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Synthesis of Substituted Benzo[*b*]thiophenes via Sequential One-Pot, Copper-Catalyzed Intermolecular C−S Bond Formation and Palladium-Catalyzed Intramolecular Arene−Alkene Coupling of Bis(het)aryl/alkyl-1,3-monothiodiketones and *o*-Bromoiodoarenes

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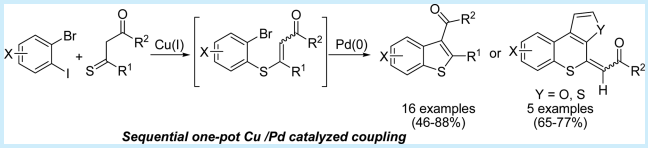
Supporting Information

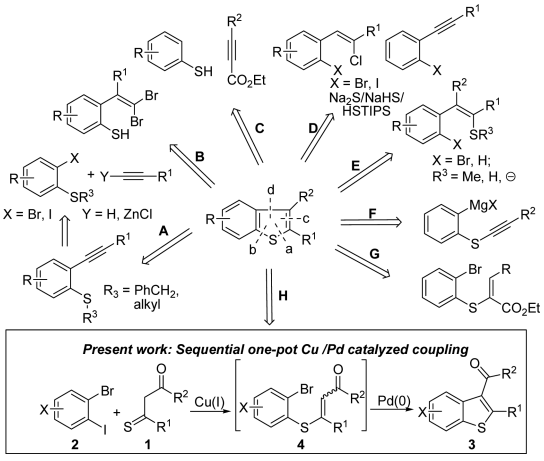
ABSTRACT: A new, convergent, one-pot synthesis of 2,3-substituted benzo[*b*]thiophenes from readily available 1,3-bis(het)aryl-1,3-monothiodiketones and *o*-bromoiodoarenes involving a sequential copper-catalyzed intermolecular C−S coupling followed by palladium-catalyzed intramolecular arene−alkene coupling of in situ generated *β*-(*o*-bromoaryl)-thiovinylketones has been described. Synthesis of a few thieno- and furano-fused 2-(het)aroylethylidenethiochromenes via intramolcular direct C−H (het)arylation of *β*-(*o*-bromoaryl)thioenones carrying 2-thienyl/furyl groups under different palladium-catalyzed conditions has also been reported.



Substituted benzothiophenes represent an important class of heterocycles displaying a broad range of biological activity and serving as useful heterocyclic cores to a host of marketed drugs.[1] In addition, benzo[*b*]thiophene and its condensed analogues are important structural components in the development of optoelectronic materials.[1] Consequently, the synthesis of this privileged structure has been actively pursued in recent years.[1]

Scheme 1 shows some of the reported procedures with various disconnections for benzothiophene synthesis. Among recent syntheses, the most common approaches for benzo[*b*]-thiophenes involve intramolecular 5-*endo*-*dig* cyclization of *o*-alkynyl arylthioethers or their surrogates employing electrophilic reagents or transition-metal catalysts (pathway A, disconnections d and a)[1−3] and tandem intramolecular palladium- or copper-catalyzed S-vinylation/interamolecular cross coupling of *o*-(*gem*-dibromovinyl)thiophenols (pathway B).[4] The crucial bond-forming event in these reactions is intramolecular attack of nucleophilic sulfur atom on the activated C−C multiple bond, leading to the formation of S(1)−C(2) bond (disconnection a). Recently, Li and co-workers have reported a direct one step synthesis of benzo[*b*]thiophenes through intramolecular oxidative cyclization between simple thiophenols and activated alkynes (pathway C, disconnections a and d).[5] These reactions, although efficient, require prior synthesis of prefunctionalized thiophenol precursors. 2-Substituted benzo[*b*]thiophenes have also been obtained through copper (or palladium)-catalyzed double thiolation of *o*-(2-halovinyl)halobenzene[6a] or 2-bromoalkynylbenzenes[6b] with metal sulfides or their surrogates (pathway D, disconnections a and b).[6c] Our research group and others[7] have recently reported syntheses of substituted benzo[*b*]-thiophenes and their heteroanalogues involving S(1)−C(7a) bond formation via copper (or palladium)-catalyzed intramolecular C−S cross-coupling/cyclization[1b] or palladium-catalyzed intramolecular oxidative C−H functionalization/thiolation of in situ generated enethiolates of *α*-aryl-*β*-(het)-aryl/alkyl-*β*-mercaptoacrylonitriles/acrylates/acrylophenones[1a] or through radical-mediated intramolecular cyclization of the corresponding thioethers (pathway E, disconnections b and c).[1c] Knochel and co-workers have developed synthesis of substituted benzo[*b*]thiophenes via copper-catalyzed carbomagnesiation of *o*-(alkynylthio) Grignard reagents (pathway F, disconnection d).[8a] Recently, 3-arylbenzothiophenes have also been synthe-

Scheme 1. Various Disconnection Approaches for the Synthesis of Benzothiophene Ring System



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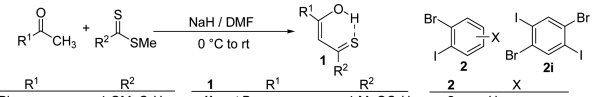
sized by intramolecular Heck reaction of 2-(phenylthio)acrylates (pathway G, disconnection d).[8b]

During the course of our studies toward design and development of new synthetic routes for five- and six-membered heterocycles from various organosulfur intermediates,[9] we now report a novel, convergent approach to 2,3-substituted benzo[*b*]thiophenes **3** via sequential one-pot, copper-catalyzed intermolecular Ullmann type C−S coupling of 1,3-monothiodiketones **1** and 2-bromoiodoarenes **2** and intramolecular Heck reaction of the resulting *β*-arylthioenones **4** (Scheme 1, pathway H, disconnections b and d).

We have recently reported synthesis and applications of unsymmetrically substituted 1,3-bis(het)aryl/alkylmonothiodiketones of the general structure **1** as a new class of easily accessible versatile 3-carbon organosulfur synthons.[9a−d] By employing these monothiodiketones, we have developed efficient regiocontrolled syntheses of unsymmetrically substituted 1-aryl-3,5-bis(het)arylpyrazoles,[9a] 3,5-bishet(aryl)-oxazoles,[9b] substituted thiophenes/fluorescent push−pull thiophene acrylates,[9c] and triisubstituted imidazoles.[9d] In continuation of these studies, we further envisaged development of a new convergent synthesis of 2,3-disubstituted benzo[*b*]thiophenes **3** by utilizing these 1,3-monothiodiketones as C═C−S coupling partners in transition-metal-catalyzed cyclization with *o*-bromoiodoarenes **2** (Scheme 1).

The desired 1,3-monothiodiketones **1a−u** were obtained by base-mediated condensation of the respective active methylene ketones with various (het)aryl dithioesters (Scheme 2).[9a] The

Scheme 2. Synthesis of 1,3-Monothiodiketones 1a−u



1	R^1	R^2	1	R^1	R^2	2	X
1a	Ph	4-OMeC$_6$H$_4$	**1l**	*t*-Bu	4-MeOC$_6$H$_4$	**2a**	H
1b	2-thienyl	3,4-OCH$_2$O-C$_6$H$_3$	**1m**	3-pyridyl	*n*-Bu	**2b**	4,5-OCH$_2$O-C$_6$H$_3$
1c	2-furyl	3-pyridyl	**1n**	2-furyl	*N*-morpholino[a]	**2c**	4,5-(MeO)$_2$-C$_6$H$_3$
1d	4-FC$_6$H$_4$	4-MeOC$_6$H$_4$	**1o**	2-thienyl	*N*-piperidinyl[a]	**2d**	4-COMe
1e	2-pyridyl	4-Me$_2$N-C$_6$H$_4$	**1p**	2-thienyl	4-MeOC$_6$H$_4$	**2e**	4-CF$_3$
1f	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	**1q**	3,4-OCH$_2$O-C$_6$H$_3$	2-thienyl	**2f**	4-F
1g	4-ClC$_6$H$_4$	3-indolyl	**1r**	2-thienyl	2-thienyl	**2g**	4-CN
1h	2-(N-Me)pyrrolyl	4-FC$_6$H$_4$	**1s**	2-(N-Me)pyrrolyl	2-thienyl	**2h**	4-Cl
1i	4-MeOC$_6$H$_4$	2-(N-Me)pyrrolyl	**1t**	2-thienyl	2-furyl	**2j**	4-CO$_2$Et
1j	4-CF$_3$C$_6$H$_4$	5-Me$_2$N-2-thienyl	**1u**	4-CNC$_6$H$_4$	2-furyl		
1k	Me	3,4-OCH$_2$O-C$_6$H$_3$					

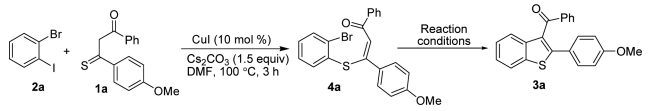
[a]Prepared by nucleophilic displacement on corresponding *β*-keto dithioesters with cyclic amines

1,3-monothiodiketone **1a** and 2-bromoiodobenzene **2a** were selected as model substrates for screening of various catalysts and optimization of reaction conditions. We first examined the possibility of developing a one-pot process for benzothiophene **3a** with a single palladium catalyst/ligand system, catalyzing both initial C−S bond formation and subsequent intramolecular arene−alkene coupling of the resulting *β*-arylthioenone **4a** (Table S1, see the Supporting Information). However, all of our all attempts to employ various Pd-based catalysts under different conditions failed to yield the desired benzothiophene **3a**.

We then switched our attention to performing the reaction in a sequential manner with the initial copper-catalyzed C−S bond formation between **1a** and **2a** to furnish *β*-(2-bromoaryl)-thioenone **4a** (Table S2, see the Supporting Information). The reaction proceeded efficiently in the presence of various copper catalysts, and the best yield (87%) of **4a** was obtained using CuI (10 mol %) as catalyst in the presence of Cs_2CO_3 (1.5 equiv) in DMF at 100 °C (3 h) (see Table S2, entry 2). The ^{1}H NMR spectra of **4a** showed the presence of only one stereoisomer, which was assigned *Z*-stereochemistry on the basis of its X-ray crystallographic data (Figure S1, see the Supporting Information).

Having established the synthesis of *β*-arylthioenone **4a** under copper catalysis, we next explored the optimized conditions for its conversion to benzothiophene **3a** with various palladium catalysts/ligand systems under varying conditions (Table 1). The

Table 1. Optimization of the Reaction Conditions for the Palladium-Catalyzed Intramolecular Cyclization of 4a to Benzothiophene 3a[a]



entry	catalyst	ligand	base	temp (°C), time (h)	solvent	yield (%)
1	$Pd(OAc)_2$		Cs_2CO_3	100, 8	DMF	82
2[b]	$Pd(OAc)_2$		Cs_2CO_3 Bu_4NBr	100, 15	DMF	77
3	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	100, 8	DMF	81
4	$Pd(OAc)_2$	P(*o*-Tol)$_3$	K_2CO_3	100, 12	DMSO	68
5	$Pd(OAc)_2$	BINAP	K_2CO_3	100, 10	DMF	64
6	$Pd(OAc)_2$	XPhos	Cs_2CO_3	100, 20	DMF	62
7	$PdCl_2$	PPh_3	Cs_2CO_3	100, 15	DMF	59
8	$PdCl_2$	BINAP	$NaHCO_3$	100, 10	dioxane	73
9	$Pd_2(dba)_3$	XantPhos	Cs_2CO_3	100, 18	DMSO	52
10	$Pd_2(dba)_3$	dppf	Cs_2CO_3	100, 20	DMF	55

[a]Reaction conditions: **4a** (0.3 mmol), catalyst (10 mol %), ligand (20 mol %), base (0.3 mmol) in 4 mL of solvent under N_2. [b]Bu_4NBr (0.3 mmol) is used.

best yields of **3a** were obtained with palladium acetate (10 mol %) under ligand-free conditions or in the presence of PPh_3 in DMF as solvent with Cs_2CO_3 as base (Table 1, entries 1 and 3). We therefore conducted all of the subsequent cyclization reactions of *β*-arylthioenones **4** using the former reaction conditions (Table 1, entry 1).

With the realization of a two-step process, we next focused to develop sequential one-pot protocol for benzothiophene **3a** by first reacting monothiodiketone **1a** with 2-bromoiodoarene **2a** under copper catalysis and subsequent in situ palladium-catalyzed intramolecular cyclization of the resulting *β*-arylthioenone **4a** under optimized conditions, which to our delight, afforded the benzothiophene **3a** in 80% yield comparable to the stepwise process (Scheme 3 vs Table 1, entry 1).

The optimized one-pot reaction conditions work effectively with an array of substituted *o*-iodobromoarenes **2a−h** bearing both electron-donating and -withdrawing groups, affording the corresponding benzothiophenes **3a−o** in good to excellent yields (Scheme 3). Similarly, it was possible to employ a range of 1,3-monothiodiketones (**1a−m**) bearing an aryl/(het)aryl substituents such as 2-furyl, 2-[(5-dimethylamino)-2-thienyl], 2-(*N*-methylpyrrolyl), 2- or 3-pyridyl, 3-(*N*-methylindolyl), or alkyl groups adjacent to either carbonyl or thiocarbonyl moieties, thus affording the corresponding 2-(het)aryl/alkyl-3-(het)-aroylbenzo[*b*]thiophenes **3a−m** in excellent yields (Scheme 3). Similarly, the corresponding 2-(*N*-morpholino)-/(*N*-piperidino)-substituted benzothiophenes **3n** and **3o** could also be prepared in moderate yields when the thioamides **1n**,**o** were used as coupling partners (Scheme 3). Finally, by employing 1,3-

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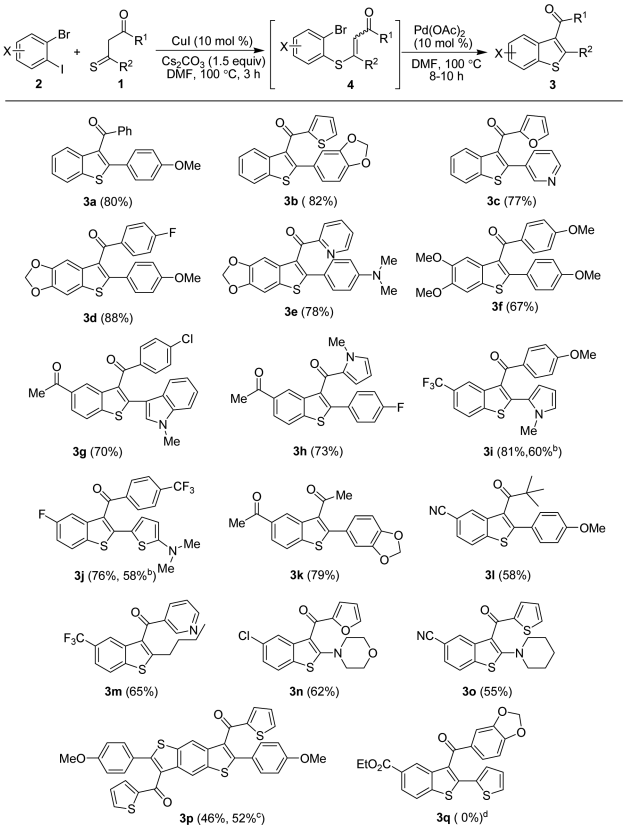
Scheme 3. Synthesis of Benzo[*b*]thiophenes 3 via Sequential One-Pot, Copper-Catalyzed Intermolecular and Palladium-Catalyzed Intramolecular Aryl−Alkene Coupling[a]

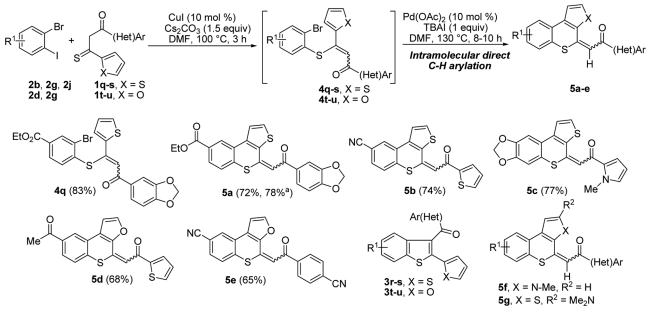


[a]Reaction conditions: **2** (0.5 mmol), **1** (0.5 mmol), CuI (0.05 mmol), Cs_2CO_3 (0.75 mmol) in DMF (4 mL) heated under N_2 atm at 100 °C for 3 h and then $Pd(OAc)_2$ (0.05 mmol), DMF, 100 °C for 8−10 h. [b]Reaction conditions: $Pd(OAc)_2$ (0.05 mmol), Bu_4NBr (0.5 mmol), DMF, 130 °C for 8−10 h. [c]Yield under two-step process. [d]**4q** obtained in 83% yield.

monothiodiketone **1p** and 1,4-dibromo-2,5-diiodobenzene **2i**, the linear benzodithiophene **3q** could also be synthesized in moderate yield under identical one-pot or two-step conditions (Scheme 3).

Interestingly, when the *o*-bromoiodoarene **2j** and the monothiodiketone **1q** (carrying a 2-thienyl moiety attached to thiocarbonyl group) were subjected to sequential copper- and palladium-catalyzed coupling under optimized conditions, the expected 2-(2-thienyl)benzo[*b*]thiophene **3q** was not obtained, and only *β*-arylthioenone **4q** was isolated in 83% yield (Schemes 3 and 4). We therefore attempted to cyclize the thiovinylketone **4q** to **3q** under modified reaction conditions by treatment with palladium acetate (10 mol %) in the presence of tetrabutylammonium iodide in DMF at 130 °C (8 h) (Scheme 4). However, workup of the reaction mixture afforded an unexpected product (78%), instead of the desired benzothiophene **3q**, which was characterized as 2-(aroylethylidene)thieno[2,3-*c*]-thiochromene derivative **5a** on the basis of its spectral and analytical data (Scheme 4).The thiochromene **5a** was obtained in 72% yield, when the reaction was conducted under sequential one-pot reaction conditions (Scheme 4). This novel transformation, which apparently involves palladium catalyzed intramolecular direct C−H arylation on thiophene ring[10] in thioenone **4q**, was found to be general with the other 1,3-

Scheme 4. One-Pot Synthesis of Thieno- and Furano-Fused 2-(Het)aroylethylidenethiochromenes 5a−e

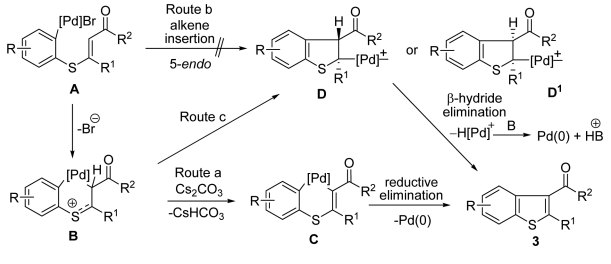


[a]Yield under two-step conditions from **4q**.

monothiodiketones **1r,s** bearing a (2-thienyl)thiocarbonyl moiety, furnishing the corresponding 2-[(het)aroylethylidene]-thieno[2,3-*c*]thiochromenes **5b−c** in overall high yields on treatment with *o*-iodobromoarenes **2g** and **2b**, respectively, under the modified sequential one-pot conditions (Scheme 4). The corresponding monothiodiketones **1t−u** bearing a (2-furyl)thiocarbonyl moiety also followed a similar trend, yielding the corresponding furano-fused 2-[(het)aroylethylidene]-thiochromenes **5d,e** exclusively in good yields on coupling with the respective *o*-bromoiodoarenes (**2d,g**) under identical conditions, and no trace of the corresponding (2-thienyl/furyl)-substituted benzothiophenes **3r−u** could be detected in the reaction mixture (Scheme 4). On the other hand, attempted intramolecular cyclization of monothioketones **1i** and **1j** carrying a [*N*-methyl-(2-pyrrolyl)]- and [5-dimethylamino(2-thienyl)]-thiocarbonyl moiety, respectively, with the appropriate *o*-bromoiodobenzenes (**2e−2f**) under modified palladium-catalyzed one-pot reaction conditions did not afford even traces of the corresponding fused thiochromenes **5f,g**, yielding only the benzothiophenes **3i** and **3j** exclusively in decreased yields (Schemes 3 and 4).

The probable mechanism for the palladium-catalyzed intramolecular arene−alkene coupling of *β*-(*o*-bromoaryl)thiovinyl ketones **4** leading to benzothiophenes **3** is depicted in Scheme 4. Thus, the insertion intermediate **A** obtained by oxidative addition of Pd(0) into bromoarene **4** could be transformed into the resonance-stabilized cationic intermediate **B**, formed by the intramolecular attack of the electron-rich thiovinyl group on the electrophilic metal center. Subsequent deprotonation of the acidic proton in intermediate **B** would lead to palladacycle **C**, which on reductive elimination affords the benzothiophene **3** (Scheme 5, route a). A mechanism involving direct Heck-type insertion into the enone double bond in the intermediate **A** to

Scheme 5. Proposed Mechanisms for Palladium-Catalyzed Intramolecular Arene−Alkene Coupling of *β*-Arylthiovinylketones 4 to Benzothiophenes 3



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give intermediates **D**/**D′** (Scheme 5, route b) appears to be disfavored energetically owing to the strain associated with the 5-*endo*-cyclization. Alternatively, the intermediates **D**/**D′** could be formed by a two-step alkene insertion process from **A** via palladacycle **B**, followed by subsequent β-hydride elimination to give benzothiophene **3** (Scheme 5, route c). The proposed mechamisms are similar to those suggested by Kurth and co-workers[11] for the palladium-catalyzed intramolecular cyclization of *N*-(2-bromoaryl) enamines to 2,3-substituted/annulated indoles on the basis of quantum chemical calculations.

The probable mechanism for the formation of thieno- and furano-fused 2-(aroylethylidene)thiochromenes **5a−e** from the corresponding thiovinyl ketones **4q−u** under the modified palladium-catalyzed conditions apparently involves intramolecular direct C−H (het)arylation[10] on the C3 position of the favorably located 2-thienyl (or 2-furyl) ring (Scheme 4). However, failure of the corresponding monothiodiketones **1i** and **1j** with 2-(*N*-methylpyrrolyl)- and [(5-dimethylamino)-2-thienylthiocarbonyl groups to furnish the corresponding fused thiochromenes **5f−g** under identical conditions (Scheme 4) suggests that the structural features along with various electronic and steric constraints present in thiovinyl ketones **4** play important role in the formation of either benzothiophenes or fused thiochromene derivatives, and further work is needed to examine various factors responsible for these observations.

In summary, we have developed an efficient, convergent, one-pot synthesis of 2-(het)aryl/alkyl-3-acylbenzo[*b*]thiophenes from readily available 1,3-bis(het)aryl-1,3-monothiodiketones and *o*-bromoiodoarenes involving a sequential copper-catalyzed Ullmann-type intermolecular C−S coupling followed by an in situ palladium-catalyzed intramolecular Heck reaction of the resulting β-(arylthio)vinyl ketones.[12] It should be noted that such kind of disconnection approach for the construction of a benzo[*b*]thiophene ring has not been reported in the literature. This new methodology provides access to a broad range of substituted benzothiophenes displaying functional group diversity at various positions. We have also reported the synthesis of few thieno-and furano-fused 2-(het)-aroylethylidenethiochromenes via intramolcular direct C−H arylation of β-(2-bromoarylthio)enone precursors under different palladium-catalyzed reaction conditions. Further work to establish generality and scope of this novel benzothiophene and fused thiochromene synthesis, along with detailed mechanistic studies regarding various factors responsible for the formation of both kinds of products, is in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00273.

Experimental details; tables for optimization of reaction conditions; spectral and analytical data (PDF)

X-ray crystallog raphy of **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Lutz F. Tietze on his 75th birthday.

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