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Efficient Synthesis of Phenoxathiines via the Cascade C–H Hydroxylation–C–S Coupling–C–O Cyclization Reaction

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Abstract—The ligand-free and simple cascade C–H hydroxylation–C–S coupling–C–O cyclization reaction has been used as the synthetic approach to disulfides and *o*-chloro-iodobenzenes using CuI as a catalyst. This approach provides an easy and convenient method of synthesis of phenoxathiin derivatives.

Keywords: ligand-free, disulfides, C–H hydroxylation, cascade reaction, phenoxathiines

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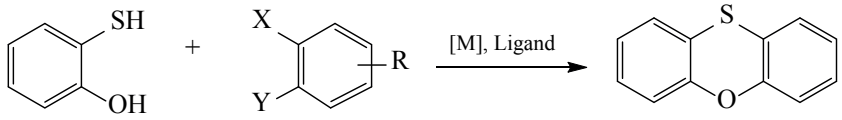
INTRODUCTION

Phenoxathiin derivatives are structural blocks of a broad number of heterocyclic compounds that demonstrate some potential as pharmaceuticals and sensors [1,2]. Therefore, development of highly efficient synthetic approach to phenoxathiin derivatives could be of considerable importance. A series of phenoxathiin derivatives was synthesized by the facile tandem coupling reaction using 2-hydroxyphenol and *o*-difluorobenzene with strong electron withdrawing groups [3]. Later synthesis of phenoxathiin derivatives by the cross coupling reaction of 1-halo-2-nitroarenes and 2-sulfanylphenol was developed [4].

The C–H hydroxylation with S atom as the directing group, remains a challenging issue, because of the strong

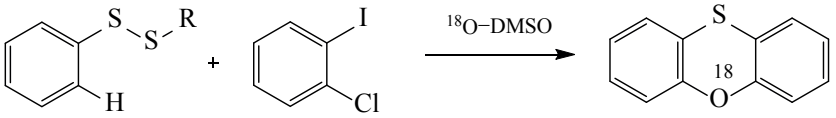
Scheme 1. One-pot synthesis of phenoxathiin derivatives.

Previous work:



X = I, NO_2 X = I or Br

This work: disulfide-directed C−S coupling−C−H hydroxylation−C−O cyclization stragegy

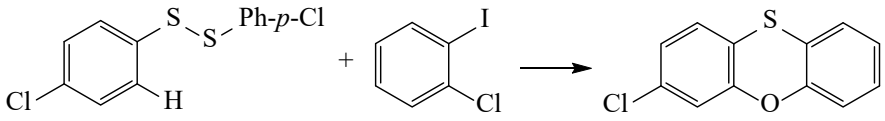


In situ C_{sp^2}-H hydroxylation
one-pot synthetic

Cascade reaction stragegy
ligand-free

[Cat.] CuI; (DG) Disulfide; (Oxidant) DMSO; (Solvent) DMSO.

Table 1. Screening of reaction conditions[a]



1a **2a** **3a**

Entry	Catalyst	Base	Sovlent	Yield, %[b]	Entry	Catalyst	Base	Sovlent	Yield, %[b]
1	CuI	NaOH	DMSO	<5	7	$PdCl_2$	Cs_2CO_3	DMSO	0
2	CuI	Na_2CO_3	DMSO	13	8	$Pd(OAc)_2$	Cs_2CO_3	DMSO	0
3	CuI	Cs_2CO_3	DMSO	62	9	CuI	Cs_2CO_3	DMF	<5
4	CuI	K_2CO_3	DMSO	22	10	CuI	Cs_2CO_3	THF	0
5	CuCl	Cs_2CO_3	DMSO	28	11	CuI	Cs_2CO_3	Toluene	0
6	$FeCl_3$	Cs_2CO_3	DMSO	0	12	CuI	Cs_2CO_3	DMSO	23[c]

[a] Conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (10 mol %), base (3 equiv), solvent (5 mL), 9 h, 120°C, N_2. [b] Isolated yields. [c] 90°C.

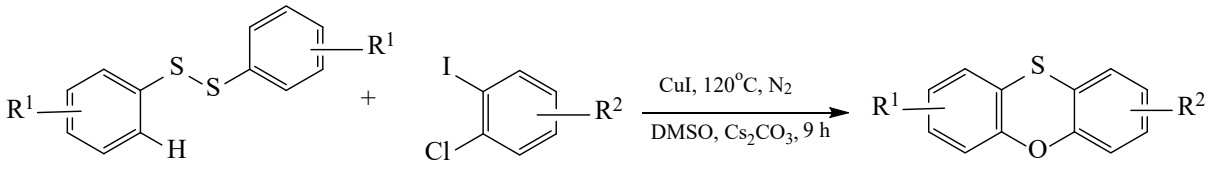
coordination between sulfur and metal cations. The copper-catalyzed C_{sp^2}-H hydroxylation involving arylthiols and aryl iodides or arylboronic acids was reported [5–9]. Our group also described the disulfide-directed C_{sp^2}-H hydroxylation reaction of disulfides and arylboronic acids or aryl iodides [10].

The presented here study is a further development of our prior research [11–20]. Here, the highly efficient cascade C–H activation–C–S coupling–C–O cyclization reaction catalyzed by CuI provided an easy and efficient method of synthesis of phenoxathiin derivatives.

RESULTS AND DISCUSSION

Initially, the reaction conditions were optimized using disulfide (**1a**) and *o*-chloro-iodobenzene (**2a**) as model substrates (Table 1**)** in the presence of different bases, including KOH, Na_2CO_3, K_2CO_3 and Cs_2CO_3 (1.8 mmol). Heating of the reaction mixture in DMSO (5 mL) at 120°C for 9 h under the atmosphere of N_2 (entries 1–4), gave the desired product **3a**. The highest yield 62% was achieved by using Cs_2CO_3 as a base. That result initiated further attempts in catalyst optimization. CuCl catalyst led to a significantly lower yield (Table 1, entry 5). Upon applica-

Table 2. Expansion of cascade C–H hydroxylation–C–S coupling–C–O cyclization reaction substrate[a]



1 **2** **3**

Comp. no.	R^1	R^2	Yield, %[b]	Comp. no.	R^1	R^2	Yield, %[b]
3a	4-Cl	H	62	**3f**	4-Cl	4-Cl	59
3b	4-CH_3	H	58	**3g**	4-Cl	5-CH_3	52
3c	4-OCH_3	H	59	**3h**	4-CH_3	4-CH_3	58
3d	2-Cl	H	41	**3i**	4-Cl	4-CH_3	53
3e	2-CH_3	H	43	**3j**	4-OCH_3	4-CH_3	55

[a] Conditions: **1** (0.5 mmol), **1** (0.5 mmol), **2** (0.6 mmol), CuI (10 mol %),Cs_2CO_3 (3 equiv), DMSO (5 mL), 9 h, 120°C, N_2. [b] Isolated yields.

tion of $FeCl_3$, $PdCl_2$ or $Pd(OAc)_2$ no desired product was detected (Table 1, entries 6–8). The effect of solvents, such as DMF, THF and toluene, was also tested, though with no improvement of the yields (Table 1, entries 6–8). Upon heating at temperature below 120□ the reaction did not occur (Table 1, entry 12). Based on the above screening, the optimized reaction conditions were determined to be 10% CuI as a catalyst, 3 equiv of Cs_2CO_3 as an alkaline reagent, DMSO as a solvent, 120°C, atmosphere of N_2, and the process time 9 h.

The optimal conditions were applied for the CuI catalyzed cascade C–H hydroxylation–C–S coupling–C–O cyclization of disulfides and *o*-chloroiodobenzenes. Generally, the cascade reactions proceeded well, and various phenoxathiin derivatives were separated with moderate to good yields. However, it was observed that *ortho*-substituted disulfides lowered the yield because formation of the C-S bond was retarded by the steric hindrance (**3d** and **3e**).

In summary, the ligand-free and simple cascade C–H hydroxylation–C–S coupling–C–O cyclization synthetic approach to disulfides and *o*-chloroiodobenzenes has been developed by using CuI as the catalyst. The simple process leads to the synthesis of phenoxathiin derivatives.

EXPERIMENTAL

All solvents were dried and purified by the known procedures and freshly distilled under the atmosphere of nitrogen prior to use. The products were isolated by column chromatography on silica gel (200–300 mesh) by using ethyl acetate and petroleum ether as the eluents. All yields are presented for the compounds isolated by column chromatography. Reactions progress and products purity were monitored by TLC using SiO_2 plates, and the spots were visualized under UV light. ^{1}H NMR spectra were measured in $CDCl_3$ on a Varian Mercury 400 spectrometer using TMS as the internal standard.

Synthesis of 3-chlorophenoxathiine (3a). CuI (10 mol %) Was added at room temperature to a mixture of disulfide **1a** (0.5 mmol) with *o*-chloro-iodobenzene **2a** (0.6 mmol) and Cs_2CO_3 (1.8 mmol) in DMSO (5 mL). The reaction mixture was stirred at 120°C for 9 h under the atmosphere of nitrogen. Upon completion of the process, the solvent was distilled off, and the residue was purified by column chromatography on silica gel (ethyl acetate–petroleum ether = 1 : 30, v:v) to give the product **3a**.

^{1}H NMR spectrum, δ, ppm: 7.06 t (1H, J = 7.2 Hz), 7.01 d (1H, J = 7.6 Hz), 6.99–6.83 m (5H).

The compounds **3b**–**3j** were synthesized according to the above method from the appropriate compounds (Table 2).

3-Methylphenoxathiine (3b). ^{1}H NMR spectrum, δ, ppm: 7.10–6.95 m (2H), 6.99–6.86 m (3H), 6.78–6.71 m (2H), 2.22 s (3H).

3-Methoxyphenoxathiine (3c). ^{1}H NMR spectrum, δ, ppm: 7.10–7.00 m (2H), 6.98–6.85 m (3H), 6.55–6.47 m (2H), 3.72 s (3H).

1-Chlorophenoxathiine (3d). ^{1}H NMR spectrum, δ, ppm: 7.09–7.02 m (2H), 6.99–6.91 m (3H), 6.89 d (1H, J = 8.0 Hz), 6.79 d (1H, J = 7.6 Hz).

1-Methylphenoxathiine (3e). ^{1}H NMR spectrum, δ, ppm: 7.03–6.98 m (2H), 6.97–6.89 m (3H), 6.81–6.75 m (2H), 2.22 s (3H).

3,7-Dichlorophenoxathiine (3f). ^{1}H NMR spectrum, δ, ppm: 7.07–7.07 m (2H), 7.05–7.01 m (3H), 6.91 d (2H, J = 8.4Hz).

7-Chloro-2-methylphenoxathiine (3g). ^{1}H NMR spectrum, δ, ppm: 6.99–6.93 m (3H), 6.95–6.83 m (3H), 2.26 s (3H).

3,7-Dimethylphenoxathiine (3h). ^{1}H NMR spectrum, δ, ppm: 6.97 d (2H, J = 7.6Hz), 6.82 d (4H J = 8.4Hz), 2.29 s (6H).

3-Chloro-7-methylphenoxathiine (3i). ^{1}H NMR spectrum, δ, ppm: 7.05–6.90 m (4H), 6.84 d (2H), 2.30 s (3H).

3-Methoxy-7-methylphenoxathiine (3j). ^{1}H NMR spectrum, δ, ppm: 6.98 d (2H J = 8.4Hz), 6.83 d (2H, J = 9.6Hz), 6.65–6.55 m (2H), 3.78 s (3H), 2.30 s (3H).

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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