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Communication

1,2-Diones

Copper-Assisted Synthesis of 2-Hydroxyphenyl-1,2-diones from Phenols and 2-Oxoaldehydes

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Abstract: An efficient copper(II)-catalyzed protocol for the *ortho*-functionalization of phenols was developed. A wide variety of 2-oxoaldehydes and phenols were tolerated, and the corresponding 2-hydroxyphenyl-1,2-diones were afforded in appreciable yields.

Introduction

Derivatives of benzils, such as 2-hydroxyphenyl-1,2-diones (HPDs), are widely distributed in nature.[1] These compounds possess intriguing structures and exhibit important biological activities such as anticancer,[1a,1b] antimicrobial,[1c] antioxidant,[1d] antibacterial, and hypertensive[1e] activities, and they also show inhibition of the enzymatic activity of carboxyl esterases[2] (Figure 1). As a result, the development of new practical methods for the synthesis of this scaffold is of considerable interest. In this context, Thasana and co-workers developed a method for the synthesis of HPDs through intramolecular cyclization of anionic benzylic esters of aryl benzyl ethers in the presence of a base followed by dioxirane oxidation.[3] This method, however, suffers with limitations in terms of using complex starting materials and the products are obtained in low yields. Li et al. reported the synthesis of HPDs by Fe^{II} catalyzed *ortho*-functionalization of phenols with α-hydroxy ketones.[4] The yields were comparatively good, but longer reaction times and an external oxidant were required. Our group also established a synthetic strategy for the generation of HPDs through an amine-catalyzed cross-coupling approach. In this

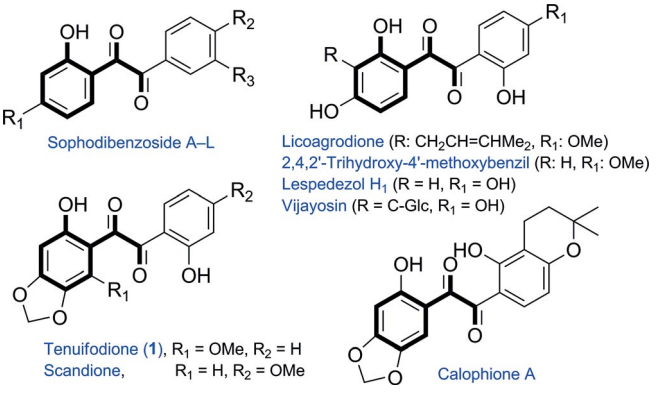
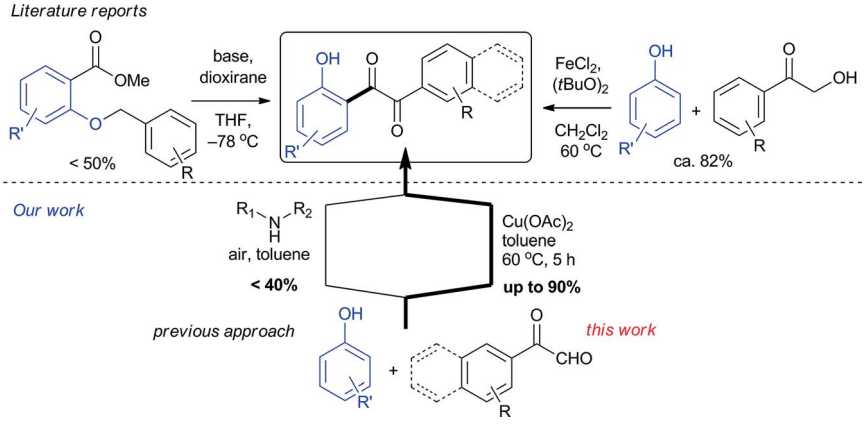


Figure 1. Naturally occurring bioactive 2-hydroxyphenyl-1,2-diones.



Scheme 1. Various synthetic approaches to 2-hydroxyphenyl-1,2-diones.

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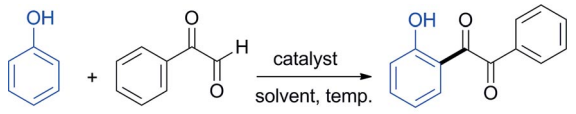
case, the required product was produced in less than 40 % yield (Scheme 1).[5]

Drawing from our recent Cu^{II}-catalyzed reactions of oxazoles and/furanones[6] and in light of the importance of HPDs, we succeeded in achieving a practical synthesis of HPDs in high yields through the Cu^{II}-catalyzed reaction of 2-oxoaldehydes with phenols.

Results and Discussion

Our initial studies focused on developing an efficient catalytic system to investigate the reaction of phenol (**1a**, 0.746 mmol) with phenylglyoxal (**2a**, 0.746 mmol) as a model system. Upon conducting this reaction with 20 mol-% $Cu(OAc)_2{\cdot}H_2O$ in toluene, to our delight we isolated product **3a** in 25 % yield (Table 1, entry 1). To improve the yield, initially we performed a screening of the reaction in the presence of various Cu^I/Cu^{II} catalysts at a loading of 20 mol-% (Table 1, entries 2–4). With the exception of $Cu(OAc)_2{\cdot}H_2O$, no catalyst gave an appreciable yield of **3a**. Next, the model reaction with $Cu(OAc)_2{\cdot}H_2O$ was investigated at various temperatures/times (Table 1, entries 5–7). We observed a better yield of desired product **3a** at 60 °C within 12 h (Table 1, entry 6). A further increase in the temperature did not have a significant effect on the reaction yield (Table 1, entry 7). Further, to interpret the solvent effect, the reaction was examined in various solvent systems (Table 1, en-

Table 1. Optimization of the *ortho*-functionalization of phenol.[a]

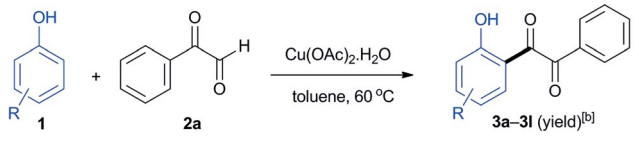


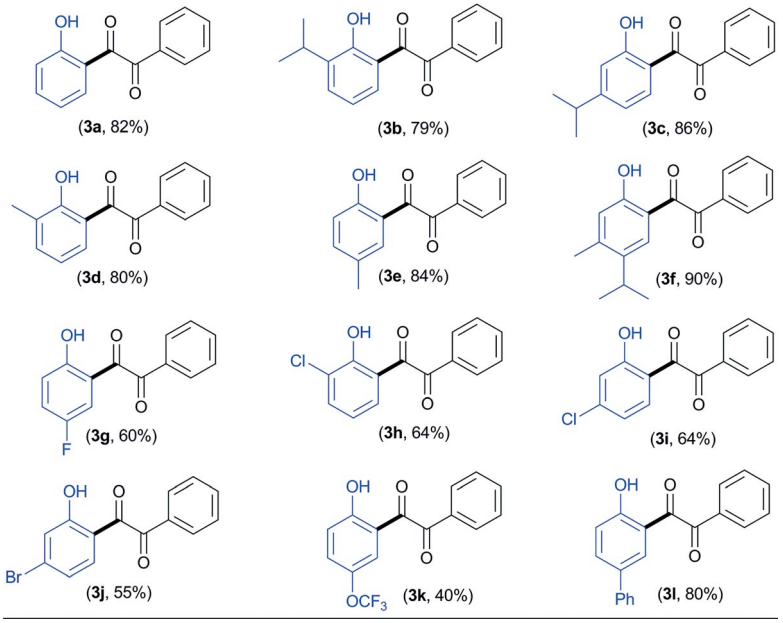
1a 2a 3a

Entry	Solvent	Catalyst (mol-%)	*T* [°C]	*t* [h]	Yield[b] [%]
1	toluene	$Cu(OAc)_2{\cdot}H_2O$ (20)	r.t.	24	25
2	toluene	$CuCl_2{\cdot}H_2O$ (20)	r.t.	24	trace
3	toluene	CuO (20)	r.t.	24	5
4	toluene	CuI (20)	r.t.	24	–
5	toluene	$Cu(OAc)_2{\cdot}H_2O$ (20)	45	12	58
6	toluene	$Cu(OAc)_2{\cdot}H_2O$ (20)	60	12	82
7	toluene	$Cu(OAc)_2{\cdot}H_2O$ (20)	80	5	82
8	MeOH	$Cu(OAc)_2{\cdot}H_2O$ (20)	60	5	12
9	CH_3CN	$Cu(OAc)_2{\cdot}H_2O$ (20)	60	5	20
10	CH_2Cl_2	$Cu(OAc)_2{\cdot}H_2O$ (20)	60	5	40
11	H_2O	$Cu(OAc)_2{\cdot}H_2O$ (20)	60	5	5
12	DMSO	$Cu(OAc)_2{\cdot}H_2O$ (20)	60	5	–
13	toluene	$Cu(OAc)_2{\cdot}H_2O$ (20)	60	5	82
14	toluene	$Cu(OAc)_2{\cdot}H_2O$ (15)	60	5	76
15	toluene	$Cu(OAc)_2{\cdot}H_2O$ (25)	60	5	82
16[c]	toluene	$Cu(OAc)_2{\cdot}H_2O$ (20)	60	5	86
17[d]	toluene	$Cu(OAc)_2{\cdot}H_2O$ (20)	60	5	10

[a] Reaction conditions: Phenol (**1a**, 0.746 mmol), phenylglyoxal (**2a**, 0.746 mmol), Cu catalyst (20 mol-%), solvent (1.5 mL), temp., 5 h. [b] Yield of isolated product. [c] Under an O_2 atmosphere (balloon). [d] Under an atmosphere of argon (balloon).

Table 2. Scope of the reaction with respect to phenols **1**.[a]





[a] Reaction conditions: Substituted phenol **1** (0.746 mmol), phenylglyoxal (**2a**, 0.746 mmol), Cu catalyst (20 mol-%), solvent (1.5 mL), 60 °C, 5 h. [b] Yield of isolated product.

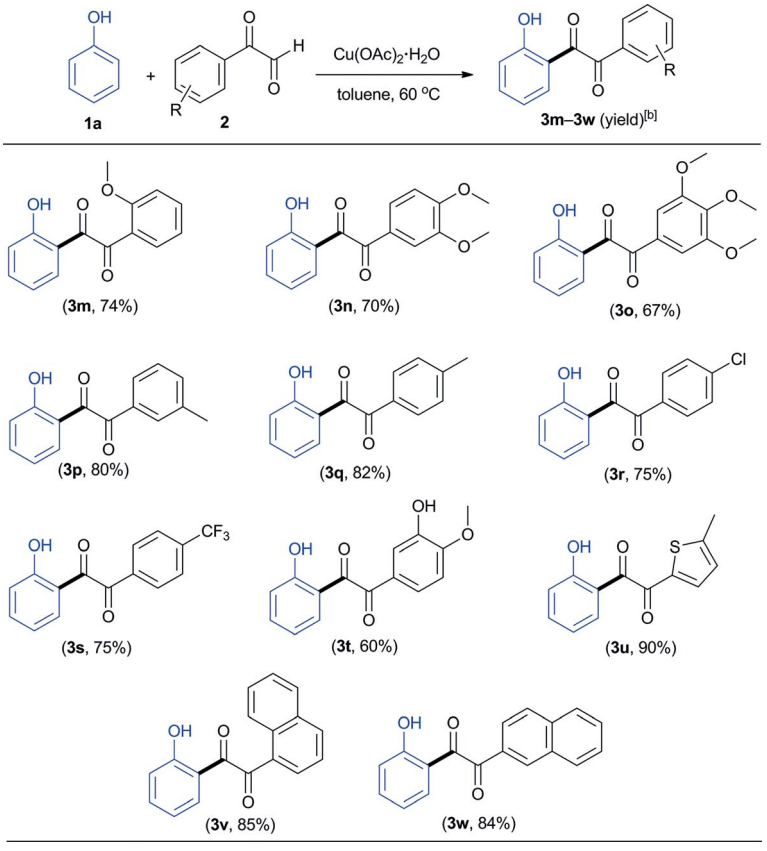
tries 8–12). Among them, toluene was found to be the best-suited solvent for the reaction. A survey of the catalyst loading was also conducted (Table 1, entries 13–15). Additionally, reactions performed under O_2 and argon atmospheres were also performed (Table 1, entries 16 and 17). These two experiments undoubtedly emphasized the role of oxygen as a promoter of the reaction. Finally, we observed that the best yield of **3a** was obtained if the model reaction was performed with 20 mol-% $Cu(OAc)_2 \cdot H_2O$ in toluene at 60 °C for 5 h (Table 1, entry 13).

With the optimized procedure in hand, to check the viability of the reaction in terms of substituted phenols **1**, we performed a series of experiments between substituted phenols **1** and phenylglyoxal (**2a**) to afford products **3a** to **3l** (Table 2). As observed, all the reactions proceeded smoothly to the desired products, which were obtained in good to excellent yields (40–90 %). More precisely, simple phenol (see product **3a**) and phenols bearing electron-donating groups, namely, isopropyl (see products **3b** and **3c**) and methyl (see products **3d** and **3e**) groups, afforded the products in high yields. Phenol substituted with both isopropyl and methyl groups produced desired product **3f** in an excellent yield, but phenols containing halogen atoms, that is, F, Cl, and Br atoms, produced products **3g**–**j** in moderate yields, whereas the phenol containing the electron-withdrawing OCF_3 group produced **3k** in a low yield owing to low nucleophilicity. Moreover, the reaction with 4-phenylphenol was also compatible with the reaction conditions and produced product **3l** in high yield.

Next, we extended the substrate scope of the reaction by conducting various reactions between phenol (**1a**) and 2-oxoaldehydes **2** to afford products **3m**–**w** (Table 3). This reaction was very compatible with all varieties of 2-oxoaldehydes **2**. It is clear that the electronic environment of the phenyl ring in substrate **2** has no appreciable effect on the reaction or the yield. On the basis of our observations, substrates **2** bearing electron-donating groups, for example, OMe (see products **3m**–**o**) and Me (see products **3p** and **3q**) groups, afforded slightly lower yields than substrates **2** with electron-withdrawing groups, for example, Cl (see product **3r**) and CF_3 (see product **3s**) groups.

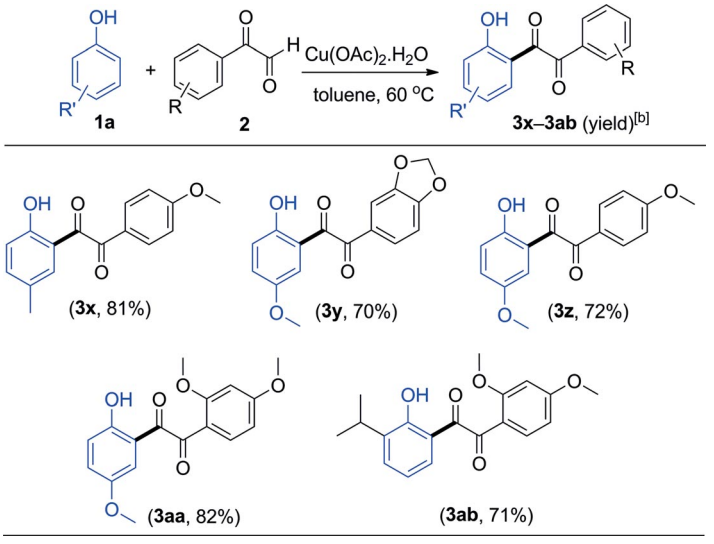
In addition, the reaction of hydroxy-substituted phenylglyoxal and a heterocyclic 2-oxoaldehyde with phenol also afforded desired products **3t** and **3u** in good yields. Along with these results, we successfully obtained comparable yields of corresponding desired products **3v** and **3w** in reactions with α- and β-naphthylglyoxals. Finally, as presented in Table 4, we generated products **3x**–**ab** in good yields by performing reactions between various phenols **1** and substituted phenylglyoxals **2**. In general, we can summarize that this protocol is applicable to all sorts of substituted phenols **1** and glyoxals **2**.

Table 3. Scope of the reaction with respect to 2-oxoaldehydes **2**.[a]



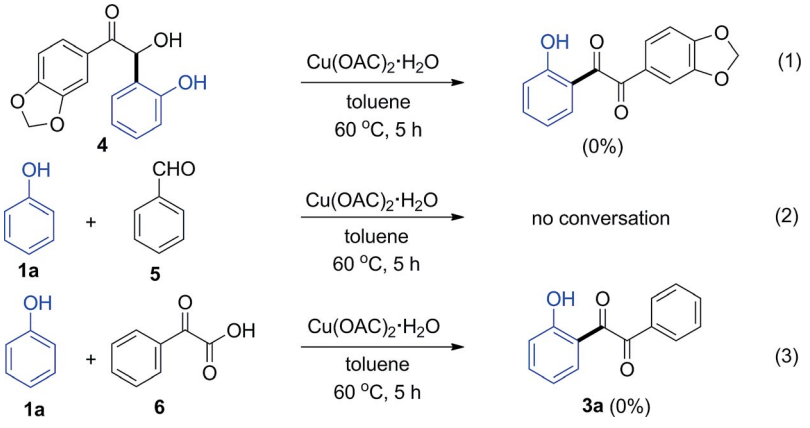
[a] Reaction conditions: Phenol (**1a**, 0.746 mmol), substituted phenylglyoxal **2** (0.746 mmol), Cu catalyst (20 mol-%), solvent (1.5 mL), 60 °C, 5 h. [b] Yield of isolated product.

Table 4. Scope of the reaction of **1** with **2**.[a]

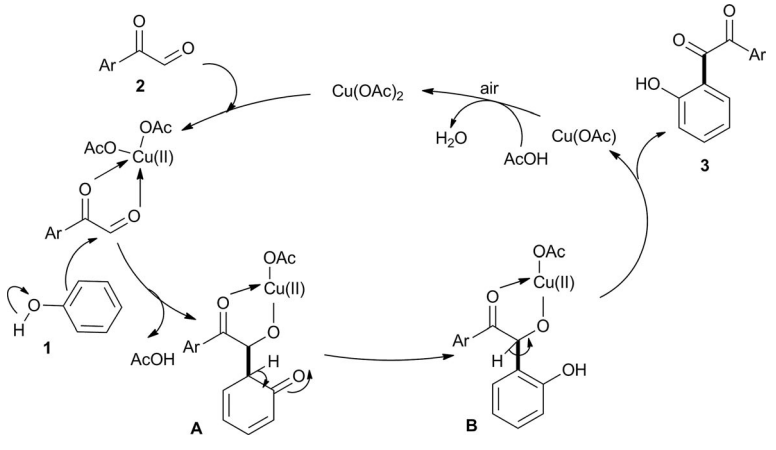


[a] Reaction conditions: Phenol **1** (0.746 mmol), substituted phenylglyoxal **2** (0.746 mmol), Cu catalyst (20 mol-%), solvent (1.5 mL), 60 °C, 5 h. [b] Yield of isolated product.

To interpret the reaction mechanism, we performed a few control experiments (Scheme 2). In experiment (1), upon subjecting substrate **4** to our reaction conditions, no product was observed, even after 24 h. This clearly ruled out the direct oxidation of **4** in the presence of the Cu^{II}/Cu^{I} system. In experiment (2), we performed a reaction between normal aldehyde



Scheme 2. Control experiments.



Scheme 3. Plausible reaction mechanism.

5 and phenol (**1a**) under the standard reaction conditions. As expected, the reaction failed to produce the corresponding *ortho*-functionalized product. This clearly indicated the role of the glyoxals/2-oxoaldehydes under the reaction conditions. Eventually, from experiment (3), it became clear that 2-oxoacids were ineffective under the reaction conditions.

On the basis of the above results and literature reports,[7] a plausible reaction mechanism for the Cu-catalyzed *ortho*-functionalization of phenols **1** with glyoxals **2** is described in Scheme 3. Initially, glyoxal **2** coordinates to Cu^{II} through its two carbonyl groups. Its reaction with phenol results in *ortho* C–C bond formation to generate adduct **A**. Adduct **A** tautomerizes to intermediate **B**, which further undergoes oxidation to produce desired product **3** with elimination of Cu^{I}, which undergoes air-assisted regeneration to Cu^{II} that ultimately re-enters the catalytic system.[7c]

Conclusions

In conclusion, we established an efficient strategy to perform the copper-catalyzed *ortho*-functionalization of simple phenols with 2-oxoaldehydes. By this technique, we achieved the synthesis of biologically interesting 2′-hydroxyphenyl-1,2-dione scaffolds in high yields. The mild reaction conditions and the generality of the substrate scope are also attractive merits of this reaction. Further, its application towards the synthesis of various natural products is in progress.

Experimental Section

General Procedure for the Synthesis of 3: A round-bottomed flask equipped with a reflux condenser was charged with a mixture of phenol **1** (0.746 mmol), arylglyoxal monohydrate **2** (0.746 mmol), and $Cu(OAc)_2{\cdot}H_2O$ (20 mol-%). Toluene (1.5 mL) was added, and the resulting mixture was stirred at 60 °C for 5 h. Upon completion of the reaction, the mixture was cooled to room temperature and water was added. The mixture was extracted with ethyl acetate (2 × 5 mL). The organic layer was collected and dried with $MgSO_4$. The organic solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography (silica gel, 100–200#; petroleum ether/EtOAc, 10:1). Desired product **3a** was produced as a white solid (138 mg, 82 %); m.p. 71–73 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.38 (s, 1 H), 7.97 (d, J = 7.4 Hz, 2 H), 7.67 (t, J = 7.4 Hz, 1 H), 7.59–7.42 (m, 4 H), 7.07 (d, J = 8.5 Hz, 1 H), 6.88 (t, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 199.35, 192.06, 163.38, 138.15, 135.26, 132.68, 132.45, 130.05, 129.18, 119.77, 118.72, 116.86 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3438, 3063, 2923, 2852, 1726, 1678, 1631, 1615, 1451, 1578, 1598, 1205, 1155, 888, 756, 719 cm^{-1}. GC–MS (EI): *m/z* (%) = 226.2 (6.57) $[M]^+$, 209.2 (3.27), 181.2 (2.04), 121.2 (100), 105.3 (34.73), 93.1 (7.2), 77.1 (30.12), 51.1 (8.5).

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Keywords: Synthetic methods · C–H activation · Copper · Phenols

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