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Synthesis of Thiazoles and Isothiazoles via Three-Component Reaction of Enaminoesters, Sulfur, and Bromodifluoroacetamides/Esters

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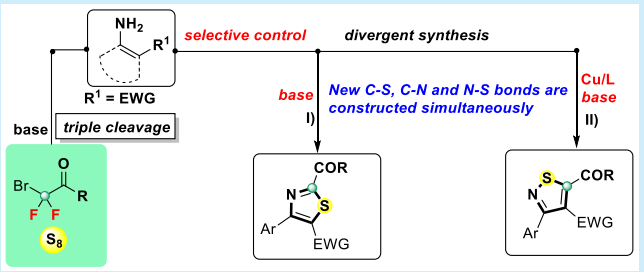
ABSTRACT: A three-component strategy for the synthesis of thiazoles and isothiazoles has been developed by employing enaminoesters, fluorodibromoiamides/ester, and sulfur. The thiazoles and isothiazoles were formed via two C−F bond cleavages along with the formation of new C−S, C−N, and N−S bonds. The strategy provides high selectivity for the synthesis of thiazoles/isothiazoles, which have vital applications in drug discovery and development.



Believed to be an important chemical feedstock, with more than 60 million tons produced annually, S_8 is employed in various fields, such as organic chemistry, inorganic chemistry, as well as polymer chemistry.[1] Meanwhile, S-containing molecules widely exist in polymeric materials, natural products, pharmaceuticals, and agrochemicals (Figure 1).[2] Despite considerable developments in S_8-involved transformations,[3,4] the regioselective installation of elemental sulfur into the various target molecules has not been supplemented.

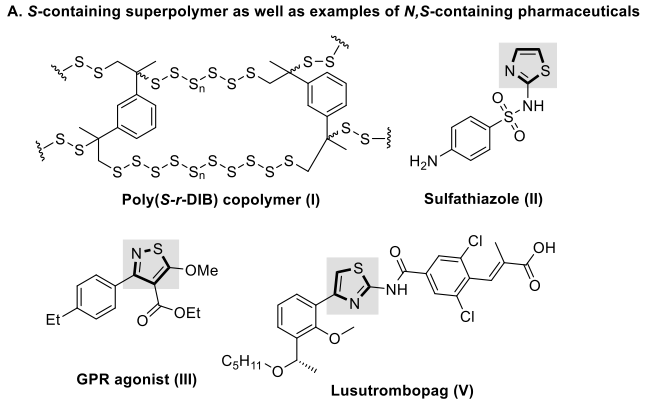


Figure 1. S-Containing superpolymer as well as pharmaceutical examples containing thiazoles and isothiazoles scaffolds.

Commercially available halodifluoroalkyl reagents (XCF_2R, X = F, Cl, Br) displaying versatile reactivities, represent one of the significant synthetic building blocks and key subunits of pharmaceutically active molecules.[5] Among the well-known organofluorine species, bromodifluoroalkyl compounds are one of the most popular reagents to forge valuable molecules in different roles, such as the difluoroalkyl radical, difluorocarbene precursors, and C1 and C2 synthons.[6−9] In a continuation of our ongoing interest in the development of new reactivity of bromodifluoroalkyl compounds as well as heteroatom chemistry,[7−9] we envisioned that S_8 as a substrate could react with certain amines and halodifluoroalkyl reagents and eventually be introduced into the final product to render N,S-heterocycles. However, there are challenges involved in the divergent synthesis of these heterocycles: (1) On the basis of previous work, S_8 acted only as a catalyst,[9b] and the incorporation of it into the target molecules is problematic. (2) S_8 reacts with difluorocarbene to generate thiocarbonyl fluoride, and thus suppressing the generation of the $F_2C{=}S$ intermediate[3b] from readily accessible difluorocarbene species under basic conditions is a big issue. (3) There are many possible side reactions, and hence precise control of the reaction is highly challenging.

Herein we report the synthesis of thiazoles and isothiazoles involving the reaction of enaminoesters[10] with bromodifluoroalkyl compounds. Besides the side reactions between the amines and bromodifluoroalkyl reagents, such as the generation of isocyanides and isothiocyanates,[9a,c] the formylation of amines[9d] as well as self-attack yielding amidine derivatives[9e] are well avoided (Scheme 1).

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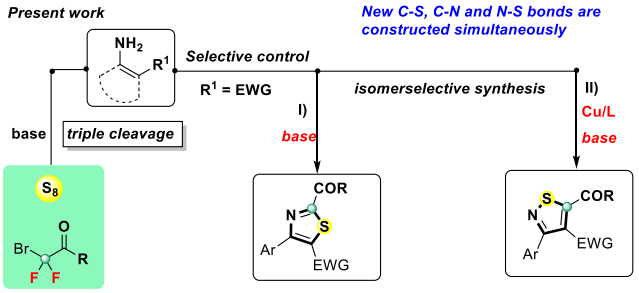
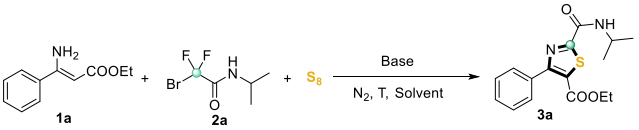
Scheme 1. Three-Component Reaction of Enaminoesters, Sulfurs, and Bromodifluoroacetamides/Esters



To verify the postulation, we reacted ethyl 3-amino-3-phenyl acrylate (**1a**), 2-bromo-2,2-difluoro-*N*-isopropylacetamide (**2a**), and S_8 to optimize the conditions for the assembly of the thiazoles (Table 1). To our delight, the desired product **3a**

Table 1. Optimization of Reaction Conditions for the Synthesis of Thiazole 3a[a]



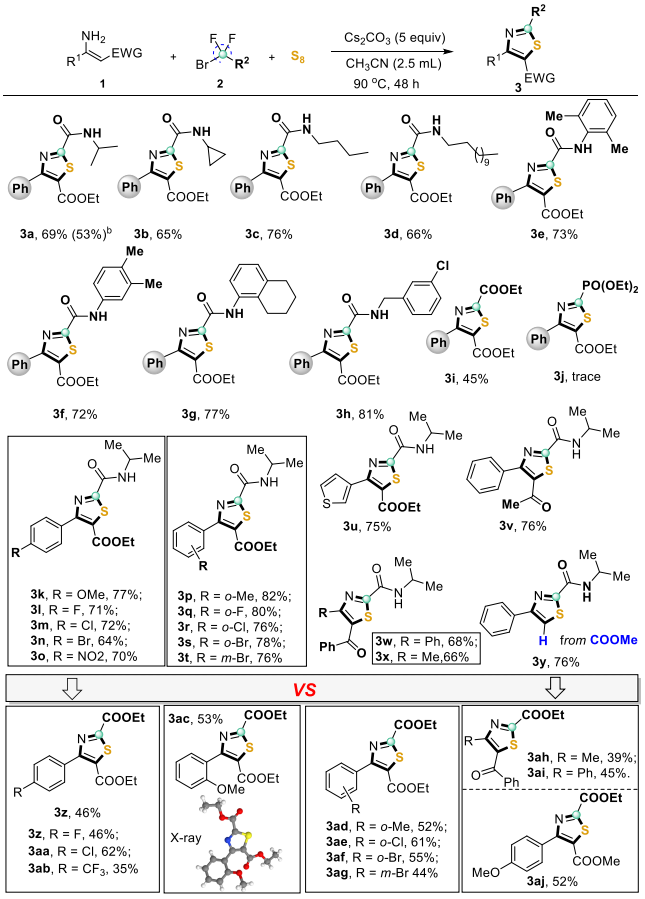
entry	base	solvent	T (°C)	yield of **3a** (%)[b]
1	Cs_2CO_3	MeCN	110	58
2	Na_2CO_3	MeCN	110	32
3	K_2CO_3	MeCN	110	19
4	DBU	MeCN	110	0
5	^{t}BuONa	MeCN	110	0
6	Cs_2CO_3	toluene	110	0
7	Cs_2CO_3	THF	110	50
8	Cs_2CO_3	dioxane	110	26
9[c]	Cs_2CO_3	MeCN	110	40
10[d]	Cs_2CO_3	MeCN	110	38
11[e]	Cs_2CO_3	MeCN	110	52
12[e]	Cs_2CO_3	MeCN	120	29
13[e]	**Cs_2CO_3**	**MeCN**	**90**	**76 (69)**[f]
14[e]	Cs_2CO_3	MeCN	80	68

[a]Reaction conditions: **1a** (0.1 mmol), 2-bromo-2,2-difluoro-*N*-isopropylacetamide (**2a**, 1.5 equiv), S_8 (60 mol %), base (5.0 equiv), and CH_3CN (2 mL) under N_2 at 90 °C for 48 h. [b]GC yield. [c]CH_3CN (1.0 mL). [d]CH_3CN (1.5 mL). [e]CH_3CN (2.5 mL). [f]Isolated yield.

could be isolated in 58% yield when the reaction was conducted using Cs_2CO_3 as the base in CH_3CN at 110 °C (Table 1, entry 1). To enhance the yield of the desired product, we screened various bases, such as Na_2CO_3, K_2CO_3, DBU, and *t*-BuONa. It turned out that Cs_2CO_3 was the optimal base (entries 2−5). We then examined the effect of solvents; however, no superior results were achieved (Table 1, entries 6−8). After screening the reaction concentrations and the temperatures (Table 1, entries 9−14), we found that the yield of thiazole **3a** was increased to 76% when 2.5 mL of CH_3CN was added, and the reaction was conducted at 90 °C for 48 h (Table 1, entry 13).

With the optimal conditions in hand, we explored the substrate scope for the synthesis of various substituted thiazoles, as shown in Scheme 2. A variety of bromodifluoroamides were tested with enaminoester **1a** under the standard

Scheme 2. Scope of the Synthesis of Thiazoles 3[a]



[a]Reaction condition 1: **1** (0.1 mmol), **2** (1.5 equiv), S_8 (60 mol %), Cs_2CO_3 (5.0 equiv), and CH_3CN (2.5 mL) under N_2 at 90 °C for 48 h. [b]**1a** (1 mmol).

reaction conditions to afford the desired products (**3a−h**) in good yields. A large-scale synthesis was further carried out under the standard conditions for the construction of **3a**. Gratifyingly, the efficiency was not significantly affected by the scale-up, and **3a** was obtained in 53% yield. (See the Supporting Information (SI) for details.) $BrCF_2COOEt$ could also react with ethyl 3-amino-3-phenyl acrylate (**1a**), and the corresponding product **3i** was obtained in 45% yield, lower than its amide counterparts, probably due to the fact that $BrCF_2COOEt$ easily decomposed into difluorocarbene under the basic conditions. However, diethyl (bromodifluoromethyl)phosphonate did not give the corresponding thiazole compound (**3j**). Subsequently, the substrate scope with respect to the R^1 and the electron-withdrawing group (EWG) on enaminoesters were also investigated (Scheme 2). Various enaminoesters with different electronic and steric properties of substituents were compatible in the process. The corresponding thiazoles (**3k−x**) were obtained in moderate to good yields under the conditions. Surprisingly, when methyl ester **1y** was used as a substrate, the deesterification product **3y** was obtained in 76% yield.

Compared with bromodifluoroamides, $BrCF_2COOEt$ delivered the corresponding thiazoles in relatively low yields, probably owing to the lower stability of $BrCF_2COOEt$ compared with its counterpart amides (**3z−aj** in Scheme 2; also see **3i**). Specifically, the steric hindrance (**3p−s**, **3ac−af**)

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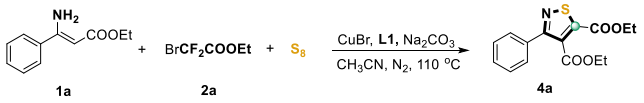
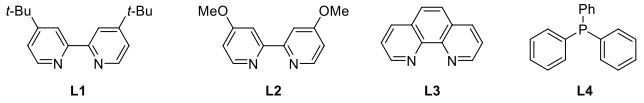
and different substituents on the aryl ring of enaminoesters have a slight effect on this transformation, furnishing the corresponding targeted thiazoles in decent yields. In addition, the absolute structure of product **3ac** was unambiguously determined by X-ray crystallography.

The success of the above transformation prompted us to investigate the feasibility of the formation of isothiazoles with the same substrates by selectively controlling the reaction conditions. The enaminoester ethyl 3-amino-3-phenyl acrylate (**1a**), $BrCF_2COOEt$, and S_8 were chosen as substrates to optimize the reaction conditions for forging such a product (Table 2). When the reaction was conducted in CH_3CN at 110 °C under a nitrogen atmosphere by using CuBr as the catalyst and Na_2CO_3 as the base, the isothiazole **4a** was obtained in 66% yield (Table 1, entry 1). Subsequently, a range of Cu salts and copper catalysts were screened, and it was found that Cu powder displayed the best reactivities. Thus we carried out a series of experiments and found that 80 mol % of Cu powder is the best choice (Table 1, entry 2). 1.10-Phen (**L3**) was proven to be the optimal ligand among the ligands tested (Table 1, entry 5). The marginal improvements in yield of the product were achieved when Na_2CO_3 was replaced by inorganic base Na_3PO_4. To our delight, the yield of the desired product **4a** was slightly raised to 88% when the reaction was conducted at 90 °C (entry 7). No product was obtained when the reaction was conducted under air (entry 8). (See the SI for details.)

Table 2. Optimization of the Reaction for Compounds 4[a]



entry	variation from the standard conditions	4a (%)[b]
1	none	66
2	CuI instead of CuBr	72
3	CuCl instead of CuBr	40
4	Cu instead of CuBr	53(71)[c] (76)[d]
5	**L**	40(80)[e] (10)[f]
6	Na_3PO_4 instead of Na_2CO_3	84
7	at 90 °C	88
8	under air	trace

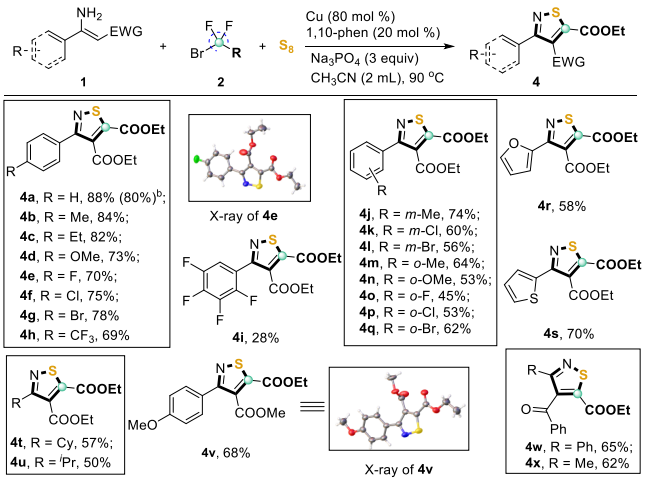


[a]Reaction conditions: **1a** (0.3 mmol), **2a** (3.0 equiv), S_8 (60 mol % equiv), CuBr (10 mol %), L1 (20 mol %), Na_2CO_3 (5.0 equiv), and CH_3CN (2.5 mL) under N_2 at 110 °C for 12 h. [b]Isolated yield, N.R. = no reaction. [c]Cu: 50 mol %. [d]Cu: 80 mol %. [e]L3 instead of L1. [f]L4 instead of L1.

After the optimized reaction condition was identified, the generality of this transformation to afford isothiazoles was investigated (Scheme 3). The enaminoesters having neutral and electron-donating groups on the aromatic ring displayed good reactivities, producing 3,4-diester 5-arylisothiazole (**4a**–**d**) in decent yields. In addition, when $BrCF_2COOEt$ was replaced with ICF_2COOEt, the desired product **4a** was obtained in 80% yield. The aromatic ring of electron-withdrawing and halo-substituted enaminoesters was also amenable, delivering the corresponding isothiazoles (**4e**–**i**) in 28–78% yield. The structure of **4e** was unequivocally confirmed by X-ray diffraction analysis. In addition to para substitution on the aromatic ring of *β*-enaminoesters, ortho- and meta-substituted enaminoesters were also compatible in the reaction, affording the corresponding isothiazoles (**4j**–**q**) in up to 74% yield. Heterocyclic-substituted enamine esters also led to the formation of **4r** and **4s** in 58 and 70% yield, respectively. Besides the aromatic enamine esters, alkyl-substituted enaminoesters under the same reaction conditions furnished the expected isothiazoles **4t** and **4u** in modest yields. To further broaden the scope of the method, several other enaminoesters were tested in the transformation. The corresponding isothiazoles (**4v**–**x**) were furnished in 68, 65, and 62% yield. The structure of **4v** was unequivocally confirmed by X-ray diffraction analysis.

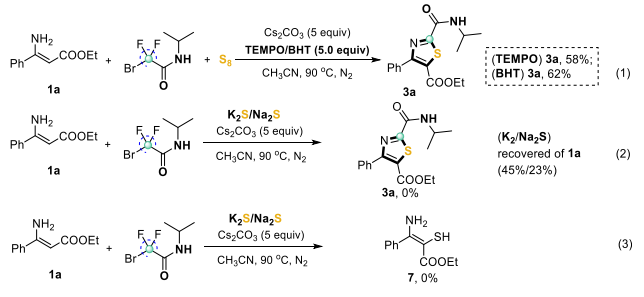
To shed light on the mechanism of the reaction, a sequence of control experiments was performed (Schemes 4 and 5).

Scheme 3. Scope for the Synthesis of Isothiazoles 4[a]



[a]Reaction conditions: 2:1 (0.3 mmol), **2** (3.0 equiv), S_8 (60 mol %), Cu (80 mol %), 1,10-phen (20 mol %), Na_3PO_4 (3.0 equiv), and CH_3CN (2 mL) under N_2 at 90 °C for 20 h. [b]**2** is ethyl difluoroiodoacetate.

Scheme 4. Control Experiments for the Formation of Thiazoles 3



First, a control experiment was conducted by using ethyl 3-amino-3-phenyl acrylate (**1a**) as a substrate and 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-ditertbutyl-4-methylphenol (BHT) as the radical inhibitor. In this case, the desired product thiazole **3a** was isolated in 58 and 62% yield (Scheme 4, eq 1), which indicated that a single-electron-transfer (SET) pathway was not involved in the formation of thiazoles **3**. Second, no target product **3a** or compound **7** was formed when S_8 was replaced with K_2S or Na_2S (Scheme 4, eqs 2 and 3), and the above results suggested that sulfion was not

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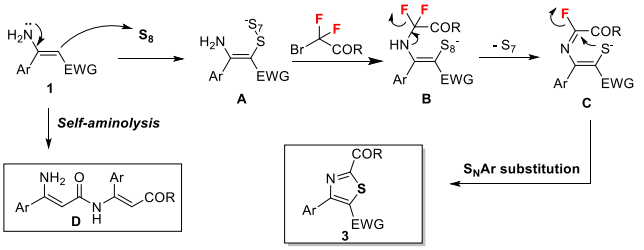
Scheme 5. Possible Reaction Pathway for the Formation of Thiazoles

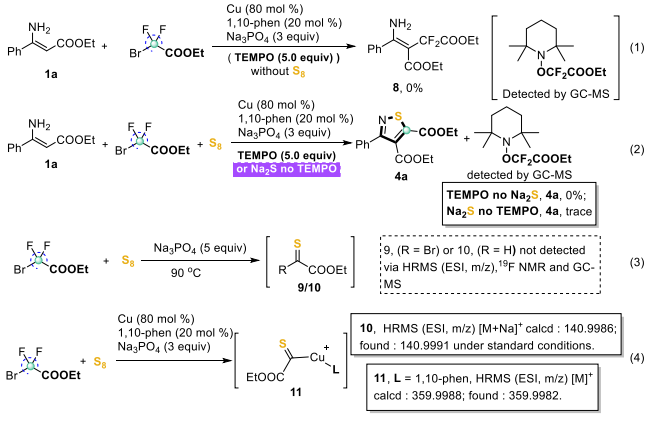


generated or involved in the construction of thiazoles **3**. We conducted multiple reactions in the absence of $BrCF_2COOEt$; no desired compound **7** was ever detected by GCMS, HRMS, or NMR (see SI for details), which demonstrated that the formation of the compound **7** must be associated with bromodifluoroalkyl reagents.

On the basis of the previously described experimental results and the previous work,[9a,b,d] the plausible mechanism for S_8-involved thiazole formation is depicted in Scheme 5. Initially, enaminoester **1** attacks S_8, rendering intermediate **A**. Then, the NH_2 of complex **A** works with bromodifluoroacetamides/esters to provide active species **B**, which further undergoes the S_8-promoted defluorination along with desulfuration to generate the active compound **C**, which is sensitive to basic conditions. Finally, the target products **3** are obtained via S_NAr substitution.[9d] Meanwhile, enaminoesters might undergo self-aminolysis to deliver the dimeric product **D** as the main byproduct (Scheme 5), which has been detected by GC−MS during the transformation.

Subsequently, the reactions for the construction of isothiazoles **4** were performed without S_8, and no corresponding compound **8** was observed (Scheme 6, eq 1). In addition,

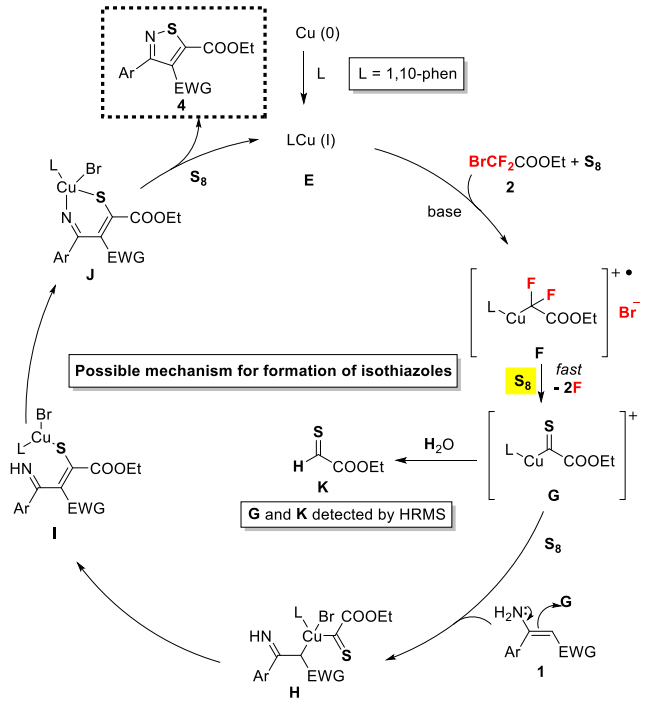
Scheme 6. Control Experiments for the Formation of Isothiazoles 4



when radical scavenger was added to this reaction, the desired product **8** was not delivered, and the TEMPO−CF_2COOEt adduct was detected by GCMS (Scheme 6, eq 2). These results suggested that the CF_2COOEt radical was generated in the construction of isothiaozles **4**, yet substrate **1a** will not directly react with this radical. No reaction was observed when Na_2S was used instead of elemental sulfur, indicating that the negative divalent sulfur was noneffective for the transformation of **4** (Scheme 6, eq 2). The previously described results prompted us to probe the role of S_8 and $BrCF_2COOEt$ (Scheme 6, eqs 3 and 4). It was found that active intermediate **10** was detected in this transformation by HRMS, and compound **11** was also detected, whereas compound **9** was not detected in the absence of Cu powder (Scheme 6, eqs 3 and 4). To further verify the possibility of compounds **10** and **11** as potential key intermediates in the isothiazole formation, we conducted the formation of isothiazole **4a** in a two-step one-pot strategy, and the corresponding target products were obtained in variable yields at different reaction times; these results provided solid information about the existence of intermediates **10** and **11** in the above two transformations. (See the SI for details.) Moreover, isothiazole **4a** could be readily accessed when we added Cu(I) instead of Cu powder, disclosing that Cu(I) might be the active catalytic species in this transformation system. (See the SI for details.)

In terms of the mechanism of the Cu-mediated synthesis of isothiazoles, first, Cu reacts with S_8 to access complex **E** (Cu(I) species). We believe that Cu^{II} radical complex **F** is furnished in the presence of $BrCF_2COOEt$ and S_8, which quickly experiences S_8-promoted defluorination to provide copper−thiocarbonyl compound **G** under basic conditions. Next, intermediate **G** is attacked by the C2 of enamine **1** to afford Cu^{III} complex **H**. Alternatively, intermediate **G** could undergo hydrolysis to form ethyl 2-thioxoacetate **K**. Intermediate **H** further converts into intermediate **I** to render species **J**. Finally, the desired product **4** is delivered via reductive elimination, regenerating the active species Cu(I) for the next catalytic cycle (Scheme 7).

Scheme 7. Possible Reaction Pathway for the Formation of Isothiazoles



In conclusion, we disclosed expedient S_8-involved transformations of bromodifluoroalkyl compounds and enaminoesters, rendering the divergent assembly of isothiazoles and thiazoles via [3 + 1 + 1] cyclization. These strategies provide straightforward and simple protocols to access a wide range of N,S-containing compounds via the selective cleavage of

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bromodifluoroalkyl compounds, in which one C−Br bond and two C−F bonds were selectively cleaved along with the formation of new C−S, C−N, as well as N−S bonds. Further studies on the synthetic application as well as the mechanisms are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01275.

General experimental procedures and spectroscopic data for the corresponding products, characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 1913896, 1913900, and 1996766 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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