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Graphical Abstract

Access to Phthalazinones via Palladium-Catalyzed Three-Component Cycloamino-carbonylation of *2*-Formylaryl Tosylates, Hydrazines and CO

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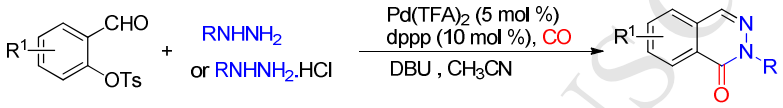
[b]*Technology Research Insititute of Shanghai Huayi (Group) Company, Shanghai 200241, People's Republic of China*



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Access to Phthalazinones via Palladium-Catalyzed Three-Component Cycloaminocarbonylation of *2*-Formylaryl Tosylates，Hydrazines and CO

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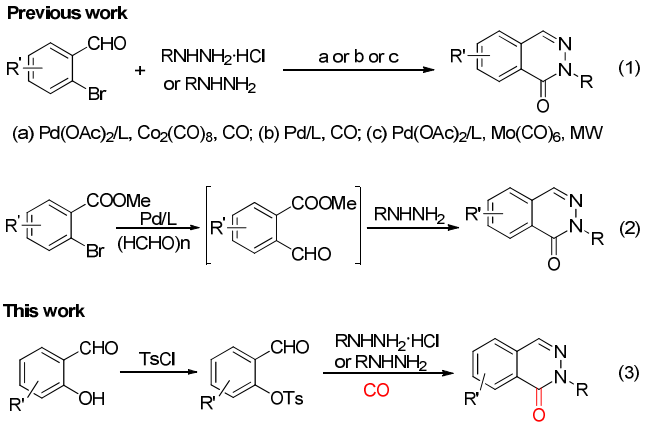
ABSTRACT

The palladium-catalyzed three-component cycloaminocarbonylation of *2*-formylaryl tosylates with hydrazines and carbon monoxide has been established, which provides an efficient method for synthesis of substituted phthalazinones. In addition, by applying this protocol as the key step, Hydralazine can easily be synthesized in 65% yield.

Introduction

Phthalazinones are important structural units of a vast array of naturally occurring and active molecules such as Azelastine,[1] PARP-1 inhibitor,[2] and PDE-4 inhibitor.[3] Many phthalazinone-based polymers[4] exhibit interesting properties for extensive applications. Furthermore, such type of heterocycles are also valuable intermediates in organic synthesis.[5] Therefore, development of new methods for synthesis of phthalazinones and new phthalazinone derivatives is of broad interest.

Since the first work by Heck and co-workers in 1974,[6] palladium-catalyzed aminocarbonylation has become a powerful tool for the construction of the amide moiety in organic synthesis.[7] In 2012, Beller and co-workers reported the synthesis of phthalazinone derivatives via Pd-catalyzed cycloaminocarbonylation of *o*-halobenzaldehydes and hydrazines using CO as a carbonyl source.[8a] More recently, the synthetic routes to phthalazinones using $Mo(CO)_6$[8b], and $Co_2(CO)_8$[8c] as the carbonyl source were also described (**Scheme 1**, eq. (1)). In 2015, Deng and co-workers developed the palladium-catalyzed carbonylative coupling reaction of *2*-halomethyl benzoates and aryl hydrazines using paraformaldehyde as the carbon source via methyl *2*-formylbenzoate intermediates (**Scheme l**, eq. (2)).[9]



Scheme 1. Comparison of metal-catalyzed cycloamino-carbonylations for synthesis of phthalazinones.

2-Formylaryl tosylates are lower toxic and cheaper than the corresponding *o*-halobenzaldehydes, replacement of aryl halides with aryl tosylates would make chemical processes more environmental tolerance by reducing the production of halide-containing wastes.[10] Inspired by our previous work on the palladium-catalyzed cycloaminocarbonylation of 2-aminomethyl and 2-alkylcarbamoylaryl tosylates with CO,[11] we become interested in the synthesis of functionalized phthalazinones from *2*-formylaryl tosylates that are readily prepared from

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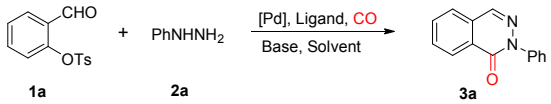
salicylaldehydes. Herein, we report our results on the development of a practical process for the multicomponent carbonylative synthesis of phthalazinones from *2*-formylaryl tosylates, hydrazines and CO as well as its application in synthesis of Hydralazine.

Results and discussion

We initiated our research on the model reaction of *2*-formylaryl tosylate (**1a**), phenylhydrazine (**2a**) and CO under different reaction conditions (Table 1). We firstly elected to employ $Pd(OAc)_2$ as the catalyst. Screening several different phosphine ligands such as 1,3-bis(diphenylphosphino)propane (dppp), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), 1,3-bis(diphenylphosphino)ferrocene (dppf), 1,3-bis(diphenylphosphino)ethane (dppe) and 1,3-bis(diphenylphosphino)butane (dppb) (**Table 1**, entries 1-5), it was found that dppp gave the best result with 43 % yield (Table 1, entry 1). Then, other Pd catalysts were examined (**Table 1**, entries 7-8). $Pd(TFA)_2$ showed a higher catalytic activity compared to $Pd(OAc)_2$. Among the bases tested, DBU gave the most promising results (**Table 1**, entries 9-11). Other solvents, such as DMSO and toluene, were less effective (**Table 1**, entries 12-13). No significant improvement on the yield appeared when the larger amount of $Pd(TFA)_2$ loading was used (**Table 1**, entry 14). Using smaller amount of dppp, $Pd(TFA)_2$ or anhydrous $MgSO_4$ led to a decrease of yields (**Table 1**, entries 15-19). Replacing anhydrous $MgSO_4$ with 4 Å molecular sieves resulted in a significant drop of yield (**Table 1**, entry 20).

Table 1. Catalyst, Ligand, Base, and Solvent Effects[a]



1a 2a 3a

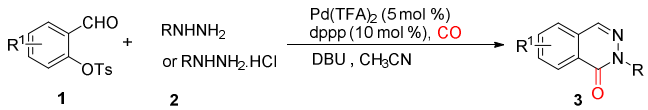
Entry	Catalyst (amount, mol%)	Ligand (amount, mol%)	Base (amount, eq)	Yield (%)[b]
1	$Pd(OAc)_2$ (5)	dppp (10)	K_2CO_3 (1.2)	43
2	$Pd(OAc)_2$ (5)	Xantphos (10)	K_2CO_3 (1.2)	trace
3	$Pd(OAc)_2$ (5)	dppf (10)	K_2CO_3 (1.2)	15
4	$Pd(OAc)_2$ (5)	dppe (10)	K_2CO_3 (1.2)	8
5	$Pd(OAc)_2$ (5)	dppb (10)	K_2CO_3 (1.2)	trace
6	$Pd(OAc)_2$ (5)	dppp (15)	K_2CO_3 (1.2)	46
7	$Pd(TFA)_2$ (5)	dppp (10)	K_2CO_3 (1.2)	65
8	$Pd(PhCN)_2Cl_2$ (5)	dppp (10)	K_2CO_3 (1.2)	46
9	$Pd(TFA)_2$ (5)	dppp (10)	Cs_2CO_3 (1.2)	trace
10	$Pd(TFA)_2$ (5)	dppp (10)	Na_2CO_3 (1.2)	58
11	$Pd(TFA)_2$ (5)	dppp (10)	DBU (1.2)	70
12[c]	$Pd(TFA)_2$ (5)	dppp (10)	DBU (1.2)	54
13[d]	$Pd(TFA)_2$ (5)	dppp (10)	DBU (1.2)	trace
14	$Pd(TFA)_2$ (10)	dppp (10)	DBU (1.2)	71
15	$Pd(TFA)_2$ (5)	dppp (5)	DBU (1.2)	60
16	$Pd(TFA)_2$ (3)	dppp (5)	DBU (1.2)	48
17		dppp (10)	DBU (1.2)	trace
18	$Pd(TFA)_2$ (5)		DBU (1.2)	trace
19[e]	$Pd(TFA)_2$ (5)	dppp (10)	DBU (1.2)	29
20[f]	$Pd(TFA)_2$ (5)	dppp (10)	DBU (1.2)	41

[a] Conditions: *2*-formylaryl tosylate (2 mmol), $PhNHNH_2$ (2 mmol), anhydrous $MgSO_4$ (2 mmol), CO (1.0 MPa), catalyst, ligand, base, CH_3CN, 140 °C, 21 h. [b] Isolated yield. [c] DMSO as solvent. [d] Toluene as solvent. [e] Without the use of anhydrous $MgSO_4$. [f] Anhydrous $MgSO_4$ was replaced by 4 Å molecular sieves (240 mg).

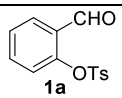
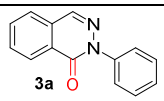
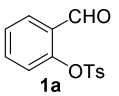
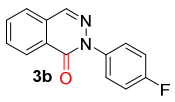
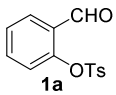
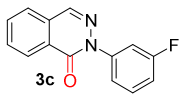
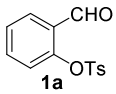
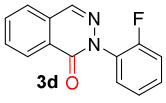
With the optimum reaction conditions in hand, we subsequently explored the scope of the reaction to various *2*-formylaryl tosylates and hydrazines. As shown in Table 2, hydrazines bearing various electron-rich or -deficient aryl substituents at the nitrogen atom were appropriate substrates for this methodology, and the corresponding substituted phthalazinones were obtained in satisfactory yields (**Table 2**, entries 1-13). The position of substituents on the benzene ring arylhydrazines slightly influenced the cyclization. *p*-Fluorophenylhydrazine gave a higher yield than its *o*- and *m*-analogues (**Table 2**, entries 2-4). It is well-known that C-Cl bonds are generally more reactive than C-O bonds in metal-mediated transformations of carbon-heteroatom bonds via oxidative/reductive mechanism.[12] Significantly, phthalazinones bearing chlorine substituent in aryl ring were also obtained in 62 % and 60 % yields (**Table 2**, entries 5-6).

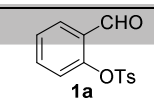
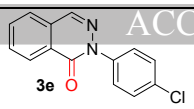
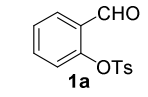
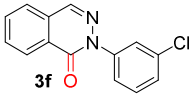
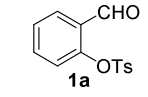
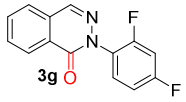
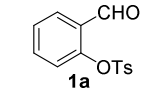
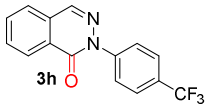
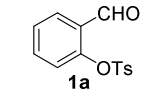
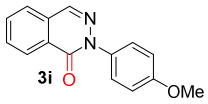
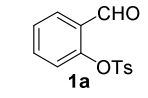
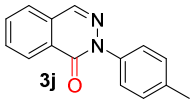
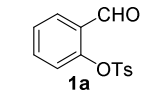
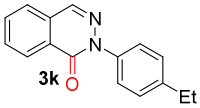
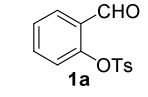
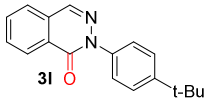
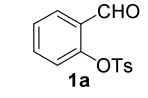
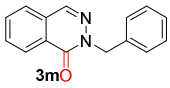
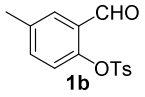
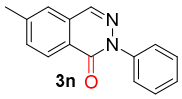
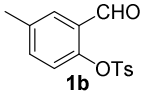
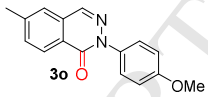
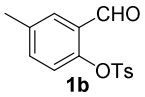
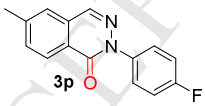
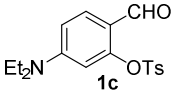
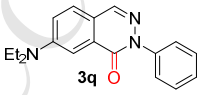
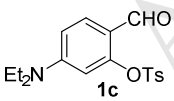
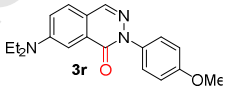
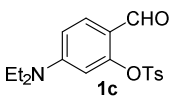
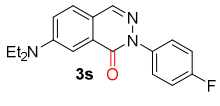
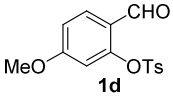
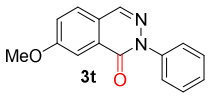
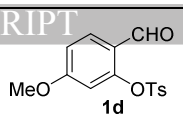
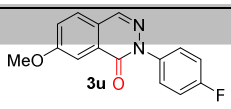
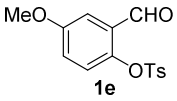
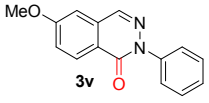
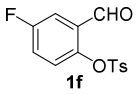
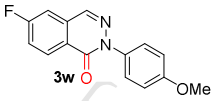
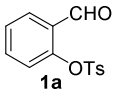
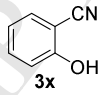
The effect of the substituents on the arene ring of *2*-formylaryl tosylates is also examined. In general, the presence of substituent such as *4*-methyl, *5*-NEt_2, *5*-MeO, *4*-MeO, or *4*-F on the benzene ring of *2*-formylaryl tosylates has a slightly negative impact on the catalytic reaction, leading to the formation of the desirable products in relatively lower yields (**Table 2**, entries 14-23). Surprisingly, replacement of hydrazines with hydroxylamine hydrochloride gave no desired carbonylative product; instead, *2*-hydroxybenzonitrile was obtained in 50% yield (**Table 2**, entry 24). Significantly, NH_2NHBoc reacted with *2*-formylphenyl tosylate and CO, giving the deprotected phthalazin-1(2H)-one (**3y**) in 68% yield (**Table 2**, entry 25).

Table 2. Cycloaminocarbonylation of 2-aminomethylaryl tosylates, hydrazines and CO [a]



1 2 3

Entry	Substrate	Product	Yield (%)[b]
1	 1a	 3a	70
2	 1a	 3b	75 [c]
3	 1a	 3c	60 [c]
4	 1a	 3d	65 [c]

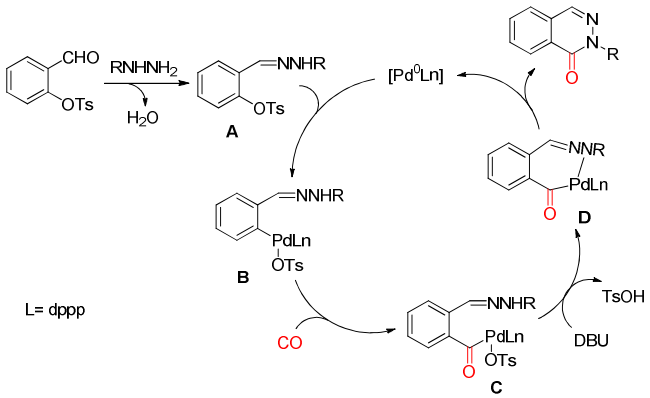
5			62 [c]
6			60 [c]
7			50 [c]
8			40 [c]
9			72 [c]
10			67 [c]
11			60 [c]
12			68 [c]
13			50
14			50
15			47 [c]
16			49 [c]
17			41
18			44 [c]
19			42 [c]
20			42
21			38 [c]
22			45
23			25 [c]
24			50 [d,e]
25			68 [d,f]

[a] Conditions: *2*-formylaryl tosylate (2 mmol), hydrazine derivative (2 mmol), $Pd(TFA)_2$ (5 mol%), dppp (10 mol%), DBU (1.2 eq), anhydrous $MgSO_4$ (2 mmol), CH_3CN (30 ml), CO (1.0 MPa), 140 °C, 21 h. [b] Isolated yield. [c] Hydrazine hydrochloride derivative (2 mmol), 150 °C, base (2.2 eq). [d] K_2CO_3 (2.2 eq). [e] $H_2NOH{\cdot}HCl$ (1 eq). [f] $H_2NNHBoc$ (1 eq).

Hydralazine (**4**) is an important antihypertensive agent.[13a] Recently, many new pharmacological properties of hydralazine derivatives, such as inhibiting malaria parasite and plasmodium falciparum[13b], recovering ischemic hepatitis[13c] and antituberculous[13d] are also discovered. Currently, hydralazine and their derivatives are primarily prepared from phthalazin-1(2H)-one (**3y**).[13,14] Several methods to synthesize phthalazin-1(2H)-one using *2*-formylbenzoic acid[15], isobenzofuran-1(3H)-one[14], phthalazine[16] or *2*-(*2*-bromoethyl)isoindoline-1,3-dione[17] as the raw materials have been reported in the literatures. Having successfully developed a new route to phthalazin-1(2H)-one, we finally turned our attention to the application of this method to synthesis of Hydralazine, which is easily functionalized. Treatment of **3y** with $POCl_3$ followed by reacting with hydrazine hydrate at refluxing temperature and sequential quenching with 15% hydrochloric acid allowed the isolation of hydralazine in 65% yield (**Scheme 2**).

Scheme 2. Synthesis of Hydralazine (antihypertensive agent).

Based on our results and other previously reported work on carbonylative cyclizations of *2*-bromobenzaldehyde or aryl sulfonate,[8a,12b,18] a possible mechanism for synthesis of **3** is proposed in **Scheme 3**. The condensation of aldehyde with hydrazine gives the imine intermediate **A**. Then, oxidative addition of the in situ generated Pd^0 species with **A** leads to the formation of the key aryl palladium complex **B**, which undergoes the CO insertion into a Pd-C bond to afford the aroyl complex **C**. The intramolecular substitution of OTs ligand by hydrazinate would give intermediate **D**. Finally, the reductive elimination forms the cycloaminocarbonylation product and regenerates the active Pd^0 species for the next catalytic cycle. Consistent with this suggestion, a $^{13}CO_{(g)}$ labeling reaction gave the desirable [^{13}C]-2-Phenylphthalazin-1(2H)-one (**3a***) in complete selectivity.



Scheme 3. Proposed mechanism for the formation of substituted phthalazinones.

In summary, we have developed an efficient and versatile method for preparation of phthalazinone derivatives via the Pd-catalyzed cycloaminocarbonylation of *2*-formylaryl tosylates, hydrazines and CO. The easy synthesis of *2*-formylaryl tosylates from cheap salicylaldehyde and their low toxicity makes them an attractive and practical alternative to commonly used *o*-halobenzaldehyde as counterparts in aminocarbonylation protocols. Further investigations on the synthetic applications of this method are underway in our lab.

Experimental Section

General procedure for the Pd-catalyzed cycloaminocarbonylation of *2*-formylaryl tosylate, hydrazine and CO.

2-Formylaryl tosylate (2 mmol), hydrazine (2 mmol), $Pd(TFA)_2$ (5 mol%), dppp (10 mol%), DBU (2.4 mmol), anhydrous $MgSO_4$ (2 mmol) and CH_3CN (30 ml) were charged in a 200 ml-autoclave. The autoclave was flushed using CO three times. The mixture was pressurized with CO to 1.0 MPa, and stirred at 140 °C for 21 h. Then, the mixture was cooled to room temperature and the excess CO was vented. Solvent was removed under reduced pressure and the crude residue was purified by column chromatography on silica gel with petroleum ether-ethyl acetate as the eluent to afford the desired product.

[^{13}C]-*2*-Phenylphthalazin-1(2H)-one (**3a***)

Brown solid; mp 100.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.48-8.55 (m, 1H), 8.30 (s, 1H), 7.78-7.89 (m, 2H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.64-7.67 (m, 2H), 7.47-7.52 (m, 2H), 7.37-7.41 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2 (^{13}C-enriched), 141.8, 138.5 (d, *J* = 6.1 Hz), 133.5, 131.9 (d, *J* = 3.4 Hz), 129.5, 128.8, 128.2, 127.8, 127.2, 126.1 (d, *J* = 2.4 Hz), 125.7. HRMS (ESI) Calcd for $C_{13}{}^{13}CH_{11}N_2O$ $[M+H]^+$: 224.0905; Found: 224.0898.

2-(*3*-Fluorophenyl)phthalazin-1(2H)-one (**3c**)

White solid; mp 104.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.49 (d, *J* = 7.6 Hz, 1H), 8.28 (s, 1H), 7.76-7.93 (m, 2H), 7.74 (d, *J* = 8.1 Hz, 1H), 7.41-7.53 (m, 3H), 7.08 (td, *J* = 8.3, 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4 (d, J_{CF} = 244 Hz), 159.0, 143.0 (d, J_{CF} = 9.9 Hz), 138.7, 133.6, 132.1, 129.7 (d, J_{CF} = 8.8 Hz), 129.3, 128.3, 127.2, 126.2, 121.1 (d, J_{CF} = 2.9 Hz), 114.5 (d, J_{CF} = 20.0 Hz), 113.2 (d, J_{CF} = 24.7 Hz). HRMS (ESI) Calcd for $C_{14}H_{10}FN_2O$ $[M+H]^+$: 241.0777; Found: 241.0775.

2-(*2,4*-Difluorophenyl)phthalazin-1(2H)-one (**3g**)

Yellow solid; mp 159.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.48 (d, *J* = 8.3 Hz, 1H), 8.28 (s, 1H), 7.80-7.90 (m, 2H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.46-7.52 (m, 1H), 6.97-7.04 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.5 (dd, J_{CF} = 250, 10.7 Hz), 158.9, 157.5 (dd, J_{CF} = 253, 12.5 Hz), 139.1, 133.8, 132.2, 129.7 (d, J_{CF} =10.0 Hz), 129.5, 127.8, 127.0, 126.3, 125.8 (d, J_{CF} = 3.6 Hz), 114.7 (dd, J_{CF} = 22.2, 3.5 Hz) 104.8 (dd, J_{CF} = 26.2, 23.7 Hz). HRMS (ESI) Calcd for $C_{14}H_9F_2N_2O$ $[M+H]^+$: 259.0683; Found: 259.0679.

6-Methyl-2-phenylphthalazin-1(2H)-one (**3n**)

Brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.39 (d, *J* = 8.1 Hz, 1H), 8.23 (s, 1H), 7.40-7.66 (m, 6H), 7.36-7.42 (m, 1H), 2.57 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.3, 144.5, 141.8, 138.5, 133.5, 129.6, 128.7, 127.7, 127.1, 126.1, 125.8, 125.7, 21.9. HRMS (ESI) Calcd for $C_{15}H_{13}N_2O$ $[M+H]^+$: 237.1028; Found: 237.1033.

2-(*4*-Methoxyphenyl)-6-methylphthalazin-1(2H)-one (**3o**)

Brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.37 (d, *J* = 8.2 Hz, 1H), 8.20 (s, 1H), 7.61 (dd, *J* = 8.2, 1.1Hz, 1H), 7.51-7.56 (m, 2H), 7.51 (s, 1H), 6.97-7.00 (m, 2H), 3.84 (s, 3H), 2.56 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.4, 158.8, 144.3, 138.3, 135.0, 133.4, 129.7, 127.1, 126.9, 126.2, 125.8, 113.9, 55.5, 21.8. HRMS (ESI) Calcd for $C_{16}H_{15}N_2O_2$ $[M+H]^+$: 267.1134; Found: 267.1146.

2-(*4*-Fluorophenyl)-6-methylphthalazin-1(2H)-one (**3p**)

White solid; mp 177.0 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.38 (d, *J* = 8.2 Hz, 1H), 8.21 (s, 1H), 7.62-7.66 (m, 3H), 7.53 (s, 1H), 7.14-7.20 (m, 2H), 2.57 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6 (d, J_{CF} = 245 Hz), 159.2, 144.6, 138.5, 137.9, 133.5, 129.6, 127.5 (d, J_{CF} =8.5 Hz), 127.2, 126.2, 125.9, 115.5 (d, J_{CF} = 23 Hz), 21.9. HRMS (ESI) Calcd for $C_{15}H_{12}FN_2O$ $[M+H]^+$: 255.0934; Found: 255.0947.

7-(Diethylamino)-2-phenylphthalazin-1(2H)-one (**3q**)

Brown solid; mp 148.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (s, 1H), 7.64 – 7.68 (m, 2H), 7.55-7.57 (m, 2H), 7.44-7.48 (m, 2H), 7.33-7.38 (m, 1H), 7.12 (dd, *J* = 8.9, 2.7 Hz, 1H), 3.51 (q, *J* = 7.1 Hz, 4H), 1.24 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.6, 150.4, 142.5, 138.5, 130.3, 128.6, 128.0, 127.3, 125.9, 118.6, 117.6, 105.6, 44.7, 12.4. HRMS (ESI) Calcd for $C_{18}H_{20}N_3O$ $[M+H]^+$: 294.1606; Found: 294.1628.

7-(Diethylamino)-2-(4-methoxyphenyl)phthalazin-1(2H)-one (**3r**)

Brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (s, 1H), 7.56 (d, *J* = 8.9 Hz, 4H), 7.11 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.96-7.00 (m, 2H), 3.85 (s, 3H), 3.51 (q, *J* = 7.1 Hz, 4H), 1.24 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.7, 158.5, 150.2, 138.4, 135.6, 130.2, 128.0, 127.0, 118.6, 117.5, 113.8, 105.4, 55.5, 44.7, 12.3. HRMS (ESI) Calcd for $C_{19}H_{22}N_3O_2$ $[M+H]^+$: 324.1712; Found: 324.1724.

7-(Diethylamino)-2-(4-fluorophenyl)phthalazin-1(2H)-one (**3s**)

Brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06 (s, 1H), 7.62-7.66 (m, 2H), 7.53-7.56 (m, 2H), 7.10-7.16 (m, 3H), 3.50 (q, *J* = 7.1 Hz, 4H), 1.23 (t, *J* = 7.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.4 (d, J_{CF} = 245 Hz), 159.6, 150.4, 138.6, 138.4 (d, J_{CF} = 2.8 Hz), 130.1, 128.0, 127.6 (d, J_{CF} = 8.5 Hz), 118.4, 117.6, 115.3 (d, J_{CF} = 23 Hz), 105.4, 44.6, 12.2. HRMS (ESI) Calcd for $C_{18}H_{19}FN_3O$ $[M+H]^+$: 312.1512; Found: 312.1519.

2-(*4*-Fluorophenyl)-7-methoxyphthalazin-1(2H)-one (**3u**)

Yellow solid; mp 167.9 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.21 (s, 1H), 7.86 (s, 1H), 7.62-7.69 (m, 3H), 7.40 (dd, *J* = 8.2,

2.0 Hz, 1H), 7.15-7.24 (m, 2H), 3.98 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 161.6 (d, J_{CF} = 245 Hz), 159.1, 138.2, 130.4, 128.1, 127.5 (d, J_{CF} =8.7 Hz), 123.7, 123.5, 122.9, 115.5 (d, J_{CF} = 22.7 Hz), 107.2, 56.0. HRMS (ESI) Calcd for $C_{15}H_{12}FN_2O_2$ $[M+H]^+$: 271.0883; Found: 271.0895.

6-Fluoro-2-(4-methoxyphenyl)phthalazin-1(2H)-one (**3w**)

Gray solid; mp 189.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.50-8.54 (m, 1H), 8.22 (s, 1H), 7.47-7.55 (m, 3H), 7.38 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.96-7.02 (m, 2H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.5 (d, J_{CF} = 254 Hz), 159.0, 158.6, 137.2, 134.6, 134.4, 131.6 (d, J_{CF} = 9.4 Hz), 130.7 (d, J_{CF} = 9.6 Hz), 126.9, 120.5 (d, J_{CF} = 23.3 Hz), 114.0, 111.2 (d, J_{CF} = 21.9 Hz), 55.5. HRMS (ESI) Calcd for $C_{15}H_{12}FN_2O_2$ $[M+H]^+$: 271.0883; Found: 271.0887.

Hydralazine hydrochloride (**4**)

Pale yellow solid; mp 277.0 °C (Lit.[14] 272-274 °C); ^{1}H NMR (D_2O, 400 MHz): δ 8.61 (s, 1H), 8.01-8.09 (m, 2H), 7.94-8.01 (m, 2H). ^{13}C NMR (D_2O, 100 MHz): 152.4, 144.9, 136.6, 134.7, 128.9, 127.6, 123.5, 118.6. HRMS (ESI) Calcd for $C_8H_9N_4$ $[M-Cl]^+$: 161.0827; Found: 161.0822.

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