (s, 3H), 7.22 (dt, *J* = 1.7 and 7.5 Hz, 1H), 7.36 (dt, *J* = 0.9 and 7.4 Hz, 1H), 7.66 (dd, *J* = 1.3 and 8.2 Hz, 1H), 8.04 (dd, *J* = 1.8 and 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 9.8, 20.6, 119.7, 120.9, 127.5, 130.4, 131.0, 133.3, 134.0, 150.6, 158.5, 168.5; IR (KBr): ν = 3050, 2917, 1766, 1549, 1366, 1202, 1116, 1011,873, 752, 440 cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{11}BrNO_2S$ ([M+H]$^+$): 311.9688, found: *m*/*z*

311.9687.

Synthesis of 4-(Benzoyloxy)-2-(2-bromophenyl)-5-methylthiazole: To a solution of 2-(2-bromophenyl)-5-methylthiazol-4-ol (0.540 g, 2.00 mmol) in THF (6 mL) was added benzoyl chloride (0.337 g, 2.40 mmol) and NEt_3 (0.304 g, 3.00 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min. To the reaction mixture was added EtOAc (30 mL) and H_2O (10 mL). After being washed with H_2O (10 mL × 2), the organic layer was dried with $MgSO_4$. After evaporation in vacuo, the residual mixture was subjected to column chromatography on silica-gel (hexane : EtOAc = 6 : 1) to give 4-(benzoyloxy)-2-(2-bromophenyl)-5-methylthiazole (0.523 g, 1.40 mmol, 70%) as white solid: mp 92–94 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.37 (s, 3H), 7.24 (dt, *J* = 1.7 and 7.7 Hz, 1H), 7.38 (dt, *J* = 1.2 and 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 7.7 Hz, 2H), 8.10 (dd, *J* = 1.7 and 7.9 Hz, 1H), 8.25 (dd, *J* = 1.4 and 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.9, 120.0, 120.9, 127.5, 128.56, 128.58, 130.41, 130.43, 131.1, 133.4, 133.9, 134.0, 150.8, 158.6, 164.3; IR (KBr): ν = 3066, 2960, 2917, 1958, 1815, 1737, 1549, 1452, 1378, 1265, 1126, 1064, 1029, 971, 758, 694, 443 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{13}BrNO_2S$ ($[M+H]^+$): 373.9845, found: *m*/*z* 373.9845.

Synthesis of 2-(2-Bromophenyl)-5-methyl-4-(methylsulfonyloxy)thiazole: To a solution of 2-(2-bromophenyl)-5-methylthiazol-4-ol (0.540 g, 2.00 mmol) in THF (6 mL) was added methanesulfonyl chloride (0.458 g, 4.00 mmol) and NEt_3 (0.304 g, 3.00 mmol) at 0 °C. The mixture was stirred at room temperature for 30 min. To the reaction mixture was added EtOAc (30 mL) and H_2O (10 mL). After being washed with H_2O (10 mL × 2), the organic layer was dried with $MgSO_4$. After evaporation in vacuo, the residual mixture was subjected to column chromatography on silica-gel (hexane : EtOAc = 20 : 1) to give 2-(2-bromophenyl)-5-methyl-4-(methylsulfonyloxy)thiazole (0.693 g, 1.99 mmol, 100%) as white solid: mp 99–100 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.48 (s, 3H), 3.47 (s, 3H), 7.28 (dt, *J* = 1.8 and 7.9 Hz, 1H), 7.41 (dt, *J* = 1.3 and 7.7 Hz, 1H), 7.70 (dd, *J* = 1.2 and 8.0 Hz, 1H), 7.97 (dd, *J* = 1.7 and 7.9 Hz, 1H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 9.8, 39.2, 121.0, 122.3, 127.6, 130.8 (large intensity), 132.9, 134.3, 149.3, 158.9; IR (KBr): ν = 3095, 3040, 3021, 2939, 2677, 2530, 1895, 1553, 1362, 1170, 1115, 1026, 972, 917, 803, 752, 631, 524, 510 cm^{-1}. HRMS (ESI) calcd for $C_{11}H_{11}BrNO_3S_2$ ($[M+H]^+$): 347.9358, found: *m*/*z* 347.9360.

Synthesis of 2-(2-Bromophenyl)-5-methyl-4-(4-tolylsulfonyloxy)thiazole: To a solution of 2-(2-bromophenyl)-5-methylthiazol-4-ol (0.540 g, 2.00 mmol) in THF (6 mL) was added 4-tolylsulfonyl chloride (0.381 g, 2.00 mmol) and 10% aqueous solution of K_2CO_3 (0.400 g, 4.00 mmol) at 0 °C. The mixture was stirred at room temperature for 2 h. To the reaction mixture was added EtOAc (30 mL) and H_2O (10 mL). After being washed with H_2O (10 mL × 2), the organic layer was dried with $MgSO_4$. After evaporation in vacuo, the residual mixture was subjected to column chromatography on silica-gel (hexane : EtOAc = 20 : 1) to give 2-(2-bromophenyl)-5-methyl-4-(4-tolylsulfonyloxy)thiazole (0.837 g,

1.97 mmol, 99%) as white solid: mp 78 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.39 (s, 3H), 2.47 (s, 3H), 7.21 (dt, *J* = 1.7 and 7.9 Hz, 1H), 7.30 (dt, *J* = 1.2 and 7.4 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.63 (dd, *J* = 1.1 and 8.0 Hz, 1H), 7.73 (dd, *J* = 1.7 and 7.9 Hz, 1H), 7.89 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.8, 21.7, 120.9, 122.5, 127.4, 128.8, 129.6, 130.5, 130.8, 133.0, 133.1, 134.1, 145.4, 149.2, 158.3; IR (KBr): ν = 3101, 3076, 3052, 2920, 2857, 1924, 1649, 1596, 1552, 1373, 1322, 1267, 1181, 1114, 1087, 914, 812, 761, 702, 673, 652, 553, 486, 442 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{15}BrNO_3S_2$ ($[M+H]^+$): 423.9671, found: *m*/*z* 423.9674.

Synthesis of 2-(2-(Phenylethynyl)phenyl)benzo[*d*]thiazole (1a): To a solution of 2-(2-bromophenyl)benzo[*d*]thiazole (0.437 g, 1.51mmol) in THF (1 mL) and NEt_3 (1.5 mL) was added PPh_3 (16.3 mg, 0.0621 mmol) and $Pd(PPh_3)_2Cl_2$ (22.2 mg, 0.0316 mmol). The solution was bubbled with N_2 for 30 min. To that solution was added CuI (13.1 mg, 0.145 mmol) and phenylacetylene (0.183 g, 1.79 mmol). The mixture was stirred for 6 h under reflux. After being cooled to room temperature, the reaction mixture was filtered with pads of Celite and Florizil washing with EtOAc. After evaporation in vacuo, the residual mixture was subjected to column chromatography on silica-gel (hexane only to hexane : EtOAc = 20 : 1) to give 2-(2-(phenylethynyl)phenyl)benzo[*d*]thiazole (**1a**) (0.417g, 1.34 mmol, 89%) as brown solid: mp 73–74 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39-7.55 (m, 7H), 7.62-7.64 (m, 2H), 7.72-7.74 (m, 1H), 7.96 (diffused d, *J* = 8.0 Hz, 1H), 8.14 (diffused d, *J* = 8.2 Hz, 1H), 8.39-8.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 88.7, 96.6, 121.5, 121.6, 123.0, 123.2, 125.2, 126.1, 128.4, 128.6, 128.8, 129.4, 129.9, 131.5, 134.0, 134.8, 136.0, 152.6, 165.7; IR (KBr): ν = 3060, 2924, 2853, 2218, 1948, 1824, 1758, 1647, 1597, 1564, 1496, 1431, 1318, 1272, 1098, 964, 759, 689, 540, 433 cm^{-1}. HRMS (ESI) calcd for $C_{21}H_{14}NS$ ($[M+H]^+$): 312.0841, found: *m*/*z* 312.0840.

Synthesis of 2-(2-(Phenylethynyl)phenyl)thiazole (1b): The titled compound was prepared with 2-(2-bromophenyl)thiazole (0.305 g, 1.27 mmol) for 9 h in 49% yield (0.163 g, 0.624 mmol) according to a procedure mentioned in **1a**: yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38-7.48 (m, 6H), 7.60-7.63 (m, 2H), 7.68 (dd, *J* = 1.4 and 7.7 Hz, 1H), 7.95 (d, *J* = 3.2 Hz, 1H), 8.35 (dd, *J* = 1.5 and 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 89.0, 96.6, 120.1, 120.5, 123.0, 128.3, 128.4, 128.67, 128.70, 129.0, 131.5, 133.7, 134.8, 142.3, 165.3; IR (KBr): ν = 3112, 3063, 2925, 2213, 1951, 1826, 1757, 1598, 1496, 1442, 1285, 1156, 1059, 971, 875, 756, 689, 636, 515, 454 cm^{-1}. HRMS (ESI) calcd for $C_{17}H_{12}NS$ ($[M+H]^+$): 262.0685, found: *m*/*z* 262.0684.

Synthesis of 4-Methoxy-5-methyl-2-(2-(phenylethynyl)phenyl)thiazole (1c): The titled compound was prepared with 2-(2-bromophenyl)-4-methoxy-5-methylthiazole (0.262 g, 0.921 mmol) for 6 h in 96% yield (0.271 g, 0.864 mmol) according to a procedure mentioned in **1a**: yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.32 (s, 3H), 4.07 (s, 3H), 7.32 (dt, *J* = 1.5 and 7.5 Hz, 1H), 7.38-7.43 (m, 4H), 7.60-7.63 (m, 3H), 8.28 (dd, *J* = 1.2 and 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 9.1, 57.5, 89.1, 96.4, 107.5, 119.2,

123.2, 127.3, 128.1, 128.4, 128.5, 128.6, 131.4, 133.8, 134.9, 156.2, 159.6; IR (KBr): ν = 3061, 2940, 2858, 2213, 1550, 1348, 1148, 973, 755, 688 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{16}NOS$ ($[M+H]^+$): 306.0942, found: *m*/*z* 306.0947.

Synthesis of 4-Acetoxy-5-methyl-2-(2-(phenylethynyl)phenyl)thiazole (1d): The titled compound was prepared with 4-acetoxy-2-(2-bromophenyl)-5-methylthiazole (0.377 g, 1.21 mmol) for 17.5 h in 67% yield (0.269 g, 0.807 mmol) according to a procedure mentioned in **1a**: brown solid; mp 100–101 °C ($CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 2.30 (s, 3H), 2.36 (s, 3H), 7.32-7.42 (m, 5H), 7.59-7.64 (m, 3H), 8.24 (diffused d, *J* = 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 9.9, 20.6, 88.8, 96.9, 118.9, 119.7, 123.0, 127.7, 128.4, 128.6, 128.7, 128.9, 131.5, 133.7, 134.2, 150.5, 158.8, 168.5; IR (KBr): ν = 3066, 3043, 2918, 2857, 2211, 2071, 1759, 1552, 1210, 1118, 769, 690 cm^{-1}. HRMS (APPI) calcd for $C_{20}H_{16}NO_2S$ ($[M+H]^+$): 334.0896, found: *m*/*z* 334.0898.

Synthesis of 4-Benzyloxy-5-methyl-2-(2-(phenylethynyl)phenyl)thiazole (1e): The titled compound was prepared with 4-benzoyloxy-2-(2-bromophenyl)-5-methylthiazole (0.523g, 1.40mmol) for 20 h in 70% yield (0.390g, 0.986mmol) according to a procedure mentioned in **1a**: white solid; mp 123–124 °C ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 2.36 (s, 3H), 7.35-7.42 (m. 5H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.62-7.69 (m, 4H), 8.25-8.28 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 10.0, 88.9, 96.9, 119.2, 119.8, 123.0, 127.8, 128.5, 128.59, 128.64, 128.7, 128.8, 128.9, 130.5, 131.5, 133.8, 133.9, 134.3, 150.7, 159.0, 164.3; IR (KBr): ν = 3066, 2921, 2855, 2218, 1954, 1740, 1549, 1494, 1255, 1121, 1059, 758, 700, 652, 546 cm^{-1}. HRMS (APPI) calcd for $C_{25}H_{17}NO_2S$ ($[M+H]^+$): 396.1053, found: *m*/*z* 396.1050.

Synthesis of 5-Methyl-4-(methylsulfonyloxy)-2-(2-(phenylethynyl)phenyl)thiazole (1f): The titled compound was prepared with 2-(2-bromophenyl)-5-methyl-4-(methylsulfonyloxy)thiazole (0.540g, 2.00mmol) for 14 h in 98% yield (0.723g, 1.96mmol) according to a procedure mentioned in **1a**: white solid; mp 140–142 °C ($CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ = 2.47 (s, 3H), 3.45 (s, 3H), 7.38-7.45 (m, 5H), 7.59-7.61 (m, 2H), 7.65-7.67 (m, 1H), 8.16-8.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 9.9, 39.3, 88.5, 97.2, 120.1, 121.5, 122.8, 127.5, 128.56, 128.64, 129.0, 129.3, 131.5, 133.8, 134.0, 149.2, 159.2; IR (KBr): ν = 3085, 3009, 2925, 2854, 2531, 2209, 1950, 1721, 1647, 1553, 1495, 1441, 1368, 1315, 1282, 1176, 1105, 978, 917, 803, 770, 686, 572, 502, 462 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{16}NO_3S_2$ ($[M+H]^+$): 370.0566, found: *m*/*z* 370.0561.

Synthesis of 5-Methyl-2-(2-(phenylethynyl)phenyl)-4-(4-tolylsulfonyloxy)thiazole (1g): The titled compound was prepared with 5-(2-bromophenyl)-4-methyl-4-(4-tolylsulfonyloxy)thiazole (0.666g, 1.57mmol) for 14 h in 65% yield (0.455g, 1.02mmol) according to a procedure mentioned in **1a**: white solid; mp 122–124 °C ($CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ = 2.39 (s, 3H), 2.47 (s, 3H), 7.32-7.42 (m, 7H), 7.58-7.62 (m, 3H), 7.86-7.91 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 9.9, 21.7, 88.6, 97.3, 119.7, 121.5, 122.8, 127.4, 128.4, 128.5, 128.9, 129.0, 129.56, 129.62, 131.4, 133.3, 133.7, 133.8, 145.3, 149.0,

158.4; IR (KBr): ν = 3083, 3049, 2985, 2924, 2857, 2210, 1993, 1962, 1922, 1741, 1656, 1595, 1550, 1495, 1440, 1370, 1321, 1193, 1088, 969, 910, 814, 767, 681, 662, 581, 550, 458 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{20}NO_3S_2$ ($[M+H]^+$): 446.0879, found: *m*/*z* 446.0868.

General Procedure for the Cyclization of 1 with I_2: To a solution of **1** (0.3 mmol) in $CHCl_3$ (3 mL) was added I_2 (1.0 mmol or 2.0 mmol) at room temperature. During the progression of the reaction, the precipitate was observed. After being stirred at that temperature, the precipitate was collected by washing *n*-hexane. After drying in vacuo, the corresponding cyclic compounds ($\mathbf{2}^+\bullet I^-$ and/or $\mathbf{2}^+\bullet I_3^-$) was obtained. The ratio of I^- and I_3^- was estimated from the results of elemental analysis.

Mixture of 5-Iodo-6-phenylbenzo[4,5]thiazolo[2,3-*a*]isoquinolin-7-ium Iodide and Triiodide ($2a^+\bullet I^-$ and $2a^+\bullet I_3^-$): Yellow solid; mp 281–282 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 6.20 (d, *J* = 9.0 Hz, 1H), 7.45 (dt, *J* = 1.4 and 7.4 Hz, 1H), 7.65-7.67 (m, 2H), 7.78 (t, *J* = 7.3 Hz, 1H), 7.81-7.85 (m, 3H), 8.19 (dt, *J* = 1.1 and 7.2 Hz, 1H), 8.37 (dt, *J* = 1.1 and 7.2 Hz, 1H), 8.53 (d, *J* = 8.2 Hz, 1H), 8.60 (dd, *J* = 1.0 and 8.2 Hz, 1H), 8.88 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 104.4, 119.8, 122.8, 125.2, 127.9, 128.2, 128.3, 129.3, 130.2, 130.4, 131.8, 132.3, 133.9, 134.5, 137.7, 138.0, 139.6, 143.7, 160.9; IR (KBr): ν = 3140, 3039, 1958, 1582, 1481, 1453, 1408, 1336, 1267, 1161, 1035, 1013, 744, 702, 574 cm^{-1}. Anal. Calcd for $C_{21}H_{13}INS^+\bullet 0.28I^-\bullet 0.72I_3^-$: C, 33.72; H, 1.75; N, 1.87. Found: C, 33.99; H, 1.61; N, 1.80 (for entry 1 of Table 1). Found: C, 33.96; H, 1.62; N, 1.76 (for entry 2 of Table 1). Anal. Calcd for $C_{21}H_{13}INS^+\bullet 0.74I^-\bullet 0.26I_3^-$: C, 39.96; H, 2.08; N, 2.22. Found: C, 39.98; H, 2.02; N, 2.22 (for entry 3 of Table 1).

Mixture of 6-Iodo-5-phenylthiazolo[2,3-*a*]isoquinolin-4-ium Iodide and Triiodide ($2b^+\bullet I^-$ and $2b^+\bullet I_3^-$): Pale brown solid; mp 293–294 °C (dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.58 (dd, *J* = 1.8 and 8.0 Hz, 2H), 7.72-7.78 (m, 3H), 7.88 (d, *J* = 4.2 Hz, 1H), 8.11 (dt, *J* = 1.0 and 7.2 Hz, 1H), 8.26 (dt, *J* = 1.2 and 7.2 Hz, 1H), 8.30 (d, *J* = 4.1 Hz, 1H), 8.45 (d, *J* = 8.3 Hz, 1H), 8.80 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 101.0, 122.8, 123.3, 127.0, 129.8, 130.0, 131.1, 131.9, 132.3, 133.2, 133.6, 136.3, 136.4, 142.4, 157.7; IR (KBr): ν = 3114, 1606, 1569, 1472, 1412, 1331, 1254, 1111, 1034, 861, 755, 696, 681, 623 cm^{-1}. Anal. Calcd for $C_{17}H_{11}INS^+\bullet 0.62I^-\bullet 0.38I_3^-$: C, 33.39; H, 1.81; N, 2.29. Found: C, 33.53; H, 1.80; N, 2.29 (for entry 4 of Table 1). Anal. Calcd for $C_{17}H_{11}INS^+\bullet 0.04I^-\bullet 0.96I_3^-$: C, 26.91; H, 1.47; N, 1.85. Found: C, 26.93; H, 1.32; N, 1.70 (for entry 5 of Table 1).

6-Iodo-2-methoxy-3-methyl-5-phenylthiazolo[2,3-*a*]isoquinolin-4-ium Triiodide ($2c^+\bullet I_3^-$): Pale brown solid; mp 148–151 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 2.56 (s, 3H), 3.33 (s, 3H), 7.50-7.54 (m, 2H), 7.58-7.63 (m, 3H), 8.08 (dt, *J* = 1.0 and 7.2 Hz, 1H), 8.22 (dt, *J* = 1.1 and 7.3 Hz, 1H), 8.44 (d, *J* = 8.1 Hz, 1H), 8.69 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 10.9, 63.8, 104.8, 116.5, 122.8, 125.2, 128.2, 129.9 (large intensity), 131.9, 132.8, 133.9, 136.2, 137.5, 141.3, 148.5, 152.7; IR

(KBr): ν = 3030, 2938, 1619, 1478, 1410, 1309, 1266, 977, 758, 703 cm^{-1}. Anal. Calcd for $C_{19}H_{15}INOS^{+}\bullet I_3^{-}$: C, 28.07; H, 1.86; N, 1.72. Found: C, 28.07; H, 1.75; N, 1.55.

2-Acetoxy-6-iodo-3-methyl-5-phenylthiazolo[2,3-*a*]isoquinolin-4-ium Triiodide ($2d^{+}\bullet I_3^{-}$): Brown solid; mp 174–175 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ = 1.57 (s, 3H), 2.45 (s, 3H), 7.47-7.50 (m, 2H), 7.67-7.69 (m, 3H), 8.11 (t, *J* = 7.2 Hz, 1H), 8.25 (t, *J* = 8.4 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 8.73 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ = 11.2, 18.9, 105.9, 121.7, 122.6, 125.5, 129.0, 130.4, 130.5, 132.1, 132.9, 133.9, 136.6, 136.7, 137.6, 140.3, 154.1, 166.2; IR (KBr): ν = 3033, 2919, 1971, 1806, 1617, 1476, 1412, 1262, 1141, 1002, 812, 754, 703 cm^{-1}. Anal. Calcd for $C_{20}H_{15}INO_2S^{+}\bullet I_3^{-}$: C, 28.56; H, 1.80; N, 1.67. Found: C, 28.64; H, 1.69; N, 1.42.

2-(Benzoyloxy)-6-iodo-3-methyl-5-phenylthiazolo[2,3-*a*]isoquinolin-4-ium Triiodide ($2e^{+}\bullet I_3^{-}$): Dark brown solid; mp 190–192 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.48 (s, 3H), 6.91 (t, *J* = 7.5 Hz, 1H), 7.20-7.45 (br, 4H), 7.48 (t, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 7.1 Hz, 2H), 7.76 (t, *J* = 7.5 Hz, 1H), 8.14 (dt, *J* = 1.0 and 7.2 Hz, 1H), 8.26 (dt, *J* = 1.2 and 7.3 Hz, 1H), 8.45 (d, *J* = 8.3 Hz, 1H), 8.78 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 11.3, 106.1, 122.0, 122.7, 124.7, 125.6, 128.7, 128.8, 129.7, 129.8, 130.6, 132.2, 133.0, 134.0, 135.6, 136.3, 136.7, 137.8, 140.5, 154.3, 161.6; IR (KBr): ν = 3045, 2989, 1966, 1835, 1761, 1622, 1475, 1408, 1321, 1222, 1126, 994, 770, 695 cm^{-1}. Anal. Calcd for $C_{25}H_{17}INO_2S^{+}\bullet I_3^{-}$: C, 33.25; H, 1.90; N, 1.55. Found: C, 33.30; H, 1.73; N, 1.42.

6-Iodo-3-methyl-2-((methylsulfonyl)oxy)-5-phenylthiazolo[2,3-*a*]isoquinolin-4-ium Triiodide ($2f^{+}\bullet I_3^{-}$): Brown solid; mp 152–153 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ = 2.82 (s, 3H), 3.00 (s, 3H), 7.74 (s, 5H), 8.19 (dt, *J* = 1.1 and 7.2 Hz, 1H), 8.34 (dt, *J* = 1.1 and 7.4 Hz, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 8.78 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6/CS_2) δ = 11.5, 36.3, 104.5, 121.8, 124.6, 125.0, 127.8, 130.0, 130.9, 131.7, 133.2, 134.0, 135.6 (large intensity), 136.3, 140.1, 154.9; IR (KBr): ν = 3063, 3026, 2992, 2916, 1601, 1478, 1411, 1386, 1182, 776, 696, 544, 513 cm^{-1}. Anal. Calcd for $C_{19}H_{15}INO_3S_2^{+}\bullet I_3^{-}$: C, 26.02; H, 1.72; N, 1.60. Found: C, 26.09; H, 1.64; N, 1.36.

6-Iodo-3-methyl-5-phenyl-2-(4-tolylsulfonyloxy)thiazolo[2,3-*a*]isoquinolin-4-ium Triiodide ($2g^{+}\bullet I_3^{-}$): Yellow solid; mp 136–138 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ = 2.05 (s, 3H), 2.52 (s, 3H), 7.56-7.63 (m, 7H), 7.74 (d, *J* = 8.5 Hz, 2H), 8.19 (dt, *J* = 1.0 and 7.2 Hz, 1H), 8.34 (dt, *J* = 1.1 and 7.3 Hz, 1H), 8.61 (d, *J* = 8.3 Hz, 1H), 8.76 (d, *J* = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ = 10.3, 20.1, 103.6, 121.9, 124.60, 124.64, 127.6, 128.6, 128.8, 129.7, 130.1, 130.3, 131.6, 133.4, 133.9, 135.0, 136.0, 136.3, 140.7, 147.8, 155.3; IR (KBr): ν = 3057, 2916, 1602, 1474, 1394, 1303, 1193, 1087, 762, 683, 565, 544 cm^{-1}. Anal. Calcd for $C_{25}H_{19}INO_3S_2^{+}\bullet I_3^{-}$: C, 31.50; H, 2.01; N, 1.47. Found: C, 31.49; H, 1.90; N, 1.34.

X-Ray Crystallography: X-Ray diffraction data for the crystals were measured on a Bruker Smart APEXII CCD diffractometer with graphite-monochromated Mo Kα (λ = 0.71073 Å) radiation and on a

Bruker Smart APEXII ultra CCD diffractometer with Cu Kα (λ = 1.54178 Å) radiation. Data collections were carried out at 173 K. All structures were solved by a direct method SHELXS-97,[17] and the non-hydrogen atoms were refined anisotropically against F^2, with full-matrix least-squares methods SHELEXL-97[18] in a computer program package from Bruker AXS. All hydrogen atoms were positioned geometrically and refined as riding. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; Fax.: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 3. Crystallographic Data for Thiazolo[2,3-*a*]isoquinolinium Salts

Compound	**2a**$^+$•I^-•DMSO	**2c**$^+$•I_3^-	**2d**$^+$•I_3^-
Formula	$C_{23}H_{19}I_2NOS_2$	$C_{19}H_{15}I_4NOS$	$C_{20}H_{15}I_4NO_2S$
Molecular weight	643.31	812.98	840.99
Crystal size / mm^3	0.300 × 0.300 × 0.200	0.300 × 0.200 × 0.050	0.300 × 0.200 × 0.100
Crystal system	triclinic	triclinic	monoclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1/n$
a / Å	8.5155(7)	8.430(4)	8.4544(6)
b / Å	10.5203(9)	11.490(5)	24.8611(16)
c / Å	13.9161(12)	12.156(6)	11.4931(8)
α / °	78.0632(11)	90.690(6)	90
β / °	10.5203(9)	90.964(6)	103.7240(10)
γ / °	83.3571(12)	100.443(6)	90
V / Å^3	1162.59(17)	1157.6(9)	2346.7(3)
Z	2	2	4
D_c / cm^{-3}	1.838	2.332	2.380
μ / mm^{-1}	2.899	5.482	5.416
reflns collect	6475	6621	13400
unique reflns [*R*(int)]	4977 [0.0161]	5019 [0.0353]	5334 [0.0343]
parameters	264	240	258
R_1 ($I > 2.0\sigma(I)$)	0.0352	0.0480	0.0289
wR_2 (all data)	0.1282	0.1399	0.0660
largest diff peak and hole (e Å^{-3})	1.548/-0.994	1.586/-2.178	0.922/-0.865
GOF	1.109	0.983	1.013
CCDC number	1820600	1820601	1820602

Table 3. (continued)

Compound	**2e**$^{+}$•I_3^-	**2f**$^{+}$•I_3^-	**2g**$^{+}$•I_3^-
Formula	$C_{25}H_{17}I_4NO_2S$	$C_{19}H_{15}I_4NO_3S_2$	$C_{25}H_{19}I_4NO_3S_2$
Molecular weight	903.05	877.04	953.13
Crystal size / mm^3	0.600 × 0.600 × 0.200	0.800 × 0.600 × 0.100	0.250 × 0.100 × 0.050
Crystal system	triclinic	monoclinic	monoclinic
Space group	$P\bar{1}$	$P2_1/n$	$P2_1/c$
a / Å	8.235(3)	8.9451(17)	13.8359(10)
b / Å	10.300(3)	24.292(5)	26.162(2)
c / Å	17.402(6)	11.397(2)	16.2382(13)
α / °	73.589(4)	90	90
β / °	88.707(4)	109.110(2)	103.443(4)
γ / °	70.107(3)	90	90
V / Å^3	1327.0(7)	2340.0(8)	5716.8(8)
Z	2	4	8
D_c / cm^{-3}	2.260	2.489	2.215
μ / mm^{-1}	4.798	5.526	35.837
reflns collect	7524	12815	36190
unique reflns [*R*(int)]	5789 [0.0361]	5347 [0.0478]	10326 [0.0509]
parameters	299	267	635
R_1 ($I > 2.0\sigma(I)$)	0.0418	0.0479	0.0949
wR_2 (all data)	0.1200	0.1449	0.2710
largest diff peak and hole (e Å^{-3})	1.379/-0.385	1.824/-2.238	7.833/-1.822
GOF	1.042	1.055	1.024
CCDC number	1820603	1820604	1823070

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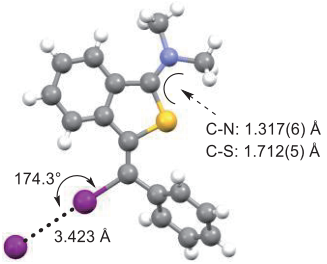

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