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Mercury(II)-Catalyzed Cyclization of 2-Alkynylphenyl Alkyl Sulfoxides Provides 3-Acylbenzo[*b*]thiophenes

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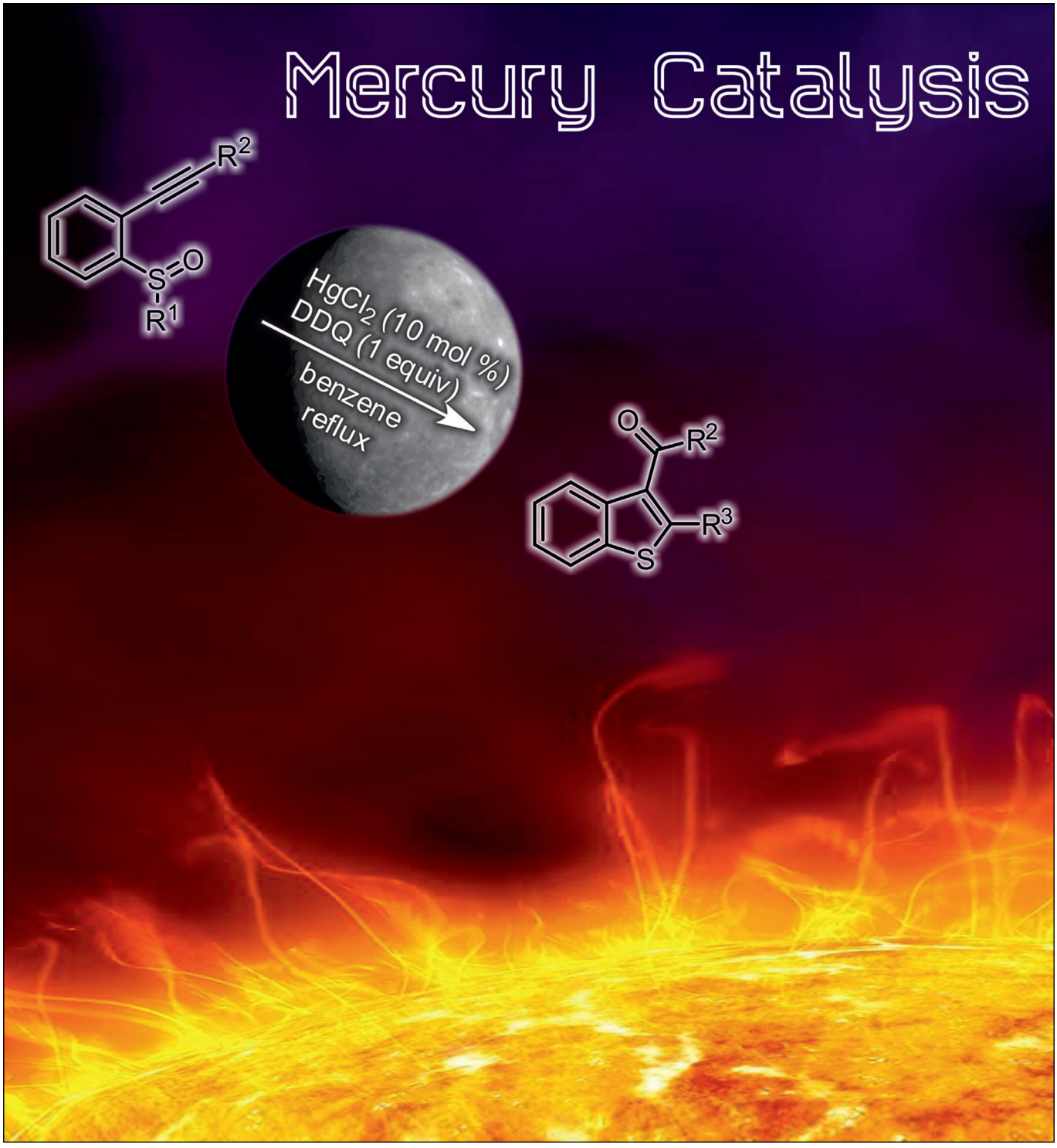
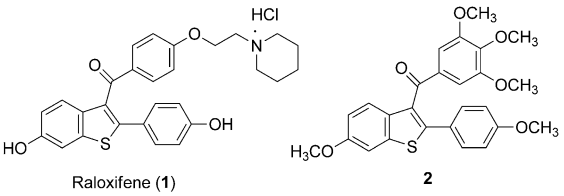
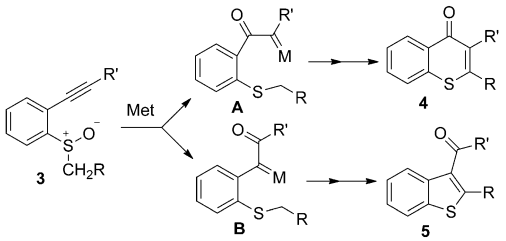


Molecules that contain the benzo[*b*]thiophene substructure often exhibit a broad spectrum of biological activities.[1] For instance, raloxifene (**1**) and compound **2** have been reported as unique selective estrogen receptor modulators (SERMs) and antitubulin agents.[2] Recently, raloxifene was found to be as effective as tamoxifen in reducing the risk of invasive breast cancer and has lower risk of thromboembolic events and cataracts.[3] Therefore, benzo[*b*]thiophenes have attracted much attention from synthetic organic chemists.[4]



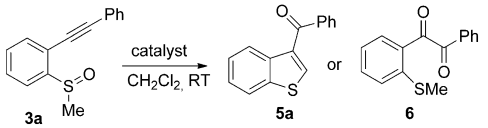
Recently, the utility of transition metals, especially gold, to catalyze the reaction of alkynes with sulfoxide to generate α-carbonyl carbenoid analogues and their synthetic applications have been widely studied.[5] We envisioned that transition-metal-catalyzed intramolecular cyclization of 2-alkynylphenyl alkyl sulfoxides **3** to generate the metal carbenoids **A** or **B** followed by a sequential C–H insertion and oxidation would lead to either benzothiopyranones **4** or 3-acylbenzo[*b*]thiophenes **5** (Scheme 1).



Scheme 1. Proposed synthesis of benzothiopyranones **4** or 3-acylbenzo[*b*]-thiophenes **5**.

To test our hypothesis, 2-alkynylphenyl alkyl sulfoxide **3a** was prepared starting from 2-iodothioanisole (**s-1a**) and 2-iodophenyl benzyl thioether (**s-1b**), respectively (see the Supporting Information). Initially, compound **3a** was treated with PPh_3AuCl (10 mol%) in CH_2Cl_2 at room temperature for 72 h. The only product obtained was **6** in 10% yield, and most of the starting **3a** was recovered (Table 1, entry 1). By using $PtCl_2$ as the catalyst, a similar result was observed (Table 1, entry 2). If the reaction was carried out in 1,4-dioxane under reflux conditions for 30 min, compound **6** was obtained in 50% yield (Table 1, entry 3).[6] Copper catalysts, including $Cu(OTf)_2$ and $CuCl_2$ as well as $SnCl_4$ were found to be ineffective in catalyzing this reaction (Table 1, entries 4–6). However, reaction of **3a** with $HgCl_2$ (10 mol%) in CH_2Cl_2 at room temperature for 72 h gave compound **5a** in low but encouraging yield (Table 1, entry 7).

Table 1. Attempted for the cyclization of **3a**.



Entry	Catalyst (+oxidant)	Equiv	Solvent	T [°C]	t [h]	Products (yield [%])
1	PPh_3AuCl	0.1	CH_2Cl_2	RT	72	**6** (10)
2	$PtCl_2$	0.2	CH_2Cl_2	RT	24	**6** (20)
3	$PtCl_2$	0.2	dioxane	80	0.5	**6** (50)
4	$Cu(OTf)_2$	0.1	CH_2Cl_2	RT	72	NR[a]
5	$CuCl_2$	0.1	CH_2Cl_2	RT	72	NR[a]
6	$SnCl_4$	0.1	benzene	reflux	24	NR[a]
7	$HgCl_2$	0.1	CH_2Cl_2	RT	72	**5a** (8)
8	$HgCl_2$	0.1	CH_2Cl_2	reflux	24	**5a** (20)
9	$HgCl_2$	0.1	dioxane	80	24	**5a** (10)
10	$HgCl_2$	0.1	DCE[b]	reflux	24	**5a** (15)
11	$HgCl_2$	0.1	benzene	reflux	24	**5a** (30)[c]
12	$HgCl_2$ (+DDQ)[d]	0.1	benzene	reflux	24	**5a** (70)
13	HgO (+DDQ)[d]	0.1	benzene	reflux	24	**5a** (55)
14	$Hg(OAc)_2$ (+DDQ)[d]	0.1	benzene	reflux	24	**5a** (50)

[a] Starting material was recovered. [b] DCE = dichloroethane. [c] 42% yield of corresponding dihydrothiophene (**7a**) isolated. [d] 1 equivalent of DDQ was added.

To optimize the reaction conditions, reactions were carried out with different solvents and at various temperatures. The results are summarized in Table 1. When the reaction of **3a** with $HgCl_2$ (10 mol%) was carried out in CH_2Cl_2 heated to reflux for 24 h, the yield of **5a** was increased to 20% (Table 1, entry 8). 1,4-Dioxane was found to be less effective for benzothiophene formation than CH_2Cl_2 (Table 1, entry 9). 1,2-Dichloroethane heated to reflux was also employed in this study but the yield was not improved (Table 1, entry 10). Heating the reaction mixture in DMSO at 80°C led to a complicated mixture of the products. Other solvents, including toluene, DMF, THF, and CH_3OH, were not effective for the product formation. Ultimately, benzene was found to be the most effective for the product formation. The reaction of **3a** with $HgCl_2$ (10 mol%) in benzene heated to reflux for 24 h provided compound **5a** in 30% yield along with 42% of dihydrobenzothiophene **7a** (Table 1, entry 11). Upon introduction of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 1 equiv) into the reaction mixture, the desired product **5a** was obtained in 70% yield

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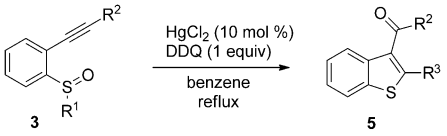
(Table 1, entry 12). HgO and $Hg(OAc)_2$ were also employed in this study and found to be less effective than $HgCl_2$ for the formation of 3-benzoylbenzo[*b*]thiophene (**5a**; Table 1, entries 13 and 14).

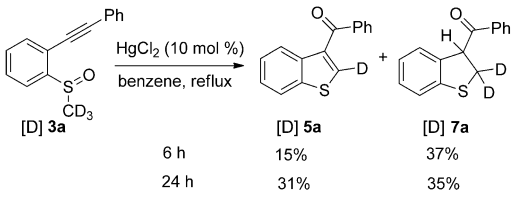
With the optimized reaction conditions in hand, the mercury-catalyzed cyclization reaction was extended to other 2-alkynylphenyl methyl sulfoxides **3b–k**. The results are summarized in Table 2. All substrates that bear either alkyl or aryl substituents on the terminal alkynes gave 3-arylcarbonylbenzo[*b*]thiophenes in modest to good yields (50–72%). The benzyl sulfoxides **3l–p** were subjected to the optimized reaction conditions to give 2-phenyl-3-arylcarbonylbenzo[*b*]-thiophenes **5l–p** in good yields (75–85%). The results indicate that steric hindrance has very little influence on the reaction. The *t*Bu does not have a significant effect. Introducing a strong electron-withdrawing group, such as a nitro group, into the phenyl ring on the terminal alkyne decreased the reaction rate and the yield. Thus, cyclization of **3g** and **3o** required 48 h to go to completion; the yields are 50 and 72%, respectively.

Table 2. Synthesis of 3-acylbenzo[*b*]thiophenes by optimized reaction conditions.



Entry	R^1	R^2	R^3	*t* [h]	Products (yield [%])
1	CH_3	Ph	H	24	**5a** (67)
2	CH_3	4-$CH_3C_6H_4$	H	24	**5b** (70)
3	CH_3	4-$CH_3OC_6H_4$	H	24	**5c** (72)
4	CH_3	2-$CH_3OC_6H_4$	H	24	**5d** (72)
5	CH_3	3,4,5-$(CH_3O)_3C_6H_2$	H	36	**5e** (68)
6	CH_3	4-BrC_6H_4	H	24	**5f** (54)
7	CH_3	4-$NO_2C_6H_4$	H	48	**5g** (50)
8	CH_3	*n*Pr	H	24	**5h** (65)
9	CH_3	*n*Pen	H	24	**5i** (63)
10	CH_3	*i*Bu	H	24	**5j** (66)
11	CH_3	*t*Bu	H	24	**5k** (65)
12	CH_2Ph	Ph	Ph	24	**5l** (80)
13	CH_2Ph	4-$CH_3OC_6H_4$	Ph	24	**5m** (85)
14	CH_2Ph	3,4,5-$(CH_3O)_3C_6H_2$	Ph	36	**5n** (78)
15	CH_2Ph	4-$NO_2C_6H_4$	Ph	48	**5o** (72)
16	CH_2Ph	*t*Bu	Ph	24	**5p** (75)

To investigate the detailed mechanism of this cyclization reaction, deuterated compound [D]**3a** was prepared.[7] Treatment of [D]**3a** with $HgCl_2$ (10 mol%) in benzene heated at reflux for 6 h without DDQ gave [D]**5a** in 15% yield along with [D]**7a** in 37% yield. On the basis of the proton NMR spectrum and mass spectroscopy of compound [D]**7a**, we found that there is only 37% deuterium incorporated at the 3-position. If the reaction mixture was stirred in benzene heated at reflux for 24 h, compounds [D]**5a** and [D]**7a** were obtained in 31 and 35% yields, respectively. The percentage of deuterium incorporation at the 3-position of [D]**7a** obtained herein was reduced to 13%. Owing to the fast hydrogen–deuterium exchange at the 3-position of product [D]**7a** under the described reaction conditions, we cannot conclude the α-carbonyl carbenoid is the key intermediate for the product formation.



In conclusion, we have demonstrated that 3-acylbenzo[*b*]thiophenes can easily be prepared by the cyclization of 2-alkynylphenyl alkyl sulfoxides catalyzed by mercury chloride. The reaction mechanism is not clear at this stage. Further studies are needed to conclude the reaction mechanism. Efforts to apply this cyclization reaction to the synthesis of pharmaceutically important compounds are also under investigation.

Experimental Section

$HgCl_2$ (5.4 mg, 0.02 mol) and DDQ (45 mg, 0.2 mmol) were added to a stirred solution of sulfoxides **3a–p** (0.2 mmol) in benzene (20 mL). The resulting solution was heated to reflux and stirred at this temperature for 24 to 48 h (monitored by TLC). After cooling to room temperature, the solution was filtered through a pad of silica gel and the solvent was removed. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc 30:1 as eluent) to give 3-acylbenzo[*b*]-thiophenes (**5**).

Acknowledgements

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Keywords: benzothiophenes · cyclization · heterocycles · mercury chloride · rearrangement

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[7] Compound [D]**3a** was prepared starting from 2-bromothiophenol. See the Supporting Information.

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