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An efficient palladium-catalyzed synthesis of benzils from aryl bromides: vinylene carbonate as a synthetic equivalent of glyoxal

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ABSTRACT

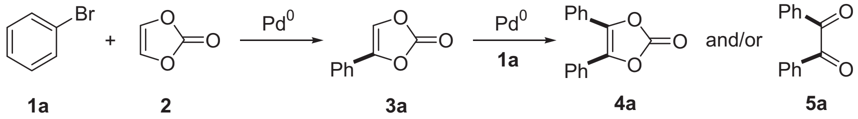
An expedient synthetic procedure of benzil derivatives from aryl bromides was developed using vinylene carbonate as a glyoxal equivalent in a palladium-catalyzed reaction. The reaction involved a sequential diarylation of vinylene carbonate to form 4,5-diaryl-1,3-dioxol-2-one, ring-opening to benzoin derivative, and an oxidation process.

1,2-Diketones are very important structural moieties in numerous biologically interesting compounds and are broadly utilized for construction of complex structures in organic synthesis.[1] Among the numerous 1,2-diketones, benzil derivatives have received a special attention. Usually benzil derivatives have been synthesized by oxidation of alkynes,[2] acyloin condensation of aldehydes and a subsequent oxidation,[3] coupling of acyl cyanide,[4] Pd-catalyzed arylation of arylglyoxals with arylboronic acids,[5a] and other methods.[5b–f] To the best of our knowledge, there is no precedent synthetic method of benzils from haloarenes.

We reasoned that vinylene carbonate (**2**) could be used as a two-carbon unit, a glyoxal equivalent, in a Pd-catalyzed Heck type reaction with bromobenzene (**1a**) to form 4,5-diphenyl-1,3-dioxol-2-one (**4a**) or benzil (**5a**), as shown in Scheme 1. The most important point in our rationale is that a Heck reaction between PhPdBr and vinylene carbonate could occur via a formal anti-elimination of HPdBr presumably via a facile formation of an oxonium ion intermediate **II** (vide infra).[6,7]

Thus, we examined the reaction of **1a** and **2** under various conditions as shown in Table 1. At the outset of our studies we used K_2CO_3 in DMF at 90 °C (entry 1); however, benzil (**5a**) was produced in low yield (5%). The use of Cs_2CO_3 in refluxing CH_3CN increased the yield of **5a** to 15% (entry 2). The reaction under DMF/Cs_2CO_3 conditions raised the yield of **5a** to 46% (entry 3). Increasing the amount of a palladium catalyst (entry 4) provided a good yield (74%) of **5a**. Finally, the yield of **5a** was improved to 81% at 120 °C (entry 5) within short time (30 min).[8] Reducing the amount of bromobenzene (entries 6 and 7) decreased the yield of **5a**. The yield of **5a** was similar with that of entry 5 when we used excess amounts of bromobenzene (entry 8). Thus we chose entry 5 as the optimum conditions. Interestingly, 4-phenyl-1,3-dioxol-2-one (**3a**) was isolated in low yield (entry 9) when we used Et_3N in DMF (vide infra). The use of iodobenzene produced low yield of **5a** (entry 10). In this case, reductive dimerization to biphenyl was the major pathway. The reaction with chlorobenzene failed completely (entry 11).

Encouraged by the successful results, we examined the reaction with various aryl bromides **1a**–**j** and the results are summarized in Table 2. The reactions with *p*-bromotoluene (**1b**), *o*-bromotoluene (**1c**), *p*-bromoanisole (**1d**), *m*-bromoanisole (**1e**), 1-bromo-4-chlorobenzene (**1f**), 2-bromonaphthalene (**1g**), 1-bromonaphthalene



Scheme 1.

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Table 1
Optimization of reaction conditions for the synthesis of benzil (**5a**) from bromobenzene (**1a**)

Entry	Conditions[a]	**5a**[b] (%)
1	**1a** (3.0 equiv), Pd(OAc)$_2$ (5 mol %), PPh$_3$ (10 mol %), K_2CO_3 (2.2 equiv), DMF, 90 °C, 1 h	5
2	**1a** (3.0 equiv), Pd(OAc)$_2$ (5 mol %), PPh$_3$ (10 mol %), Cs_2CO_3 (2.2 equiv), CH_3CN, reflux, 2 h	15
3	**1a** (3.0 equiv), Pd(OAc)$_2$ (5 mol %), PPh$_3$ (10 mol %), Cs_2CO_3 (2.2 equiv), DMF, 90 °C, 1 h	46
4	**1a** (3.0 equiv), Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), Cs_2CO_3 (2.2 equiv), DMF, 90 °C, 1 h	74
5	**1a** (3.0 equiv), Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), Cs_2CO_3 (2.2 equiv), DMF, 120 °C, 30 min	81
6	**1a** (2.2 equiv), Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), Cs_2CO_3 (2.2 equiv), DMF, 120 °C, 30 min	55
7	**1a** (1.0 equiv), Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), Cs_2CO_3 (1.0 equiv), DMF, 120 °C, 30 min	60[c]
8	**1a** (4.0 equiv), Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), Cs_2CO_3 (3.0 equiv), DMF, 120 °C, 30 min	79
9	**1a** (3.0 equiv), Pd(OAc)2 (10 mol %), Et_3N (3.0 equiv), DMF, 120 °C, 30 min	0[d]
10	Iodobenzene (3.0 equiv), Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), Cs_2CO_3 (2.2 equiv), DMF, 120 °C, 30 min	36
11	Chlorobenzene (3.0 equiv), Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), Cs_2CO_3 (2.2 equiv), DMF, 120 °C, 1 h	0

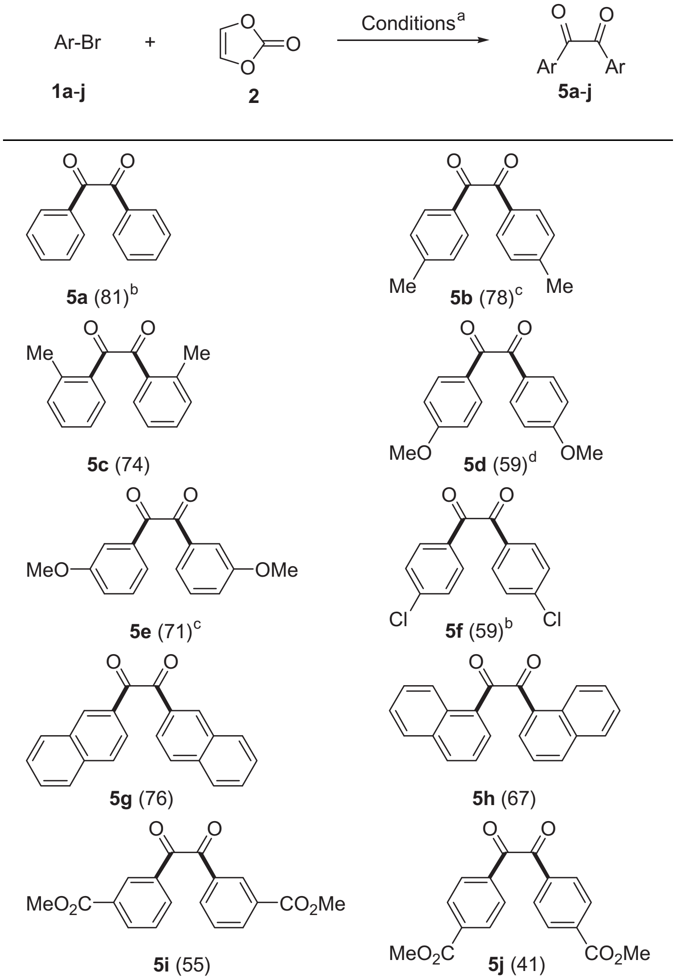
[a] Vinylene carbonate (**2**, 1.0 equiv) is common.

[b] Isolated yield based on **2**, and appreciable amounts of biphenyl were observed.

[c] Yield based on **1a.**

[d] 4-Phenyl-1,3-dioxol-2-one (**3a**) was isolated in 27%.

Table 2
Synthesis of benzil derivatives **5a-j**



[a] ArBr (**1a–j**, 3.0 equiv), vinlyene carbonate (**2**, 1.0 equiv), Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), Cs_2CO_3 (2.2 equiv), DMF, 120 °C, 1 h.

[b] Reaction time is 30 min.

[c] Mixed benzil derivative was formed in trace amounts (<5%).

[d] Mixed benzil **7** was isolated in 12% (see Scheme 2).

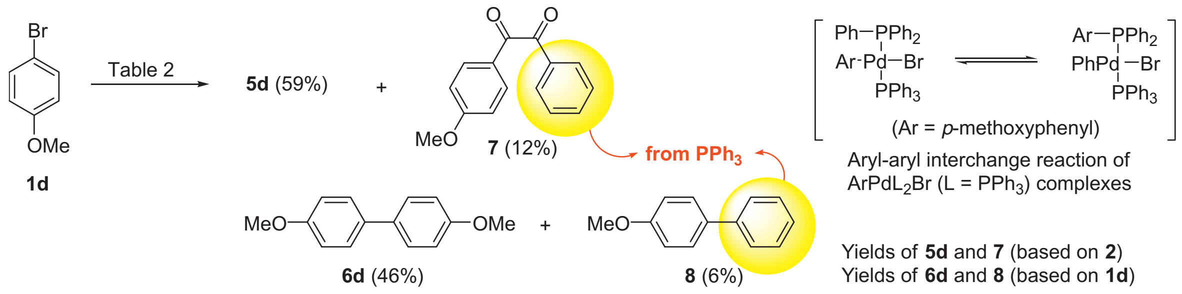
(**1h**), methyl 3-bromobenzoate (**1i**), and methyl 4-bromobenzoate (**1j**) were examined. The corresponding benzil derivatives **5b**–**i** were obtained in good to moderate yields (55–78%) except **5j** (41%). In all entries, the corresponding biaryl derivatives (24–46% based on **1a**–**j**) and arenes (0–7%) were formed as side products. The reactions with aryl bromides having an electron-withdrawing substituent showed a sluggish reactivity in the reaction. As examples, we could not obtain the corresponding benzils in appreciable amounts for the reactions of 2-bromobenzaldehyde and 2-bromopyridine.

It is interesting to note that appreciable amounts of aryl–aryl interchange reaction of ArPdL$_2$Br (L = PPh$_3$) complexes[9] has been observed when we used aryl bromides having a methoxy group such as **1d** and **1e**. As an example, mixed benzil **7** (12%) and mixed biaryl **8** (6%) were formed together when we used *p*-bromoanisole (**1d**), as shown in Scheme 2.[10]

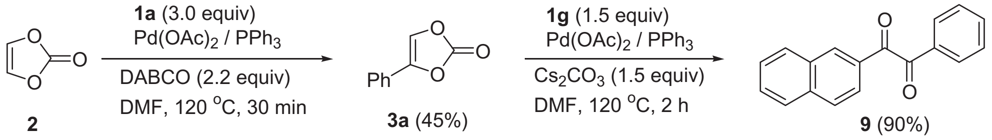
In order to prepare an unsymmetrical benzil derivative such as **9** (Scheme 3), we examined the synthesis of 4-phenyl-1,3-dioxol-2-one (**3a**). As stated above (entry 9 in Table 1), compound **3a** was isolated in 27% when Et_3N was used as a base. After a few trials we could increase the yield of **3a** to 45% when we used DABCO as a base.[11] With this **3a** in our hands, compound **9** was synthesized in high yield (90%) by the reaction with 2-bromonaphthalene (**1g**).

The mechanism for the formation of benzil (**5a**) could be postulated as shown in Scheme 4. Syn-carbopalladation of PhPdBr to vinylene carbonate (**2**) produced an intermediate **I.** The intermediate has no syn-β-hydrogen atom with respect to -PdBr moiety, thus compound **3a** cannot be formed by usual β-H elimination. Instead, **3a** could be formed via a facile deprotonation of the oxonium ion intermediate **II** that produced via an S_N1 type solvolysis process.[6,12] A subsequent arylation of **3a** produced **4a** by following the same mechanism. Compound **4a** might be ring-opened to produce benzoin **III** presumably by the moisture in the basic reaction mixture.[11] The oxidation of **III** to **5a** could be conducted, in part, by a base-mediated aerobic oxidation.[3a,13] In another part, a Pd^0/**1a**-mediated redox process[14] could convert **III** to **5a** as well as **1a** to biphenyl (**6a**) at the same time. Biphenyl (**6a**) was isolated in 28% (based on **1a**) along with **5a** (81%, based on **2**) under the typical reaction conditions (entry 5 in Table 1), while the reaction of **1a** without vinylene carbonate (**2**) produced **6a** in only 5%. The results stated that the presence of **III** increased the yield of **6a**, and a redox process is obviously contributing to the formation of **5a** and **6a**.

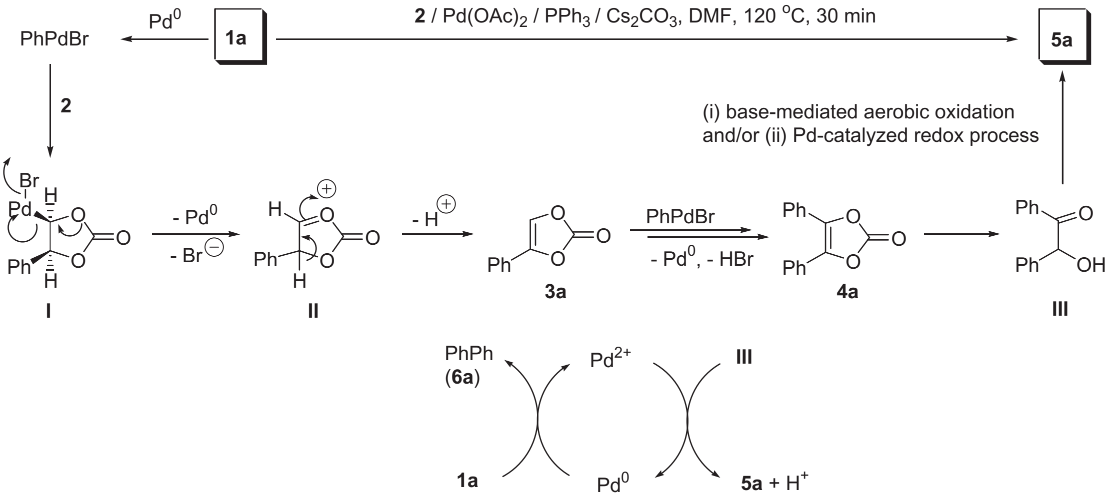
In summary, a facile synthetic procedure of benzil derivatives from aryl bromides was developed using vinylene carbonate as a glyoxal equivalent in a palladium-catalyzed reaction. The reaction involved a sequential diarylation of vinylene carbonate to form 4,5-diaryl-1,3-dioxol-2-ones, ring-opening to benzoin derivatives, and an oxidation process.



Scheme 2.



Scheme 3.



Scheme 4.

Acknowledgments

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8. *Typical procedure for the synthesis of benzil* (**5a**): A stirred mixture of bromobenzene (471 mg, 3.0 mmol), vinylene carbonate (86 mg, 1.0 mmol), $Pd(OAc)_2$ (22 mg, 10 mol %), PPh_3 (52 mg, 20 mol %), and Cs_2CO_3 (715 mg, 2.2 mmol) in DMF (1.5 mL) was heated to 120 °C for 30 min under nitrogen atmosphere. After aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc, 20:1) benzil was obtained as a pale yellow solid, 170 mg (81% based on vinylene carbonate), along with biphenyl (65 mg, 28% based on bromobenzene) as a white solid. Other compounds were synthesized similarly and the representative spectroscopic data of **3a**, **4a**, **5i**, **7** and **9** are as follows.

   Compound **3a**:[15a] white solid, mp 81–82 °C (Lit.[15a] 82–83 °C); IR (KBr) 3140, 1868, 1807, 1077 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34 (s, 1H), 7.40–7.50 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 123.82, 123.41, 124.60, 129.04, 129.91, 143.54, 152.61; ESIMS *m/z* 185 $[M+Na]^+$.

   Compound **4a**:[15b] white solid, mp 73–74 °C (Lit.[15b] 75–76 °C); IR (KBr) 2930, 1819, 1735, 1211 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.41–7.44 (m, 6H), 7.56–7.59 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 125.51, 126.46, 128.95, 130.07, 137.04, 151.74; ESIMS *m/z* 261 $[M+Na]^+$.

   Compound **5i**: 55%; yellow solid, mp 166–167 °C; IR (KBr) 2929, 1728, 1668, 1280 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.96 (s, 6H), 7.66 (t, *J* = 7.8 Hz, 2H), 8.23 (d, *J* = 7.8 Hz, 2H), 8.36 (d, *J* = 7.8 Hz, 2H), 8.63 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.49, 129.33, 131.03, 131.20, 132.96, 133.78, 135.66, 165.64, 192.50; ESIMS *m/z* 349 $[M+Na]^+$. Anal. Calcd for $C_{18}H_{14}O_6$: C, 66.26; H, 4.32. Found: C, 66.43; H, 4.25.

   Compound **7**:[2f,5a] pale yellow solid, mp 63–64 °C (Lit.[2f] 65 °C); IR (KBr) 2934, 1672, 1597, 1265, 1166 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.89 (s, 3H), 6.95–7.01 (m, 2H), 7.48–7.53 (m, 2H), 7.62–7.68 (m, 1H), 7.92–8.00 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.63, 114.34, 126.04, 128.94, 129.89, 132.38, 133.15, 134.71, 164.97, 193.17, 194.86; ESIMS *m/z* 263 $[M+Na]^+$.

   Compound **9**:[15c] pale yellow solid, mp 85–86 °C; IR (KBr) 3060, 1670, 1626, 1594, 1174 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.55 (m, 3H), 7.59–7.67 (m, 2H), 7.85–7.95 (m, 3H), 7.98–8.11 (m, 3H), 8.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 123.56, 127.14, 127.89, 129.00, 129.13, 129.51, 129.87, 129.94, 130.23, 132.26, 133.03, 133.51, 134.87, 136.32, 194.62 (2C); ESIMS *m/z* 283 $[M+Na]^+$.

9. For the aryl-aryl interchange reaction of $ArPdL_2X$ (L = PPh_3) complexes, see: (a) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441–12453; (b) Sakamoto, M.; Shimizu, I.; Yamamoto, A. *Chem. Lett.* **1995**, 1101–1102.
10. In order to prohibit an aryl–aryl interchange reaction, we examined the reaction of **1d** without PPh_3. However, the reaction failed to obtain **5d**. The reaction of **1d** under Jeffery ligandless conditions (TBAC, Cs_2CO_3, DMF, 120 °C, 2 h) in the presence of $Pd(OAc)_2$ did not produce **5d** also.
11. 4,5-Diphenyl-1,3-dioxol-2-one (**4a**) was also isolated albeit in low yield (8%) during the synthesis of **3a** in Scheme 3. Compound **4a** was converted quantitatively to benzil under the influence of Cs_2CO_3 in DMF within 10 min (120 °C).
12. The reaction of **1a** and **2** in toluene, xylene, and CH_3CN (entry 2 in Table 1) showed a sluggish reactivity, while the reaction in a polar solvent such as DMA, NMP and sulfolane showed very similar results with that in DMF. The results are well coincidence with an involvement of solvolysis mechanism.
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