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Palladium-Catalyzed Phthalazinone Synthesis Using Paraformaldehyde as Carbon Source

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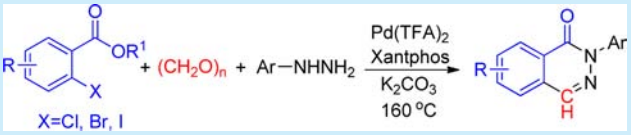
Supporting Information

ABSTRACT: A palladium-catalyzed one-pot synthesis of phthalazinones from 2-halomethyl benzoates, paraformaldehyde, and aryl hydrazines is described. Various substituted phthalazinones were selectively obtained in good yields using paraformaldehyde as the cheap carbon source (CH).



Nitrogen-containing heterocycles are frequently found in pharmaceutical drugs, agrochemicals, and functional materials.[1] Among the numerous nitrogen-containing heterocycles, phthalazinones represent a class of annulated six-membered *N*-heterocycles and exhibit many important biological activities. Phthalazinones show great potential in the treatment of a variety of disorders, such as diabetes,[2] hepatitis B,[3] asthma,[4] and arrhythmia.[5] For example, Astelin is an antihistamine and is used to treat nasal allergy symptoms (Figure 1, 2008

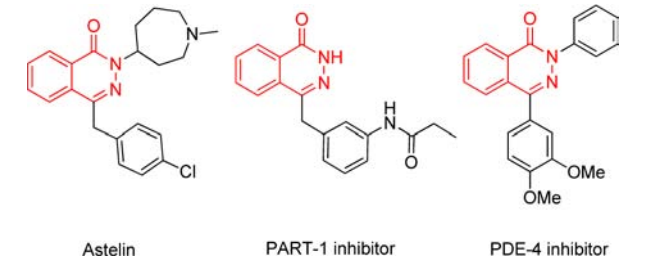
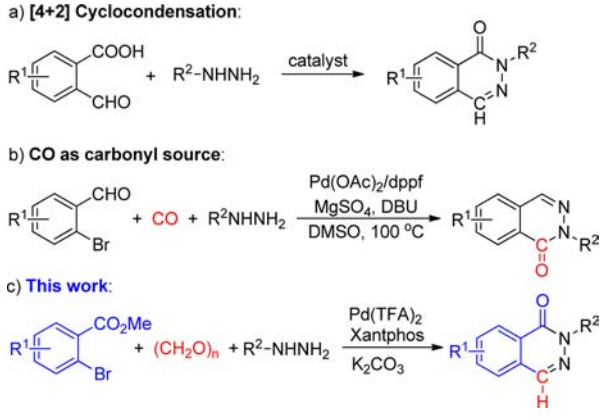


Figure 1. Selected drugs containing phthalazinone moiety.

sales $0.24 billion).[6] Moreover, phthalazinone derivatives are used as potent inhibitors of poly(-ADP-ribose)polymerase-1 (PARP-inhibitor).[7] The phthalazinone moiety can serve as the key building block for the preparation of the phosphodiesterase-4 (PDE-4) inhibitor.[8]

Because of their significant value in pharmaceuticals, the synthesis of phthalazinone and its derivatives has attracted considerable interest.[9] In general, two classes of reactions are developed to assemble the six-membered heterocycle moiety. One is based on the two-component cyclocondensation [4 + 2] of 2-carboxybenzaldehydes and hydrazines generally under transition-metal-free conditions (Scheme 1a).[10] In this process, the 2-carboxybenzaldehydes afford four carbons and hydrazines afford two nitrogen atoms. However, the substrate scope based on 2-carboxybenzaldehydes is very limited. The second-class reactions are mainly based on the [3 + 2 + 1] three-component

Scheme 1. Various Procedures for the Phthalazinone Synthesis



procedure. Carbon monoxide (CO) is frequently used as the carbonyl source to construct various carbonyl-containing compounds such as aldehydes, amides, and esters.[11] In 2012, Beller and co-workers reported a palladium-catalyzed procedure for the synthesis of phthalazinones from 2-bromobenzaldehydes, CO, and hydrazines (Scheme 1b).[12] In this transformation, a broad range of substituted phthalazinones were efficiently prepared using CO as the carbonyl source. To avoid the use of toxic CO gas, solid metal carbonyl complexes such as $Mo(CO)_6$ and $Co_2(CO)_8$ also could be used as the carbonyl source for this kind of transformation.[13] In a similar transformation, the isocyano group could serve as an efficient carbon source to afford 4-aminophthalazin-1(2*H*)-ones using palladium as the catalyst.[14]

Paraformaldehyde is an abundant, easy to handle, and inexpensive one carbon source. In recent years, various methods

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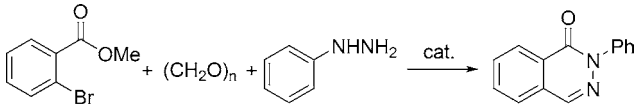
have been developed to introduce paraformaldehyde into more complex molecules as carbonyl or carbon source.[15] Very recently, Beller and co-workers disclosed a palladium-catalyzed carbonylation of aryl bromides to selectively afford aromatic aldehydes using paraformaldehyde as the CO source.[16] Although there are few other methods available to prepare phthalazinones, efficient methods for construction of them using readily available and nontoxic starting materials are highly desirable. Herein, we report a palladium-catalyzed three-component procedure [3 + 2+1] to prepare phthalazinones from 2-halomethyl benzoates, aryl hydrazines and paraformaldehyde (Scheme 1c). Various substituted phthalazinones were selectively obtained in good yields using paraformaldehyde as the carbon source (CH).

We began our investigation by subjecting methyl 2-bromobenzoate (**1a**), paraformaldehyde, and phenylhydrazine (**2a**) to the catalytic system of $Pd(OAc)_2$, 4,5-bis-(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), and K_2CO_3 in toluene at 150 °C for 24 h, which gave the target product **3a** in 71% GC yield (Table 1, entry 1). Several other phosphine ligands were investigated, and lower yields were observed (entries 2−6). Among the various base investigated, K_2CO_3 showed the best efficiency (entries 7−11). The screening of different palladium salts demonstrated that $Pd(TFA)_2$ was best for this reaction, and the corresponding product was obtained in 74% yield (entry 15). Other organic solvents, such as DMSO, anisole, PhCl, and NMP, did not give any improvement in the reaction yield (entries 16−19). Gratifyingly, the reaction yield could be increased to 85% when the reaction was performed at a slightly elevated temperature (entry 20). When the model reactions were performed without palladium, ligand or base, none or a trace amount of the product **3a** was observed (entries 21−23).

Having established the optimized reaction conditions (Table 1, entry 20), the scope and generality of the reaction were first explored by using a series of arylhydrazines. Under the optimized reactions, the model reaction of **1a** and **2a** in the presence of paraformaldehyde afforded **3a** in 81% isolated yield (Table 2, entry 1). Phenylhydrazines bearing an alkyl or alkoxyl group at the *para* position, such as $-CH_3$, $-CH_2CH_3$, $-C(CH_3)_3$, $-OCH_3$, and $-OCF_3$, coupled smoothly with **1a** to give the corresponding products in 78% (**3b**), 75% (**3c**), 61% (**3d**), 75% (**3e**), and 76% (**3f**) yields, respectively. Halogen substituents on the benzene ring, including F and Cl, were compatible for this kind of cyclization (entries 7 and 8). An electron-withdrawing functional group, such as 4-CN (**2i**), was well tolerated to give the desired product **3i** in 49% yield (entry 9). In addition, a slight steric effect was observed since the substrates bearing a *meta*- or *ortho*-substituent led to relatively lower yields compared to *para*-substituted variant (51%−70% yields, entries 10−13). When 3,5-dimethylphenylhydrazine (**2n**) was used, the desired product **3n** could be obtained in 68% yield (entry 14).

Subsequently, the reaction scope with respect to ester substrates is presented in Table 3. In addition to aryl bromides, aryl chloride **1b** and aryl iodide **1c** also smoothly reacted with **2a**

Table 1. Optimization of the Reaction Conditions[a]

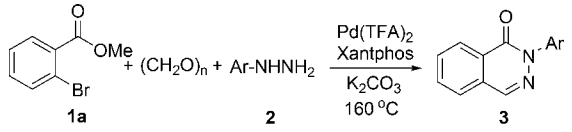


1a **2a** **3a**

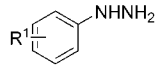
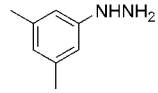
entry	catalyst	ligand	base	solvent	yield[b] (%)
1	$Pd(OAc)_2$	Xantphos	K_2CHO_3	toluene	71
2	$Pd(OAc)_2$	DPEphos	K_2CO_3	toluene	65
3	$Pd(OAc)_2$	X-phos	K_2CO_3	toluene	trace
4	$Pd(OAc)_2$	DPPF	K_2CO_3	toluene	40
5	$Pd(OAc)_2$	DPPE	K_2CO_3	toluene	trace
6	$Pd(OAc)_2$	PPh_3	K_2CO_3	toluene	trace
7	$Pd(OAc)_2$	Xantphos	K_3PO_4	toluene	11
8	$Pd(OAc)_2$	Xantphos	KOH	toluene	50
9	$Pd(OAc)_2$	Xantphos	$KHCO_3$	toluene	17
10	$Pd(OAc)_2$	Xantphos	Na_2CO_3	toluene	4
11	$Pd(OAc)_2$	Xantphos	*t*-BuOK	toluene	14
12	PdI_2	Xantphos	K_2CO_3	toluene	49
13	$Pd(OH)_2$	Xantphos	K_2CO_3	toluene	48
14	$Pd(COD)Cl_2$	Xantphos	K_2CO_3	toluene	41
15	$Pd(TFA)_2$	Xantphos	K_2CO_3	toluene	74
16	$Pd(TFA)_2$	Xantphos	K_2CO_3	DMSO	8
17	$Pd(TFA)_2$	Xantphos	K_2CO_3	anisole	16
18	$Pd(TFA)_2$	Xantphos	K_2CO_3	PhCl	65
19	$Pd(TFA)_2$	Xantphos	K_2CO_3	NMP	37
20[c]	**$Pd(TFA)_2$**	**Xantphos**	**K_2CO_3**	**toluene**	**85**
21[c]		Xantphos	K_2CO_3	toluene	7
22[c]	$Pd(TFA)_2$		K_2CO_3	toluene	2
23[c]	$Pd(TFA)_2$	Xantphos		toluene	trace

[a]Conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), paraformaldehyde (0.4 mmol), catalyst (5 mol %), ligand (10 mol %), base (0.24 mmol), solvent (0.6 mL), 24 h, 150 °C. [b]GC yield. [c]At 160 °C.

Table 2. Reactions of 1a with Various Hydrazines[a]



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

entry	2		product	yield[b] (%)
				
1	R^1 = H	**2a**	**3a**	81
2	R^1 = 4-Me	**2b**	**3b**	78
3	R^1 = 4-Et	**2c**	**3c**	75
4	R^1 = 4-*tert*-butyl	**2d**	**3d**	61
5	R^1 = 4-OMe	**2e**	**3e**	75
6	R^1 = 4-OCF_3	**2f**	**3f**	76
7	R^1 = 4-F	**2g**	**3g**	80
8	R^1 = 4-Cl	**2h**	**3h**	63
9	R^1 = 4-CN	**2i**	**3i**	49
10	R^1 = 2-Me	**2j**	**3j**	60
11	R^1= 2-Cl	**2k**	**3k**	60
12	R^1= 3-Me	**2l**	**3l**	70
13	R^1= 3-Cl	**2m**	**3m**	51
14		**2n**	**3n**	68

[a]Conditions: **1a** (0.2 mmol), **2** (0.4 mmol), paraformaldehyde (0.4 mmol), $Pd(TFA)_2$ (5 mol %), Xantphos (10 mol %), K_2CO_3 (0.24 mmol), toluene (0.6 mL), 24 h, 160 °C. [b]Isolated yields based on **1a**.

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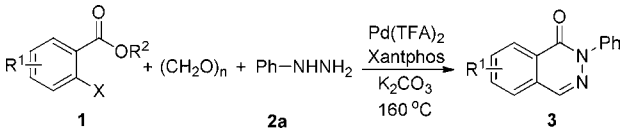
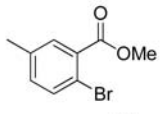
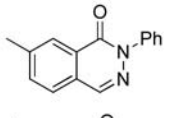
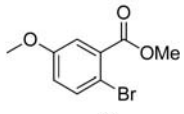
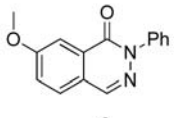
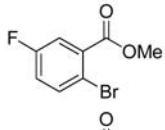
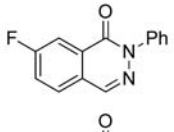
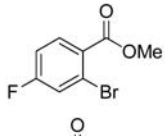
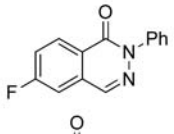
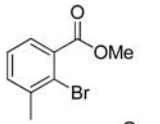
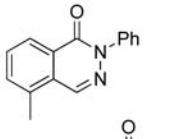
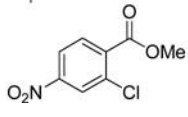
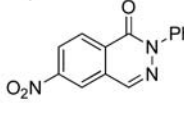
Table 3. Reactions of 2a with Various Esters[a]



1 2a 3

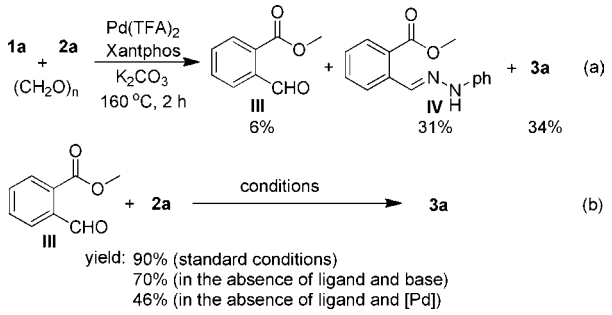
entry	ester		product		yield[b] (%)
1	X = Cl, R^2 = Me	1b	3a		78
2	X = I, R^2 = Me	1c	3a		82
3	X = Br, R^2 = Et	1d	3a		77
4	X = Br, R^2 = *iso*-propyl	1e	3a		61
5		1f		3o	78
6		1g		3p	81
7		1h		3q	83
8		1i		3r	78
9		1j		3s	88
10		1k		3t	25

[a]Conditions: **1** (0.2 mmol), **2a** (0.4 mmol), paraformaldehyde (0.4 mmol), $Pd(TFA)_2$ (5 mol %), Xantphos (10 mol %), K_2CO_3 (0.24 mmol), toluene (0.6 mL), 24 h, 160 °C. [b]Isolated yields based on **2a**.

and paraformaldehyde to provide the same product **3a** in 78% and 82% yields, respectively (entries 1 and 2). Moreover, ethyl 2-bromobenzoate (**1d**) and isopropyl 2-bromobenzoate (**1e**) coupled well with **2a** to provide **3a** in 77% and 61% yields, respectively (entries 3 and 4). The reaction was generally practicable with methyl 2-bromobenzoate bearing either electron-withdrawing or electron-donating substituents. Methyl (**1f**, **1j**), methoxy (**1g**), and fluoro (**1h**, **1i**) functionalities were all tolerated, affording the corresponding products in excellent yields (78%−88%, entries 5−9). Finally, methyl 2-chloro-4-nitrobenzoate (**1k**) was proved to be a less efficient coupling partner, which resulted in the desired product in only 25% yield (entry 10).

To define the reaction mechanism, several control reactions were investigated (Scheme 2). When the model reaction was performed within 2 h, methyl 2-formylbenzoate (**III**) and (*E*)-methyl 2-((2-phenylhydrazono)methyl)benzoate (**IV**) were detected by GC−-MS in 6% and 31% yields, respectively (Scheme 2a). Then, **III** was reasonably speculated to be a

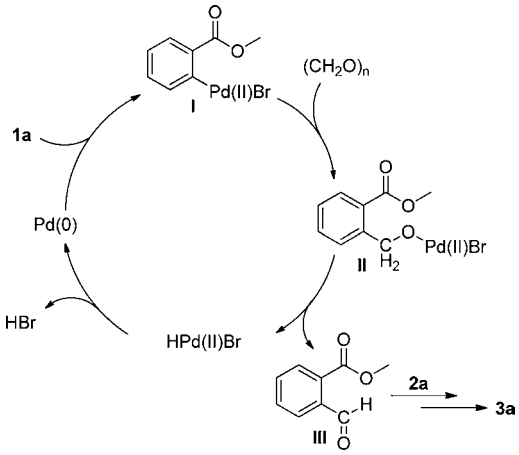
Scheme 2. Control Experiments



possible intermediate product, which as expected coupled well with **2a** under the standard conditions to give **3a** in 90% GC yield (Scheme 2b). Further investigation indicated that $Pd(TFA)_2$ and K_2CO_3 could independently promote this condensation reaction, affording **3a** in 70% and 46% yields, respectively (Scheme 2b). These results suggested that the Pd catalyst probably played a dual role, as a transition metal to initiate carbonylation and as a Lewis acid to facilitate condensation.

On the basis of the above observation and previous work by others,[12−14,17] a plausible mechanism for the three-component reaction is proposed in Scheme 3. The reaction starts with the in

Scheme 3. Possible Reaction Mechanism



situ generation of a Pd(0) species from the Pd(II) catalyst. Oxidative addition of the carbon−halogen bond of **1a** to the Pd(0) species affords intermediate **I**. Then, the migratory insertion of paraformaldehyde into the Ar−Pd bond gives intermediate **II**, with a subsequent *β*-hydrogen elimination to produce methyl 2-formylbenzoate **III** and palladium hydrobromide complex. Finally, intermolecular [4 + 2] cyclocondensation of **III** and hydrazine **2a** delivers the desired product **3a**. The catalytically active Pd(0) is regenerated through reductive elimination of the PdHBr complex. Alternatively, Beller[16] et al. proposed that paraformaldehyde would be first converted into CO in the reported carbonylation and alkoxycarbonylation of aryl bromides. Another possible mechanism might be also reasonable. Paraformaldehyde is first decomposed into CO and H_2; subsequently, a typical reductive carbonylation can occur to generate the aldehyde intermediate **III**. Finally, the desired product **3a** was generated from cyclocondensation of **III** and hydrazine **2a**.

In summary, we have discovered an efficient palladium-catalyzed three-component coupling reaction of 2-halomethyl-

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benzoates, paraformaldehyde, and hydrazines, providing facile access to pharmaceutically significant phthalazinones with a broad functional group tolerance. In this transformation, the use of paraformaldehyde as a one-carbon source features low toxicity, low cost, and easy operation. Thus, this protocol should inspire other cases of one-carbon design in organic synthesis. A detailed reaction mechanism and further application of this reaction are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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