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Convenient method for the synthesis of phthalazinones via carbonylation of 2-bromobenzaldehyde using $Co_2(CO)_8$ as a CO source

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ABSTRACT

A simple one-pot synthesis of phthalazinones by the condensation and intra-molecular carbonylative cyclization of 2-bromobenzaldehydes with hydrazines is reported. This method utilizes solid $Co_2(CO)_8$ as carbonyl source making it readily accessible in small-scale laboratory applications.

Keywords: Phthalazinone, palladium, carbonylation, aryl halides, $Co_2(CO)_8$, hydrazines

Phthalazinones are biologically active compounds and have widespread use in the treatment of asthma, diabetes, hepatitis B, arrhythmia, vascular hypertension and cardiovascular diseases.[1] Some of the phthalazinone derivatives are evaluated for the inhibitory activities to the five different forms of PDEs isolated from guinea pig cardiac ventricle (PDE1, 2 and 3) and lung (PDE4 and 5) *in vitro*.[2] Due to their diverse biological activities, significant effort has been devoted towards the development of mild and general synthetic methodologies for their preparation. More specifically, methods including cyclocondensation reaction, cyclo-additions, reduction by ultrathin Pt nanowires and biotechnological approaches[3] have been developed for its synthesis. Recently, Xiao-Feng Wu *et al.* has reported a direct methodology for the carbonylative synthesis of phthalazinones by using commercially available starting materials like 2-bromobenzaldehydes and hydrazines using $CO_{(g)}$ in autoclave.[4] But the reaction involves initial evacuation of the toxic $CO_{(g)}$ and high pressure of CO gas (10 bar). Although the methodology is useful on an industrial scale,

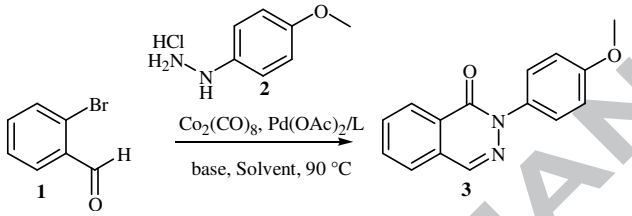
the toxicity and flammability of carbon monoxide make it inconvenient to use in a laboratory scale synthesis. Mats Larhed *et al.* have demonstrated that metal carbonyl can be used as the alternate CO source for the carbonylation reactions.[5] Using this strategy, phthalazinones have also been synthesised from *o*-bromoarylaldehydes and hydrazines using $Mo(CO)_6$ as an alternative to the toxic CO (g) in moderate yields. But the reaction needed high temperature (140°C) and higher equivalence of CO source (2.5 mmol of $Mo(CO)_6$ required for 1 mmol of aryl halide).[6]

Based on our previous work on the palladium-catalyzed carbonylation of aryl halides to esters and amides,[7] we became interested in the synthesis of valuable phthalazinone derivatives by using $Co_2(CO)_8$ as an effective alternate metal carbonyl source. Herein, we report a general carbonylation method using $Co_2(CO)_8$ as CO source for the synthesis of phthalazinones by reacting 2-bromobenzaldehyde and 2-bromobenzophenones with a variety of hydrazine hydrochlorides in classical heating as well microwave irradiation conditions.

Guided by the literature and our own results, we began our study of the carbonylation reaction between 2-bromobenzaldehyde **1** and 4-methoxyphenyl hydrazine hydrochloride **2** as the model reaction for optimizing the reaction conditions. In the presence of 5 mol % $Pd(OAc)_2$, 6 mol % of xantphos, $Co_2(CO)_8$ and TEA as base in 1,4-dioxane at 120 °C for 8 h, phthalazinone **3** was obtained in 10% isolated yield (Entry 1). Among the different bases studied (Entries 2-6), the isolated yield improved to 42% (Entry 4) when DBU was used as the base. Increase in the reaction temperature to 130 °C and 140 °C (Entries 8 and 7) decreased the yield of **3** indicating that temperature plays an important role in the reaction. The isolated yield of **3** increased at lower reaction temperatures (Entry 9 and 10). Further reduction of the reaction temperature to 80 °C gave lower yield of **3** (Entry 11). To improve the yield further, the reactions were performed in different solvents like THF, toluene,

DMSO, DMF, NMP (data not shown in the Table 1) and it was found that DMF afforded **3** in good yield (Entry 12). During the above optimization reactions, we observed the formation of the corresponding acid derivative (2-[(4-methoxy-phenyl)-hydrazonomethyl]-benzoic acid) in lower percentages. This may be formed by the attack of the water molecule present in the reaction mixture (from imine formation).

TABLE-1: Optimization of reaction conditions for the synthesis of 2-(4-methoxy-phenyl)-2H-phthalazin-1-one.



Entry	Ligand [a]	Base[b]	Solvents	Temp	Additive[c]	Yield[d]
1	Xantphos	TEA	Dioxane	120	-	10
2	Xantphos	DIPEA	Dioxane	120	-	7
3	Xantphos	DMAP	Dioxane	120	-	19
4	Xantphos	DBU	Dioxane	120	-	42
5	Xantphos	Pyridine	Dioxane	120	-	20
6	Xantphos	DABCO	Dioxane	120	-	14
7	Xantphos	DBU	Dioxane	140	-	21
8	Xantphos	DBU	Dioxane	130	-	28
9	Xantphos	DBU	Dioxane	110		45
10	Xantphos	DBU	Dioxane	90	-	57
11	Xantphos	DBU	Dioxane	80	-	49
12	Xantphos	DBU	DMF	90	-	66
13	Xantphos	DBU	DMF	90	$MgSO_4$	55
14	Xantphos	DBU	DMF	90	Na_2SO_4	41
15	Xantphos	DBU	DMF	90	M.sieves	74
16	BINAP	DBU	DMF	90	M.sieves	26
17	DPPB	DBU	DMF	90	M.sieves	60
18	TPP	DBU	DMF	90	M.sieves	44
19	dppf	DBU	DMF	90	M.sieves	81
20	dppf	DBU	DMF	90	M.sieves	85[e]
21	dppf	DBU	DMF	90	M.sieves	80[f]
22	dppf	DBU	DMF	90	M.sieves	49[g]

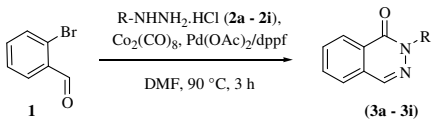
All the reactions were executed with 1 mmol of 2-bromobenzaldehyde **1**, 1.5 mmol of (4-methoxy-phenyl)-hydrazine hydrochloride **2**, 5 mol % of $Pd(OAc)_2$, 6 mol % of ligand, base and 0.3 mmol of $Co_2(CO)_8$ in DMF were heated in a seal tube for 8 h. M.sieves = Molecular sieves, [a] 6 mol % of ligands were used, [b] 2.5 eq of corresponding bases were used, [c] additives were used by w/w of the aryl halide used in the reaction, [d] the

isolated yields by column chromatography, [e] the reaction were performed at 90 °C for 3 h, [f] the reaction were performed in M/W condition at 90 °C for 30 min, [g] The reaction performed using $Mo(CO)_6$ as an CO source.

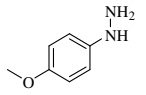
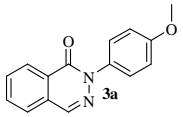
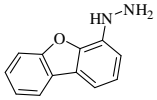
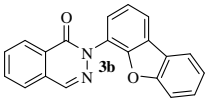
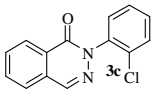
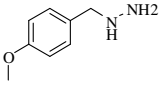
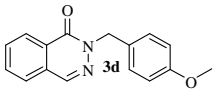
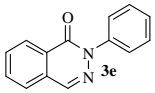
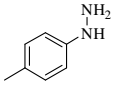
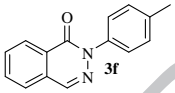
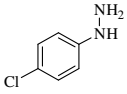
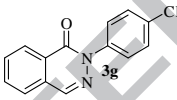
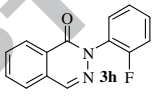
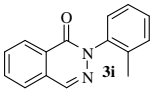
So, we evaluated the effect of dehydrating agents such as $MgSO_4$, Na_2SO_4 and molecular sieves in the reaction (Entry 13-15). To our delight, addition of molecular sieves significantly increased the desired phthalazinone yield as the unwanted acid derivative was not formed (Entry 15). Encouraged by the above results, we explored the scope of increasing the yield of the aminocarbonylation reaction by changing the ligand used. On the basis of our success using xantphos, we examined a number of other bidentate ligands as well. Advantageously, excellent yield was isolated when dppf was used as ligand (Entry 19). Moreover, the reaction was complete even at 3 h at 90 °C with an increase in the isolated yield (Entry 20). Using the optimized condition we then carried out the reaction under microwave irradiation. The conversion of reactants was complete after 30 min at 90 °C (entry 21) and **3** was isolated with 80% yield. With an aim to examine the effectiveness of CO source used in this study, the reaction was also carried out using $Mo(CO)_6$ as an alternate metal carbonyl source using the optimized reaction conditions and **3** was isolated in lower yield (Entry 22).

To determine the scope of this process, a set of hydrazine derivatives were examined as substrates by adopting the optimized condition (Table 1, Entry 20), with which this method demonstrated good generality and the results are summarized in Table 2. Also, some of the reactions were performed in microwave irradiation conditions and results are included in Table 2. This was exemplified by the high yielding transformation of both aliphatic and aromatic hydrazines to give various N-substituted phthalazinone derivatives **(3a- 3i)**.

Table-2 Synthesis of *N*-substituted phthalazinone derivatives



1 **(3a - 3i)**

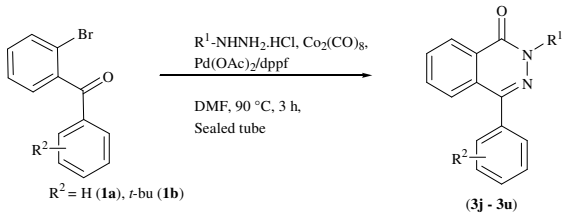
Entry	R-NHNH$_2$.HCL (**2a - 2i**)	Product (**3a-i**)	Yield (%)[a]
1		 **3a**	85/80[b]
2		 **3b**	64.6
3		 **3c**	74.2/ 70[b]
4		 **3d**	67.6
5		 **3e**	85.5/ 77[b]
6		 **3f**	84.7
7		 **3g**	66.4/71[b]
8		 **3h**	62.5
9		 **3i**	76.2

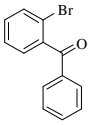
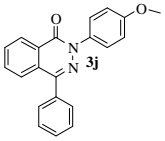
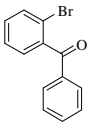
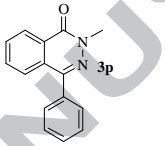
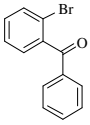
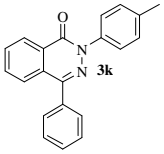
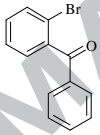
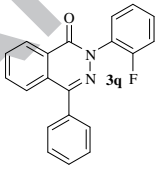
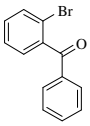
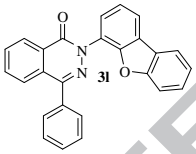
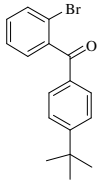
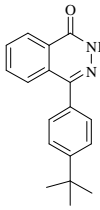
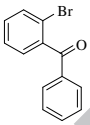
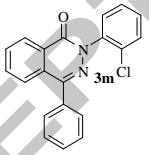
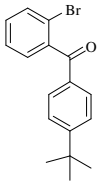
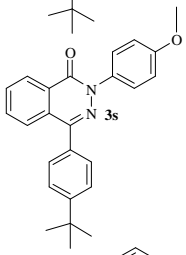
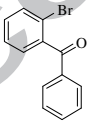
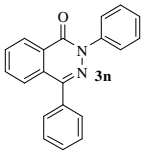
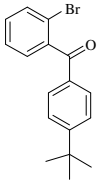
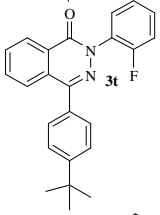
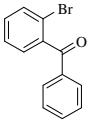
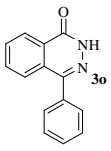
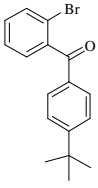
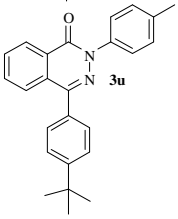
All the reactions were executed with 0.5 mmol of 2-bromobenzaldehyde, 0.6 mmol of hydrazine derivatives, 5 mol % of $Pd(OAc)_2$, 6 mol % of dppf, 1.25 mmol of DBU, 0.15 mmol of $Co_2(CO)_8$ were heated at 90 °C in a seal tube for 3 h. [a] the isolated yields by column chromatography. [b] The isolated yields from M/W reaction condition.

Next, to further explore the application of this method, we sought to apply the conditions to synthesize of 4-substituted phthalazinones by the carbonylation of the

corresponding 2-bromobenzophenones with different hydrazines and the results are outlined in the Table 3. Also, some of the reactions were performed in microwave irradiation

Table 3 Synthesis of 4-substituted phthalazinone derivatives



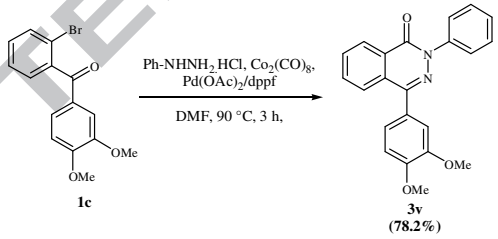
Entry	Reactant	Product (**3j-u**)	Yield(%)[a]	Entry	Reactant	Product (**3j-u**)	Yield(%)[a]
1		 **3j**	80.3/66[b]	7		 **3p**	72/ 64[b]
2		 **3k**	86.5	8		 **3q**	63.2
3		 **3l**	82.9	9		 **3r**	72
4		 **3m**	66.2/ 60[b]	10		 **3s**	83.3
5		 **3n**	87.2	11		 **3t**	64.5
6		 **3o**	76.5	12		 **3u**	84.2/ 74[b]

[a] the isolated yields by column chromatography. [b] The isolated yields from M/W reaction condition.

conditions and results are included in Table 3. Both aliphatic and aromatic hydrazines were found to be suitable substrates and produced the corresponding 4-substituted phthalazinones (**3j-3u**) in good to excellent yields. Despite the wide scope indicated by the results described in Table 3, the yield was slightly reduced in the case of ortho substituted phenyl hydrazines **(3m, 3q and 3t)**.

Having demonstrated a wide scope for the direct preparation of phthalazinones, we further validated our methodology by synthesizing 4-(3,4-dimethoxy-phenyl)-2-phenyl-2H-phthalazin-1-one **3v,** a selective PDE4 inhibitor,[2a] starting from (2-bromo-phenyl)-(3,4-dimethoxy-phenyl)-methanone **1c,** in good yield (78.2%) as shown in Scheme 1. To get more information on the synthesis of ketones **1a**, **1b** in Table 1 and **1c** in Scheme 1, refer supplementary data.

Scheme 1 Synthesis of 4-(3,4-dimethoxy-phenyl)-2-phenyl-2H-phthalazin-1-one (PDE4 inhibitor)



In conclusion, a general and efficient procedure[8] for the production of phthalazinone derivatives has been established. By starting from easily available *o*-halobenzaldehydes and benzophenones with various hydrazines in one pot using $Co_2(CO)_8$ as effective carbonyl source, the corresponding phthalazinones have been produced in moderate to good yields. The reaction is simple, efficient, tolerates a range of different functional groups and the desired products were obtained in good yields with short reaction times. More importantly, these methods utilise nearly stoichiometric amount of solid CO source (0.3 eq for 1 eq of aryl

halide) to get high yield at low temperature. It is especially suitable in medicinal chemistry to rapidly enlarge compound library for biological evaluation.

Supplementary data

Supplementary data (synthesis procedures, characterization of compounds) associated with this article can be found, in the online version, at http:

References and notes

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8. General procedure for the synthesis of phthalazinones: To a stirred mixture of 2-bromobenzaldehyde (0.5 mmol) and the corresponding hydrazine hydrochloride (0.6 mmol) in DMF taken in a 25 mL sealed tube, was added $Pd(OAc)_2$ (5 mol %), dppf (6 mol %), molecular sieves (W/W), DBU (1.25 mmol), and $Co_2(CO)_8$ (0.15 mmol). The reaction vessel was closed immediately and heated at 90 °C for 3h. The reaction mixture was cooled to room temperature, filtered through celite bed. The filtrate was diluted with water and extracted with ethyl acetate. The ethyl acetate layer was washed with water, brine solution, dried over $MgSO_4$, evaporated in vacuum and purified using column chromatography on silica gel (60-120 mesh) to afford the pure products.