

Construction of 2-Arylbenzo[4,5]thieno[2,3-*d*]thiazole Skeleton via CuCl/S-Mediated Three-Component Reaction

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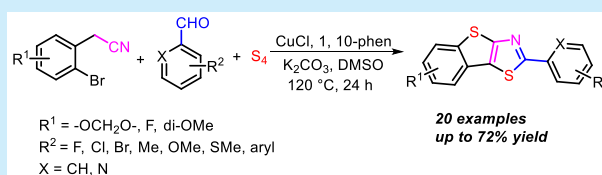
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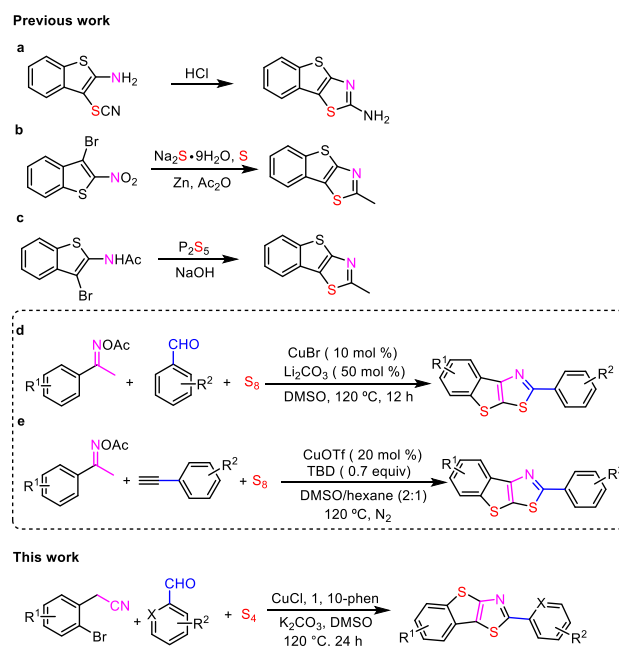
Supporting Information

ABSTRACT: An exclusive thiophene-fused polycyclic π -conjugated 2-arylbenzo[4,5]thieno[2,3-*d*]thiazole skeleton was constructed via a one-pot CuCl-mediated three-component reaction, using 2-(2-bromophenyl)acetonitrile and aromatic aldehydes as substrates and elemental sulfur as sulfur source in the presence of K₂CO₃ and 1,10-phen in DMSO. A plausible reaction mechanism was proposed, which involved formation of benzo[*b*]thiophen-2-amines through cyclization of 2-bromophenyl acetonitrile and sulfur, and subsequent intramolecular condensation/dehydrogenation with aromatic aldehydes.



Both thiophene and thiazole frameworks are ubiquitous in natural products,^{1–6} pharmaceuticals,^{7–13} organic materials,^{14–18} dyes,^{19–21} and particularly in biologically active molecules.^{22–25} Accordingly, many synthetic methods have been reported for the construction of thiophene^{26–32} and thiazole³³ skeletons, respectively. However, to the best of our knowledge, there has been less study on the construction of the fused heterocyclic ring systems containing both thiophene and thiazole moieties. Specifically, benzo[4,5]thieno[2,3-*d*]thiazole, being an exclusive S-containing fused heterocyclic ring system, has received attention from both synthetic and medicinal chemists. Accordingly, several synthetic methods have been reported for the assemblage of this unique heterocyclic skeleton. For example, Heikel and co-workers reported an intramolecular cyclization of 3-thiocyanatobenzo[*b*]thiophen-2-amines forming the corresponding benzo[4,5]thieno[2,3-*d*]thiazol-2-amines under acidic conditions (Scheme 1, method a).³⁴ In 1942, Middleton et al. realized the construction of the same skeleton from the reaction of 3-bromo-2-nitrobenzo[*b*]thiophene with Na₂S·9H₂O/S followed by reduction of the formed thioether intermediate with zinc (Scheme 1, method b).³⁵ Zhiryakov reported that the framework could also be built by treating *N*-(3-bromobenzo[*b*]thiophen-2-yl)acetamide with P₂S₅ (Scheme 1, method c).³⁶ Each of these methods has respective merits in preparing the substituted benzo[4,5]thieno[2,3-*d*]thiazole products. However, one obvious drawback of these methods is that all of the substituted benzo[4,5]thieno[2,3-*d*]thiazole products had to be derived from the preformed benzothiophenes skeleton in the starting material. Furthermore, nearly all the aforementioned methods

Scheme 1. Synthetic Strategies for the Construction of Benzothienothiazole Skeleton



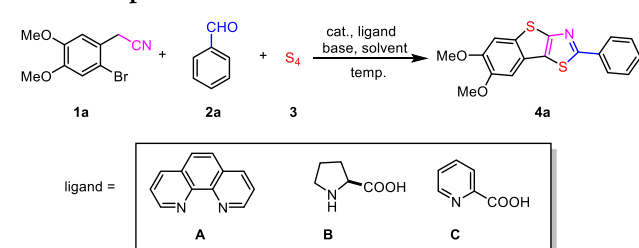
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were restricted to the synthesis of methyl or amino substituted benzo[4,5]thieno[2,3-*d*]thiazole. Our literature search revealed that no method was available for the construction of 2-aryl substituted benzo[4,5]thieno[2,3-*d*]thiazole to date. It is worthy to note that Deng and co-workers developed a facile copper-catalyzed system for the construction of a similar skeleton, a fused thieno[3,2-*d*]thiazole motif, through a bis-heteroannulation of methyl aromatic ketoximes with aromatic aldehydes and elemental sulfur (Scheme 1, method d).³⁷ Recently, Jiang also reported the synthesis of benzo[4,5]-thieno[3,2-*d*]thiazole from a three-component system, i.e., oxime esters/alkenyl azide, phenylacetylene/benzaldehyde, and S₈ via a copper-catalyzed tandem cyclization (Scheme 1, method e).³⁸

As shown above, the construction of the S-containing polyheterocyclic ring systems often relied on the introduction of sulfur atom by a variety of sulfur sources including potassium thiosulfate, potassium sulfide, DMSO, potassium ethylxanthate,^{39–42} the use of elemental sulfur as sulfur source is undoubtedly highly desirable owing to its inexpensive, nontoxic, inodorous, and stable characteristics.^{43–51} In this communication, we report a one-pot protocol for a convenient assemblage of the 2-arylbenzo[4,5]thieno[2,3-*d*]thiazole framework using elemental sulfur as sulfur source. To the best of our knowledge, this could represent the first synthesis of aryl substituted benzo[4,5]thieno[2,3-*d*]thiazole up to date. Furthermore, it is worthy to note that the current benzo[4,5]-thieno[2,3-*d*]thiazole skeleton is different from the ones reported by Deng and Jiang, as the positions of the sulfur and nitrogen atoms in the thiazole ring are not the same.

During our study on the synthesis of S-containing heterocycles, we serendipitously found that 6,7-dimethoxy-2-phenylbenzo[4,5]thieno[2,3-*d*]thiazole **4a** could be obtained in 22% yield from the reaction of 2-(2-bromo-4,5-dimethoxyphenyl)acetonitrile **1a**, benzaldehyde **2a** and S₄ **3** in the presence of copper catalyst. Further condition screening was carried out to establish the most optimal conditions using 2-(2-bromo-4,5-dimethoxyphenyl)acetonitrile **1a** and benzaldehyde **2a** as model substrates, elemental sulfur **3** as sulfur source, and 1,10-phenanthroline **A** as ligand. Initially, several copper catalysts including CuCl₂, CuI, Cu(OAc)₂, CuBr, and CuCl were screened, and the results showed that CuCl was the most effective additive (Table 1, entries 1–5). The use of copper combining with other ligands, namely, L-proline or picolinic acid, were also attempted. However, no desired product was observed in each case (Table 1, entries 6–7). We found that 1,10-phenanthroline, which was frequently used as a high efficient ligand to achieve C–S bond formation,^{52–57} proved to be the optimal ligand for this three-component reaction (Table 1, entry 5). Other solvents including toluene, CH₃CN, pyridine, H₂O, DMF, and DMSO were also tested, and DMSO was found to be the most effective solvent, while the others afforded inferior results (Table 1 entries 8–12). Reaction temperature screening revealed that the best yield could be achieved if the reaction was carried out at 120 °C (Table 1, entries 13–15). It is worthy to note that running this reaction in a sealed tube did not make obvious improvement on the reaction outcome (Table 1, entry 16). Other additives including DBU, Et₃N, and Cs₂CO₃ were also introduced to the system; however, K₂CO₃ still showed the highest efficiency, and its most suitable dosage was confirmed to be 1 mmol (Table 1, entries 17–20). In the absence of the catalyst and ligand, the yield of the reaction significantly decreased to 6%,

Table 1. Optimization of the Reaction Conditions^a



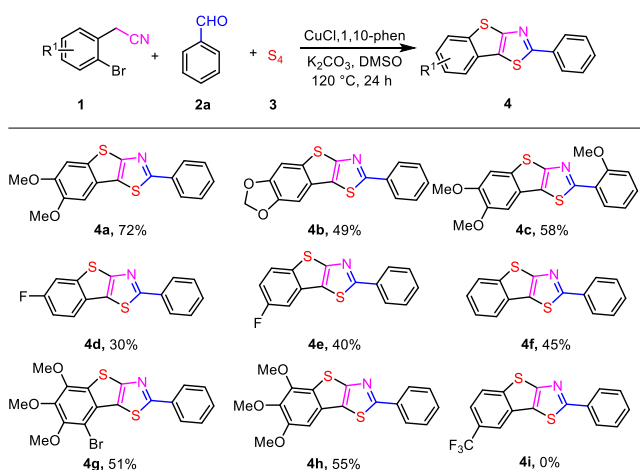
entry	catalyst	ligand	base	solvent	temp (°C)	yield (%) ^b
1	CuCl ₂	A	K ₂ CO ₃	DMSO	100	22
2	CuI	A	K ₂ CO ₃	DMSO	100	46
3	Cu(OAc) ₂	A	K ₂ CO ₃	DMSO	100	18
4	CuBr	A	K ₂ CO ₃	DMSO	100	25
5	CuCl	A	K ₂ CO ₃	DMSO	100	60
6	CuCl	B	K ₂ CO ₃	DMSO	100	0
7	CuCl	C	K ₂ CO ₃	DMSO	100	0
8	CuCl	A	K ₂ CO ₃	toluene	100	0
9	CuCl	A	K ₂ CO ₃	CH ₃ CN	100	9
10	CuCl	A	K ₂ CO ₃	pyridine	100	30
11	CuCl	A	K ₂ CO ₃	DMF	100	28
12	CuCl	A	K ₂ CO ₃	H ₂ O	100	41
13	CuCl	A	K ₂ CO ₃	DMSO	80	28
14	CuCl	A	K ₂ CO ₃	DMSO	120	72
15	CuCl	A	K ₂ CO ₃	DMSO	140	66
16 ^c	CuCl	A	K ₂ CO ₃	DMSO	120	62
17	CuCl	A	DBU	DMSO	120	47
18	CuCl	A	Et ₃ N	DMSO	120	17
19	CuCl	A	Cs ₂ CO ₃	DMSO	120	28
20 ^d	CuCl	A	K ₂ CO ₃	DMSO	120	33
21 ^e	CuCl	A	K ₂ CO ₃	DMSO	120	69

^aReaction conditions: **1** (1 mmol), **2** (2 mmol), sulfur powder **3** (1.5 mmol), catalyst (20 mol %), ligand (20 mol %), base (1 mmol), solvent (25 mL), 24 h. ^bIsolated yield. ^cIn a sealed tube. ^dBase (2 mmol). ^eS₈ instead of S₄ (1.5 mmol).

which indicated that both the catalyst and the ligand were indispensable for this reaction. It is worthy to note that S₄ could also be replaced with S₈, as the reaction delivered the target product **4a** in 69% yield (Table 1, entry 21). Finally, the best reaction conditions were determined to be 2-(bromo-methyl)-4,5-dimethoxybenzonitrile **1** (1 mmol), benzaldehyde **2** (2 mmol), sulfur powder **3** (1.5 mmol) with CuCl (20 mol %), 10-phenanthroline (20 mol %) and K₂CO₃ (1 mmol) in DMSO (25 mL) for 24 h.

With the optimal conditions in hand, we came to investigate the scope and limitations of this newly established method. First, a series of substrates bearing various R¹ substituents were studied. The results showed that 2-(2-bromophenyl)acetonitriles bearing either electron-donating or electron-withdrawing groups smoothly gave the corresponding 2-arylbenzo[4,5]thieno[2,3-*d*]thiazole products (Scheme 2, **4a–h**), and the former gave slightly better results. It is worthy to note that the reaction of **1f** also gave a mixture of many byproducts, in addition to the desired product **4f**. The most obvious byproduct (by TLC analysis) has been confirmed, by X-ray crystal analysis, to be dibenzo[*b,f*]thiopyrene-10,11-dicarbonitrile (see SI for details). Disappointingly, when 2-(2-bromophenyl)acetonitrile **1i** bearing an electron-withdrawing trifluoromethyl group was applied, the reaction failed to provide the desired product **4i**. Regarding the R² groups, both

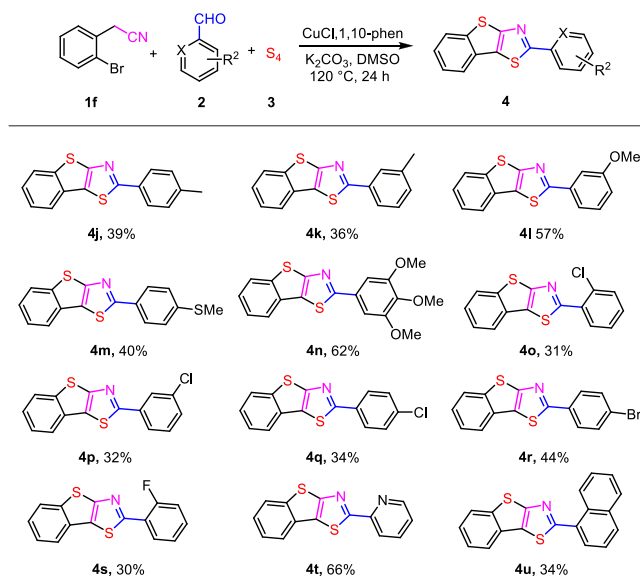
Scheme 2. Scope Studies of 2-(2-Bromophenyl)acetonitriles^{a,b}



^aReaction conditions: **1** (1 mmol), **2a** (2 mmol), sulfur powder **3** (1.5 mmol), CuCl (20 mol %), 1,10-phenanthroline (20 mol %), K₂CO₃ (1.0 mmol), DMSO (25 mL), 120 °C, 24 h. ^bIsolated yield.

electron-rich and electron-deficient aryl substituents were well tolerated during the process. The substrate carrying electron-withdrawing F group provided the lowest yield (Scheme 3, 4j–

Scheme 3. Scope Studies of Aromatic Aldehydes^{a,b}



^aReaction conditions: **1f** (1 mmol), **2** (2 mmol), sulfur powder **3** (1.5 mmol), CuCl (20 mol %), 1,10-phenanthroline (20 mol %), K₂CO₃ (1.0 mmol), DMSO (25 mL), 120 °C (oil bath), 24 h. ^bIsolated yield.

s). It is worthy to note that the method was also applicable to the substrates with the phenyl R² group being replaced with a pyridinyl or naphthyl ring (Scheme 3, 4t–u). Other aliphatic aldehydes including *n*-butylaldehyde, pentanal, 2-chloroacetaldehyde, and paraformaldehyde were also investigated under the standard conditions; however, no desired product was obtained in each case (not shown). Despite this result, the method is complementary to the existing methods, which are only applicable to the synthesis of 2-methyl substituted benzo[4,5]thieno[2,3-*d*]thiazole.^{35,36} To our disappointment, the method was not applicable to the synthesis of the

analogous selenazole, as the reaction using elemental selenium with the other conditions unchanged did not afford the expected Se-containing heterocyclic compound (not shown).

The structures of the products were confirmed by detailed study of their spectroscopic data. Furthermore, the structure of **4f** was unambiguously confirmed by X-ray crystallographic analysis (Figure 1). To our delight, all the 2-arylbenzo[4,5]-

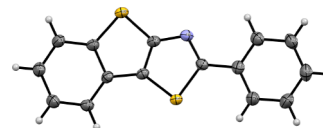


Figure 1. X-ray crystal structure of **4f**.

thieno[2,3-*d*]thiazole compounds listed in Scheme 2 were found to possess striking fluorescent features due to their existing polycyclic π -conjugated systems. According to the X-ray crystal structure of compound **4f**, we believe that the compound is basically planar and can serve as a novel fluorophore, since the rigidity and π -conjugation are commonly recognized as positive structural factors in enhancing the fluorophore brightness because of the reduction of the energy consumption from rotation and vibration. As shown in Table 2, compound **4f** exhibited maximum

Table 2. Optical Data of Representative Products

product	λ_{abs}^a (nm)	ϵ^{max} (M ⁻¹ cm ⁻¹) ^b	λ_{em}^a (nm)	Stokes shift (nm)	ϕ^c
4j	349	24 880	410	60	0.89
4t	354	22 520	424	69	0.82
4r	353	22 660	420	65	0.88
4p	351	22 000	420	70	0.80
4l	350	23 570	412	62	0.62
4b	359	28 960	446	86	0.62

^aWavelengths of maximum absorbance (λ_{abs}) or emission intensity (λ_{em}). ^bExtinction coefficient. ^cQuantum yield.

absorption at 348 nm with a moderate extinction coefficient ($2.24 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$) and maximum emission at 412 nm with a high quantum yield ($\phi = 0.89$) in DMSO. All those compounds exhibited very strong blue fluorescence when excited at around 365 nm. In general, the alkoxy substitution on the α -phenyl ring led to red shifts of the maximum absorbance and improvements in the Stokes shift (Figure 2).

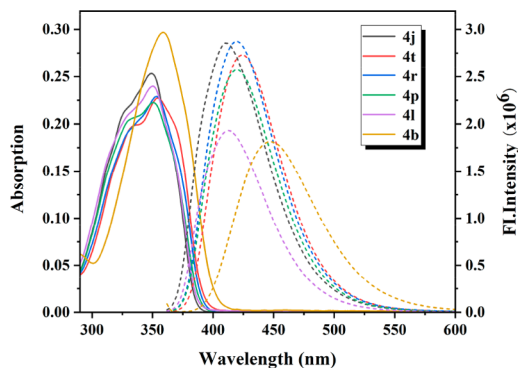
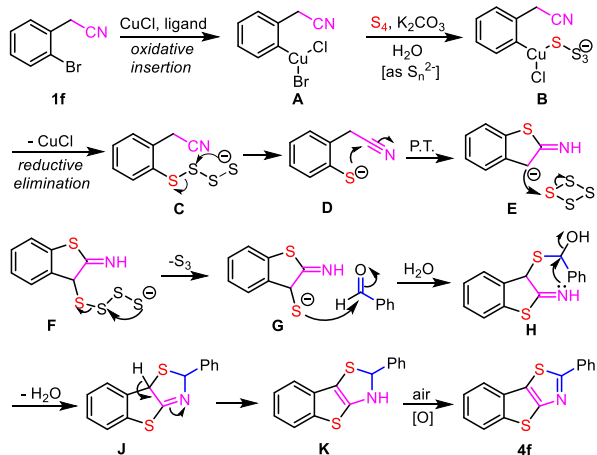


Figure 2. Absorption spectra (solid line) and fluorescence spectra (dashed line) in DMSO.

Substitution with the electron-donating group and halide in the β -phenyl ring at 4-position did not lead to the substantial change of the quantum yield. As shown in the SI, compound **4u** was poorly fluorescent, exhibiting larger Stokes shift (94 nm) and lower fluorescence quantum yield (11%). This may be due to the increasing of the π conjugation at the β -phenyl ring, which is a well-known phenomenon between Stokes shift and emission efficiency.

On the basis of results from the previous literature research,^{58–62} a plausible mechanism (Scheme 4) is proposed

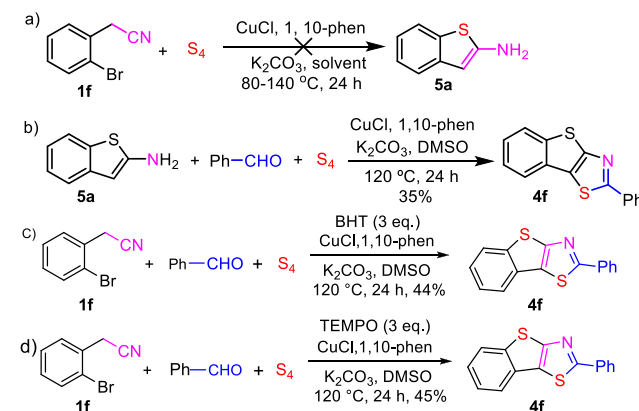
Scheme 4. Proposed Mechanistic Pathway



for this newly discovered three-component one-pot reaction. First, in the presence of the copper catalyst, 2-(2-bromophenyl)acetonitrile **1f** was converted to intermediate **A** via an oxidative insertion. Then intermediate **A** reacted with sulfur, H_2O , and K_2CO_3 to afford intermediate **B**. It is worthy to note that sulfur might be converted to S_n^{2-} species, as elemental sulfur undergoes disproportionation to give an oligosulfide anion and sulfite under basic conditions.^{61,62} Next, reductive elimination of intermediate **B** delivered intermediate **C**, which was converted to intermediate **D**⁶³ through the removal of three-membered sulfur ring. Intramolecular cyclization followed by proton shift in **D** gave intermediate **E**, which furnished intermediate **G** via a nucleophilic attack to the electrophilic S_4 . Next, the condensation of **G** with aromatic aldehyde afforded intermediate **J**, via intermediate **H**. Finally, the automatic air-oxidation of **K** delivered the target compound.

Control experiments (Scheme 5) were carried out to further corroborate the postulated mechanistic pathway. First, 2-(2-bromophenyl)acetonitrile and S_4 were subjected to the standard reaction conditions, and the benzo[*b*]thiophen-2-amine was expected to be detected and characterized under the conditions without the involvement of aromatic aldehyde. However, to our disappointment, no desired benzo[*b*]thiophen-2-amine **5a** could be observed.^{32,64} We also changed the temperature to 60, 80, 100, 140 °C, respectively, or switched the solvent to DMF/glycol (20:1).³² However, no desired product could be observed in each case. Second, when benzo[*b*]thiophen-2-amine, prepared via the reaction of 2-(2-bromophenyl)acetonitrile with $\text{Pd}(\text{dppf})\text{Cl}_2$, dppf , $\text{Na}_2\text{S}_2\text{O}_3$, and Cs_2CO_3 ,³² reacted with benzaldehyde and S_4 under the conditions, the title 2-arylbenzo[4,5]thieno[2,3-*d*]thiazole could be achieved in 35% yield. These results might indicate that benzo[*b*]thiophen-2-amine serves as the crucial inter-

Scheme 5. Control Experiments



mediate for this three-component reaction, but was impractical to be detected and isolated due to its high reactivity under the conditions. Besides, we found that upon the introduction of 3 equiv of BHT or TEMPO to the reaction of **1f** under standard conditions, the yield of **4f** was not significantly decreased (Scheme 5c and 5d). This result might indicate that the reaction did not undergo a radical mechanistic pathway.

In summary, a copper-based catalytic annulation has been developed and applied to a one-pot synthesis of the exclusive 2-arylbenzo[4,5]thieno[2,3-*d*]thiazoles from 2-(2-bromophenyl)acetonitrile, aromatic aldehydes, and sulfur powder. To our knowledge, this could represent the first three-component construction of benzothienothiazole skeleton via the successive formation of the thiophene and thiazole rings. Further studies on the reaction mechanism as well as its application are in progress in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.9b04206>.

Experimental procedures, data of compounds characterization (PDF)

Accession Codes

CCDC 1951852 and 1972173 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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