Article

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Synthesis of Xanthones by Palladium-Catalyzed Tandem Carbonylation/C–H Activation via 2-Iodo Diaryl Ethers

Rui-Yue Ma, Ya-Fang Chen, Jun-Ru Wang and Zhen-Ting Du *

College of Chemistry and Pharmacy, Northwest A&F University, Yangling 712100 Shaanxi Province, P. R. China

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The ring closure of 2-iodo diaryl ether in the presence of a palladium catalyst to xanthone under carbon monoxide atmosphere is studied. A series of xanthones could be successfully obtained through this protocol, with $Pd(OAc)_2$ as the catalyst, $P(Cy)_3$ as ligand, $PivONa{\cdot}H_2O$ as base, and PivOH and tetrabutylamonium bromide as additives in DMSO, in moderate to good yields.

Keywords: Xanthone; Palladium-catalyzed reaction; Heterocycle synthesis.

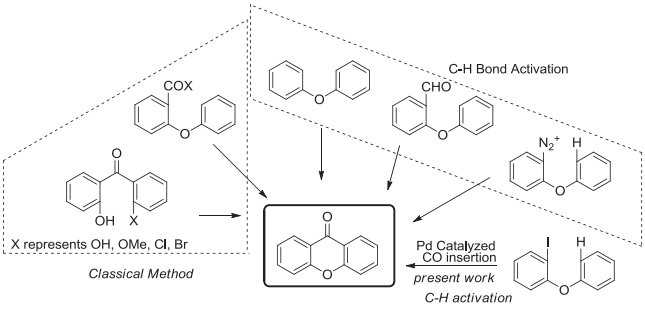
INTRODUCTION

Xanthones, also known as 9*H*-xanthen-9-ones, can be found frequently in many natural products[1] and other bioactive heterocyclic molecules,[2] and exhibit a broad spectrum of biological or pharmaceutical activities.[3–9] As shown in Scheme 1, the syntheses of xanthone can be broadly classified into two types. The first is the "classical method" involving an intramolecular SN_{Ar}[10–14] or Friedel–Crafts reaction.[15–22] Since the 1980s, transition-metal-catalyzed C–H bond activation of the derivatives of diaryl ether, as the second methodology to form xanthones, has been developed remarkably in the synthesis of xanthones.[23–29] Intriguingly, Larock reported a tandem coupling–cyclization of arynes to xanthones[30–32] as a strategy to construct a phenyl ring. Nonetheless, apart from these worthy developments, the syntheses of the xanthone skeleton typically involved multistep procedures generally requiring functionalized benzophenone or diaryl ether motif often under harsh reaction conditions or with unpredictable yields. Recently, we reported a palladium-catalyzed carbonylation and C–H activation to synthesize xanthones through the *ortho*-diazonium salt of diaryl ether in excellent yields.[33] Therefore, we envisaged that 2-iodio of diaryl ether could be employed to prepare xanthones (Scheme 1) in the presence of CO after a catalytic de-iodide ring-closure sequence. To the best of our knowledge, there has been no systematic study on the ring closure of 2-iodio diaryl ether. Therefore, as a supplement to our previous study, we were interested in seeking a protocol of this ring closure of 2-iodio of diaryl ether in the presence CO. Here, we present these newest results using this method.

RESULTS AND DISCUSSION

At the outset of the investigation, we examined the ring-closure reaction of 2-iodo diphenyl ether using 5 mol% palladium acetate as catalyst, 20 mol% triphenylphosphine as ligand, 3 equiv of cesium carbonate as base, and *N,N*-dimethyl formamide as solvent under 0.2 MPa pressure of CO. To our disappointment, the desired xanthone was obtained only in 5% yield. Even then, encouraged by this promising result, we next screened different catalysts and phosphine ligands (Table 1, entries 1–4) to select best ligand. Obviously, among PPh_3, $P(Cy)_3$, dppe, and dppp, tricyclohexylphosphine was found to be the best. As far as the catalysts were concerned, $PdCl_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$, and $Pd(TFA)_2$ proved ineffective in this reaction. It is worth mentioning that neopentanoic acid had a remarkable beneficial effect in the reaction (Table 1, entries 11, 14–21). We then tried to change the base and found that different bases affected the reaction markedly. Thus, if K_2CO_3 was used, a similar yield was obtained. These results revealed that that $PivONa{\cdot}H_2O$ was the most suitable base for the transformation. Next, we turned our attention to varying the conditions with $PivONa{\cdot}H_2O$ as base (Table 1, entries 14–21). With $PivONa{\cdot}H_2O$ as the base and pivalic acid and tetrabutylammonium bromide as additives, the highest yield of

*Corresponding author. Email: duzt@nwsuaf.edu.cn



Scheme 1. Synthesis of xanthones from dibenzoketone and functionalized diaryl ether.

product could be obtained. Our studies subsequently showed that the nature of reaction solvent was very important for this reaction. In toluene, dioxane, and acetonitrile, a yield of more or less than 40% could be obtained (Table 1, entries 15–17). In contrast, by using DMSO (Table 1, entry 19) as the reaction solvent, the best yields could be obtained. Lastly, we screened the pressure of CO and found that it did not have a significant effect upon this transformation between 0.1 and 0.4 MPa. Finally, we found the optimum reaction conditions with DMSO as solvent, 5 mol% $Pd(OAc)_2$ as catalyst, a temperature of 90°C, 100 mol% PivONa·H_2O as base, and 100 mol% pivalic acid and 10 mol % TBAB as additives (Table 1, entry 19).

With the optimized conditions, we next examined the scope of $Pd(OAc)_2$-catalyzed cyclization of 2-iodo diaryl ether for the synthesis of substituted xanthones. The results are summarized in Table 2. A range of structurally diverse 2-iodio diaryl ehters (Table 2), including different R^1 and R^2 groups as well as chloro and methoxy groups were proved amenable to the reaction conditions, delivering the corresponding xanthones in moderate to good yields under this protocol. R^1 can be H or CH_3; as for the variations of R^2, electron-

Table 1. Optimization of conditions

Entry[a]	Catalyst (5%)	Ligand (0.2)	Base (3.0)	Additive (2.0)	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	None	DMF	5
2	$Pd(OAc)_2$	$P(Cy)_3$	Cs_2CO_3	None	DMF	26
3	$Pd(OAc)_2$	dppe	Cs_2CO_3	None	DMF	5
4	$Pd(OAc)_2$	dppp	Cs_2CO_3	None	DMF	7
5	$PdCl_2$	$P(Cy)_3$	Cs_2CO_3	None	DMF	15
6	$Pd(PPh_3)_4$	$P(Cy)_3$	Cs_2CO_3	None	DMF	9
7	$Pd_2(dba)_3$	$P(Cy)_3$	Cs_2CO_3	None	DMF	0
8	$Pd(TFA)_2$	$P(Cy)_3$	Cs_2CO_3	None	DMF	22
9	$Pd(OAc)_2$	$P(Cy)_3$	K_2CO_3	None	DMF	20
10	$Pd(OAc)_2$	$P(Cy)_3$	NaOAc	None	DMF	33
11	$Pd(OAc)_2$	$P(Cy)_3$	PivONa·H_2O	None	DMF	37
12	$Pd(OAc)_2$	$P(Cy)_3$	*t*-BuOK	None	DMSO	17
13	$Pd(OAc)_2$	$P(Cy)_3$	NaOAc	PivOH	DMF	56
14	$Pd(OAc)_2$	$P(Cy)_3$	PivONa·H_2O	PivOH	DMF	69
15	$Pd(OAc)_2$	$P(Cy)_3$	PivONa·H_2O	PivOH	Toluene	44
16	$Pd(OAc)_2$	$P(Cy)_3$	PivONa·H_2O	PivOH	Dioxane	41
17	$Pd(OAc)_2$	$P(Cy)_3$	PivONa·H_2O	PivOH	CH_3CN[c]	39
18	$Pd(OAc)_2$	$P(Cy)_3$	PivONa·H_2O	PivOH	DMSO	68
19	$Pd(OAc)_2$	$P(Cy)_3$	PivONa·H_2O	PivOH, TBAB(10%)[d]	DMSO	70
20	$Pd(OAc)_2$	$P(Cy)_3$	PivONa·H_2O	PivOH, TBAB[e]	DMSO	68
21	$Pd(OAc)_2$	$P(Cy)_3$	PivONa·H_2O	PivOH, TBAI[f]	DMSO	40

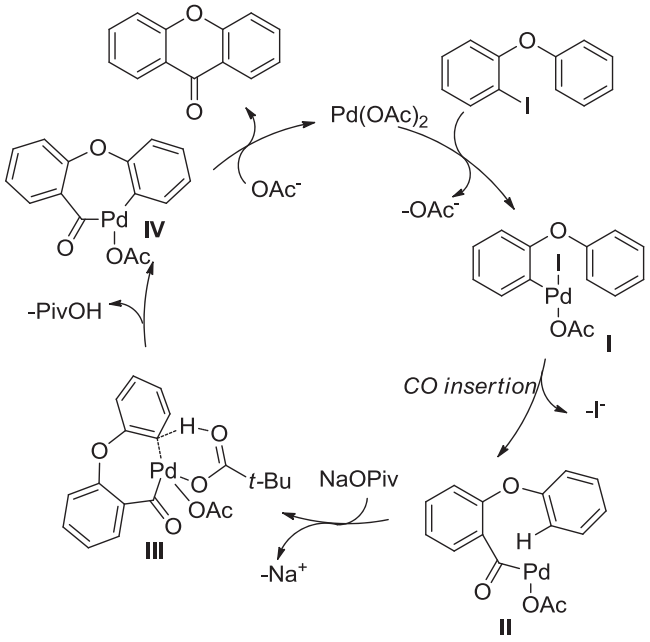
[a] All reactions were carried out under 5 mol% catalyst loading, 20 mol% ligand loading, 3 equiv of base, 2 equiv of additive at 90°C, and at the atmosphere of 0.4 MPa CO if not noted otherwise.
[b] Isolated yields.
[c] At 80°C.
[d] 10 mol% of tetrabutylammonium bromide.
[e] 50 mol% of tetrabutylammonium bromide.
[f] 10 mol% of tetrabutylammonium bromide iodide.

Table 2. Expansion of palladium-catalyzed reaction to form xanthones

Entry	Reactant	Product	Yield (%)
1	R^1=R^2=H, **1a**	R^1=R^2=H, **2a**	70
2	R^1=H, R^2=Me, **1b**	R^1=H, R^2=Me, **2b**	67
3	R^1=H, R^2=OMe, **1c**	R^1=H, R^2=OMe, **2c**	70
4	R^1=H, R^2=*t*-Bu, **1d**	R^1=H, R^2=*t*-Bu, **2d**	65
5	R^1=Me, R^2=H, **1e**	R^1=Me, R^2=H, **2b**	69
6	R^1=Me, R^2=OMe, **1f**	R^1=Me, R^2=OMe, **2f**	70
7	R^1=Me, R^2=*t*-Bu, **1g**	R^1=Me, R^2=*t*-Bu, **2g**	71
8	R^1=Me, R^2=Cl, **1h**	R^1=Me, R^2=Cl, **1h**	35

neutral (Table 2, entries 1–3, 5) or electron-rich (Table 2, entry 4) entities were good substrates for this reaction, providing the desired xanthone in good yields. But if the R^2 was electron-deficient (Table 2, entry 6), the yield was not satisfactory. All the products obtained in the reactions listed in Table 2 were easily characterized on the basis of their physical and spectral data and also by comparison with authentic samples.

As to the cyclization mechanism, it may be assumed that the cyclization reaction proceeds through the initial oxidative addition leading to the intermediate I (Scheme 2). Subsequently, chelation of CO and migration of intermediate II take place. Then Pd promotes activation of an *ortho* aromatic C–H with the assistance of $PivO^-$, leading to the intermediate IV. Reductive elimination from IV finally affords the xanthone, with the regeneration of Pd for the next catalytic cycle.



Scheme 2. Proposed mechanism of the palladium-catalyzed reaction to form xanthones.

In conclusion, we have developed a Pd-catalyzed intramolecular carbonylation/C–H activation of 2-iodo diaryl ether for the synthesis of substituted xanthones. Obviously, this method has several unique merits, such as the stability of the substrates, cost effectiveness, and acceptable yields. Thus, we believe that this methodology will not only be a practical alternative to existing procedures for the synthesis of bioactive xanthones but also extend the application of palladium-catalyzed heterocycles formation.

EXPERIMENTAL

Unless otherwise stated, all the solvents and reagents were purchased from commercial sources and used directly. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at room temperature on a Bruker NMR spectrometer (DRX 500) if not noted otherwise. The chemical shifts scale is based on internal TMS, and the coupling constants (*J*) are reported in hertz (Hz). Standard flash chromatography was employed to purify the crude reaction mixture using 200–300 mesh silica gel (Tsingdao Ocean Company, Tsingdao, China) under a positive nitrogen pressure.

Typical synthetic procedure: An autoclave was charged with *ortho*-iodo diaryl ether (1 mmol), $Pd(OAc)_2$ (12 mg, 0.05 mmol), $P(Cy)_3$ (56 mg, 0.2 mmol), $PivONa{\cdot}H_2O$ (280 mg, 2 mmol), PivOH (10 mg, 0.1 mmol) and 3 mL DMSO. The atmosphere in the autoclave was exchanged by CO five times, and CO was charged at the pressure of 0.4 MPa. Then the autoclave was heated to 90°C and maintained at this temperature for 5 h. Then the reaction mixture was diluted by ethyl acetate (30 mL), and the organic layer was washed by saturated aqueous $NaHCO_3$ and brine and dried with anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the residue was purified through column chromatography to give different xanthones (Table 2).

9H-Xanthen-9-one (**2a**): mp 176–178°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.36 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.74 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 2H), 7.51 (dd, *J* = 8.4, 0.5 Hz, 2H), 7.48–7.34 (m, 2H).^{13}C NMR (100 MHz,

$CDCl_3$) δ = 177.2, 156.1, 134.7, 126.6, 124.2, 121.8, 117.9.

2-Methyl-9H-xanthen-9-one (**2b**): mp 122–124°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.35 (dd, J = 8.0, 1.5 Hz, 1H), 8.13 (dd, J = 1.4, 0.4 Hz, 1H), 7.72 (ddd, J = 8.7, 7.1, 1.7 Hz, 1H), 7.58–7.52 (m, 1H), 7.49 (dd, J = 8.5, 0.6 Hz, 1H), 7.42–7.36 (m, 2H), 2.48 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 177.2, 156.4, 154.6, 136.0, 135.0, 134.0, 127.0, 125.9, 124.0, 121.8, 121.6, 118.0, 117.8, 20.9.

2-Methoxy-9H-xanthen-9-one (**2c**): mp 131–133°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (dd, J = 8.0 Hz, 1.6 Hz, 1H), 7.75–7.71 (m, 2H), 7.50 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 9.2 Hz, 1H), 7.40–7.33 (m, 2H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.90, 156.14, 155.73, 150.74, 134.29, 126.86, 125.06, 123.28, 122.14, 121.27, 119.12, 117.91, 105.68, 55.95.

2-(tert-Butyl)-9H-xanthen-9-one (**2d**): mp 114–116°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.36 (dd, J = 8.0, 1.6 Hz, 1H), 8.33 (d, J = 2.5 Hz, 1H), 7.80 (dd, J = 8.8, 2.5 Hz, 1H), 7.72 (ddd, J = 8.6, 7.2, 1.7 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.45 (d, J = 8.8 Hz, 1H), 7.38 (td, 1H, J = 7.6, 0.8 Hz), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.54, 156.37, 154.59, 147.16, 134.20, 132.86, 126.79, 123.92, 122.45, 177.93, 177.61, 34.82, 31.23.

2-Methoxy-7-methyl-9H-xanthen-9-one (**2f**): mp 143–145°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ =8.16 (s, 1H), 7.74 (d, J = 2.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 9.1 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.35 (dd, J = 9.1, 2.5 Hz, 1H), 3.96 (s, 3H), 2.51 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ = 177.16, 155.87, 154.39, 151.05, 135.92, 133.50, 125.92, 124.81, 122.07, 120.88, 119.39, 117.74, 105.81, 55.94, 20.86.

2-(tert-Butyl)-7-methyl-9H-xanthen-9-one (**2g**): mp 175–177°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.37 (d, J = 2.4 Hz, 1H), 8.17 (s, 1H), 7.82 (dd, J = 8.8, 2.5 Hz, 1H), 7.56 (dd, J = 8.5, 1.9 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 2.51 (s, 3H), 1.45 (s, 9H).^{13}C NMR (125 MHz, $CDCl_3$) δ = 177.56, 154.44, 154.39, 146.87, 135.91, 133.48, 132.64, 126.07, 122.43, 121.49, 121.13, 117.71, 117.59, 34.78, 31.40, 20.87.

2-Chloro-7-methyl-9*H*-xanthen-9-one **2h**: mp 173–174°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.31 (d, J = 2.4 Hz, 1H), 8.13 (s, 1H), 7.67 (dd, J = 8.9, 2.6 Hz, 1H), 7.58 (dd, J = 8.5, 1.6 Hz, 1H), 7.47 (d, J = 8.9 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 2.51 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ = 176.18, 154.52, 154.32, 136.45, 134.73, 134.16, 129.51, 126.09, 126.04, 122.67, 121.11, 119.72, 117.81, 20.85.

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