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Regioselective Synthesis of Substituted 4-Alkylamino and 4-Arylaminophthalazin-1(2*H*)-ones

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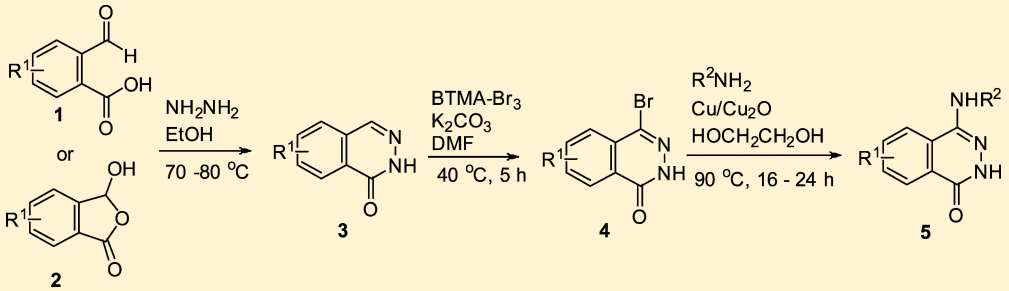
Supporting Information



ABSTRACT: An efficient regioselective synthesis of substituted 4-alkylamino and 4-arylaminophthalazin-1(1*H*)-ones **5** is described. This new method features the formation of substituted phthalazin-1(1*H*)-ones **3** by the reaction of 2-formylbenzoic acids **1** or 3-hydroxyisobenzofuran-1(3*H*)-ones **2** with hydrazine to generate phthalazin-1(2*H*)-ones **3**. Subsequent regioselective bromination of phthalazin-1(2*H*)-ones **3** with benzyltrimethylammonium tribromide (BTMA-Br_3) followed by mixed copper−copper oxide-catalyzed amination of 4-bromophthalazin-1(2*H*)-ones **4** with primary amines generates aminophthalazin-1(2*H*)-ones in good overall yields.

INTRODUCTION

Phthalazine derivatives are a class of attractive heterocycles found to be potentially useful to treat many diseases, for instance, Carbazeran for congestive heart failure,[1] Vatanalib as a tyrosine kinase inhibitor of angiogenesis,[2] Zopolrestat as a potent aldose reductase inhibitor for chronic diabetes,[3] p38 MAP kinase inhibitor for inflammatory disease,[4] and Aurora-A kinase inhibitors as antitumor agents[5] (Figure 1).

Despite interest in the pharmaceutical industry, the reported synthetic methods for the substituted and functionalized phthalazines are quite limited and not easily accessible due to lengthy synthesis with lack of regio control and chemoselectivity, particularly for 4-aminophthalazin-1(2*H*)-ones. The most straightforward previously published synthesis involves condensation of phthalic anhydride with substituted hydrazines, dehydroxyhalogenation, and Buchwald−Hartwig amination or condensation of phthalic anhydride with hydrazine, bis-dehydroxyhalogenation, monodehalogenhydrolysis, *N*-alkylation, and Buchwald−Hartwig amination[5] or monoamination of 1,4-dichlorophthalazine followed by hydrolysis.[6,7] These methods have two limitations: (1) limited commercial availability of substituted hydrazines and phthalic anhydride and (2) lack of regiochemistry control in condensation of substituted phthalic anhydrides with substituted hydrazines, monodehalogenhydrolysis, and monoamination of dichlorophthalazine derivatives. To overcome these limitations, Orru and co-workers recently reported the multicomponent synthesis of 4-aminophthalazin-1(2*H*)-ones via palladium-catalyzed isocyanide insertion, which allowed regioselective introduction of substituents; however, only tertiary-substituted isocyanides were used.[8]

We envisioned that phthalazin-1(2*H*)-ones **3**, which can be readily prepared by condensation of 2-formylbenzoic acids **1** or 3-hydroxyisobenzofuran-1(3*H*)-ones **2** with hydrazine,[9] would be selectively brominated at the 4-position to give 4-bromophthalazin-1(2H)-ones **4**. Subsequent metal-catalyzed C−N coupling of **4** with amines would give the desired 4-alkylamino and 4-arylaminophthalazin-1(2*H*)-ones **5** (R^2 = alkyl or aryl) (Scheme 1).

RESULTS AND DISCUSSION

2-Formylbenzoic acids **1a−c** are commercially available and can be easily converted to phthalazin-1(2*H*)-ones **3a−c** by heating with hydrazine in EtOH (Scheme 2). To demonstrate the convenient access to **3**, we prepared 3-hydroxy-4-bromoisobenzofuran-1(3*H*)-one **2** through lithiation of 3-bromobenzoic acid formylation and cyclization based on a literature

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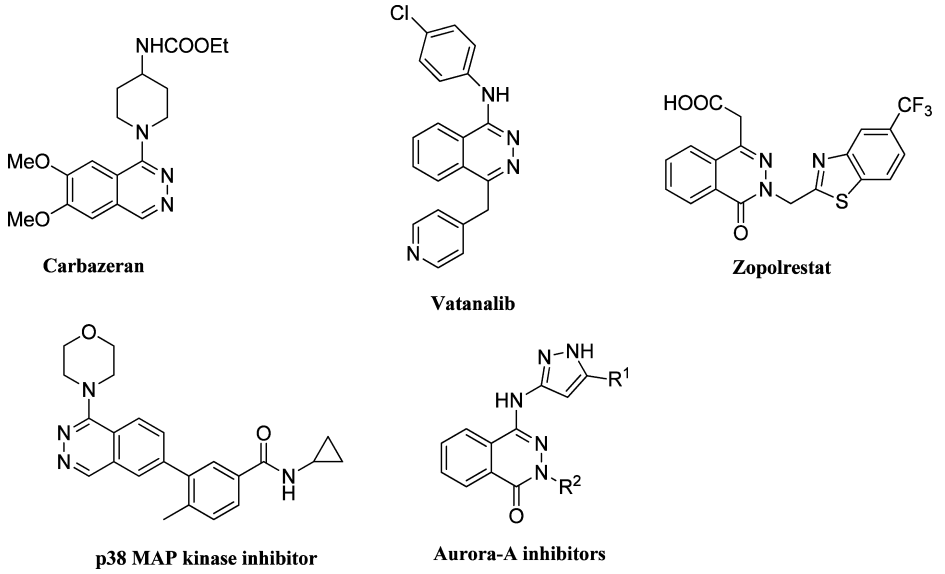
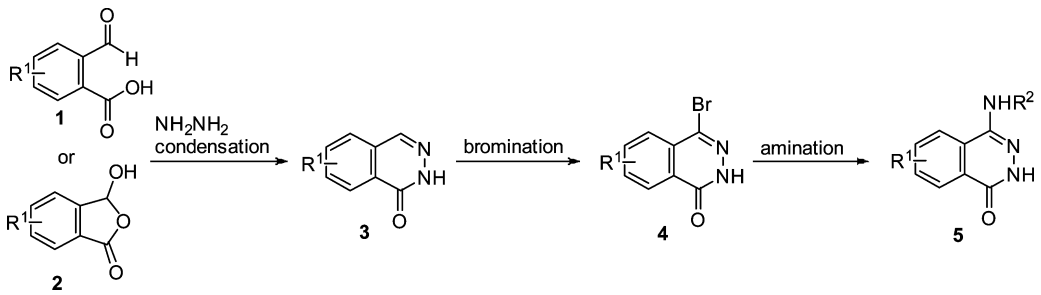


Figure 1. Some bioactive phthalazine derivatives.

Scheme 1. Regioselective Synthesis of Aminophthalazin-1(2*H*)-ones 5



procedure.[10] Following the same procedure as for 2-formylbenzoic acids **1**, **2** was readily condensed with hydrazine to give **3e** in good yield. **3e** was converted to **3f** via Suzuki reaction in 82% yield. Besides the above synthesis, the other attractive approach to 4-unsubstituted phthalazin-1(2*H*)-ones **3** was reported by Knochel and Crestey[11] via condensation of isoindolinone with hydrazine in glacial acetic acid.

We began our investigation on the selective 4-bromination of phthalazin-1(2*H*)-ones **3** using 5-phenylphthalazin-1(2*H*)-one **3f** as the substrate, NBS (4 equiv) as the brominating agent, and potassium carbonate (5 equiv) as the base in various solvents such methanol, THF, acetonitrile, NMP, and DMF at room temperature for 16 h. Only when DMF was used as the solvent was the desired product 4-bromo-5-phenylphthalazin-1(2*H*)-one **4e** observed in the reaction mixture by LCMS; however, bromination occurred at multiple positions, and the reaction did not go to completion. Nevertheless, encouraged by the result, we examined the reaction utilizing benzyltrimethylammonium tribromide (BTMA-Br_3) as the brominating agent. To our delight, BTMA-Br_3 had a cleaner reaction profile, and bromination at other positions was not detected by LCMS. After further optimization, the reaction of **3f** with BTMA-Br_3 (2 equiv) in the presence of K_2CO_3 (2 equiv) at 40 °C for 5 h gave **4e** in 80% isolated yield. Similarly, intermediates **3a**–**d** were converted to the corresponding 4-bromophthalazin-1(2*H*)-ones **4a**–**d** in satisfactory yields (Scheme 2).

With **4e** in hand, we explored the amination reaction under thermal coupling, palladium-, and copper-catalyzed conditions (Table 1). No reaction occurred by heating **4e** with **6** at 130 °C for 48 h (entry 1). However, when DMSO was used as the solvent and the reaction mixture was heated in a sealed tube at 130 °C for 16 h, desired product **5k** was observed in 30% yield by LCMS (entry 2). Prolonged heating did not improve the conversion. Under Buchwald conditions[12] using $Pd_2(dba)_3$ (5 mol %) as the catalyst and JohnPhos (10 mol %) as the ligand in the presence of *t*-BuONa (1.4 equiv), no product **5k** was observed (entry 3). The conditions using copper powder as the catalyst, without solvent (entry 4) or with DMSO as the solvent (entry 5), failed to give any product after heating at 100 °C for 1 h. When ethylene glycol, a superior solvent for copper-catalyzed amination,[13] was used (entry 6), desired product **5k** was observed in 23% conversion. In the presence of K_3PO_4 as a base, we were pleased to see **5k** as the major product, which was isolated in 44% yield (entry 7). The condition was further optimized by using the combination of Cu powder and Cu_2O as the catalysts, which were first reported by Wolf and co-workers[14] (entry 8). Thus, a mixture of **4e**, **6** (3 equiv), Cu powder (0.1 equiv), Cu_2O (0.05 equiv), and K_3PO_4 (2.2 equiv) in glycol was heated to 90 °C for 4 h to give **5k** in 72% isolated yield.

It must be noted that, under the same conditions, Cu_2O (0.15 equiv) alone promoted the reaction; however, a lower yield (40%) was obtained. The role of Cu/Cu_2O in the amination reaction was not clear. The use of K_3PO_4 was critical as K_2CO_3 and Cs_2CO_3 failed to faciliate the reaction under the same conditions. Although Kormendy and Ruff reported that

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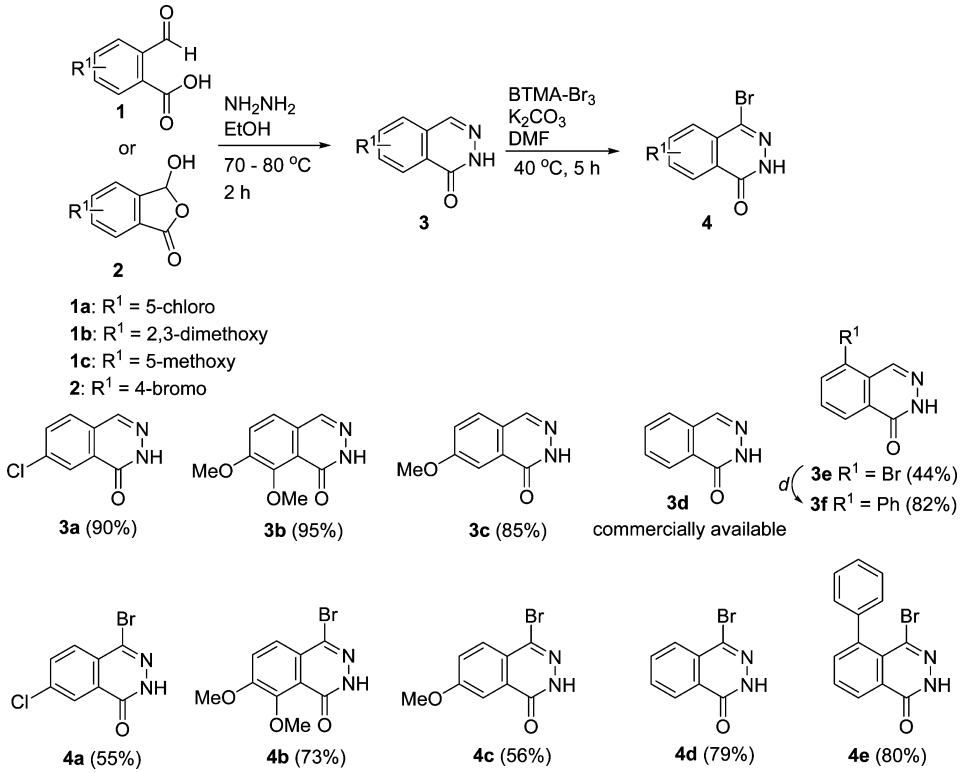
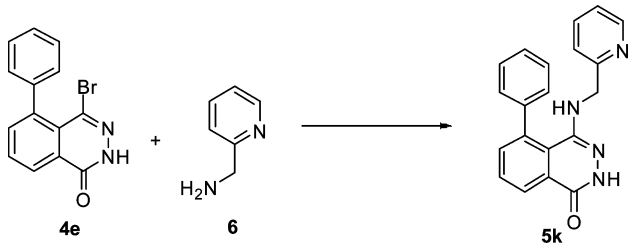
Scheme 2. Regioselective Synthesis of 4-Bromophthalazin-1(2*H*)-ones 4[a,b,c]



[a]A mixture of **1** or **2** and NH_2NH_2 (5 equiv) in EtOH was heated to 70−80 °C for 2 h. [b]A mixture of **3**, K_2CO_3 (2 equiv), and BTMA-Br_3 (2 equiv) in DMF was heated to 40 °C for 5 h. [c]Isolated yields (%) are in parentheses and were not optimized. [d]A mixture of **3e**, phenylboronic acid (1.2 equiv), sodium carbonate monohydrate (3 equiv), and $PdCl_2$(dppf) (5 mol %) in a mixture of dioxane and water (4:1) heated at 90 °C for 1.5 h.

Table 1. Amination Reaction Screening



entry	equiv of **6**	catalyst	base	solvent	temp (°C)	time (h)	yield of **5k** (%)[a]
1[b]	10	none	none	neat	130	48	0
2[b]	10	none	none	DMSO	130	16	30
3	1.2	$Pd_2(dba)_3$ (5 mol %) JohnPhos (10 mol %)	*t*-BuONa (1.4 equiv)	toluene/EtOH (2:1)	100	24	0
4	10	Cu powder (1 equiv)	none	neat	100	1	0
5	10	Cu powder (1 equiv)	none	DMSO	100	1	0
6	2	Cu powder (0.5 equiv)	none	glycol	75	2.5	23
7	3	Cu powder (1 equiv)	K_3PO_4 (2.2 equiv)	glycol	90	4	44[c]
8	3	Cu powder (0.1 equiv)/Cu_2O (0.05 equiv)	K_3PO_4 (2.2 equiv)	glycol	90	4	72[c]

[a]Based on LCMS unless otherwise noted. [b]The reaction was ran in a sealed tube. [c]Isolated yield.

glycol can have a catalytic effect to promote amination of chlorophthalazin-1(2*H*)-one with aniline to give 4-(phenylamino)phthalazin-1(2*H*)-one (**5h**) at high temperature,[15] in our hands, the reaction of the bromo analogue **4d** and aniline (5 equiv) in glycol did not occur below 190 °C, and only <30% conversion was observed by LCMS after heating at 190 °C for 20 h.

Having found optimized conditions for the amination of **4e** with amine **6**, we examined the reaction scope of **4a**−**e** with a range of amines. As shown in Scheme 3, aliphatic primary amines **5a**−**d**, **5g**, and **5i**−**l** generally had better conversions than the aromatic primary amines **5e**−**f** and **5h**. With the cyclic secondary amine, such as piperidine, the reaction only showed a trace amount of product **5m** based on LCMS. No product **5n** was observed in the case of 4-methoxy-*N*-methylaniline as the secondary amine. This could be due to the steric hindrance of secondary amines as the nucleophiles in the copper-catalyzed C−N coupling with aryl halides as also observed by Jiao and co-

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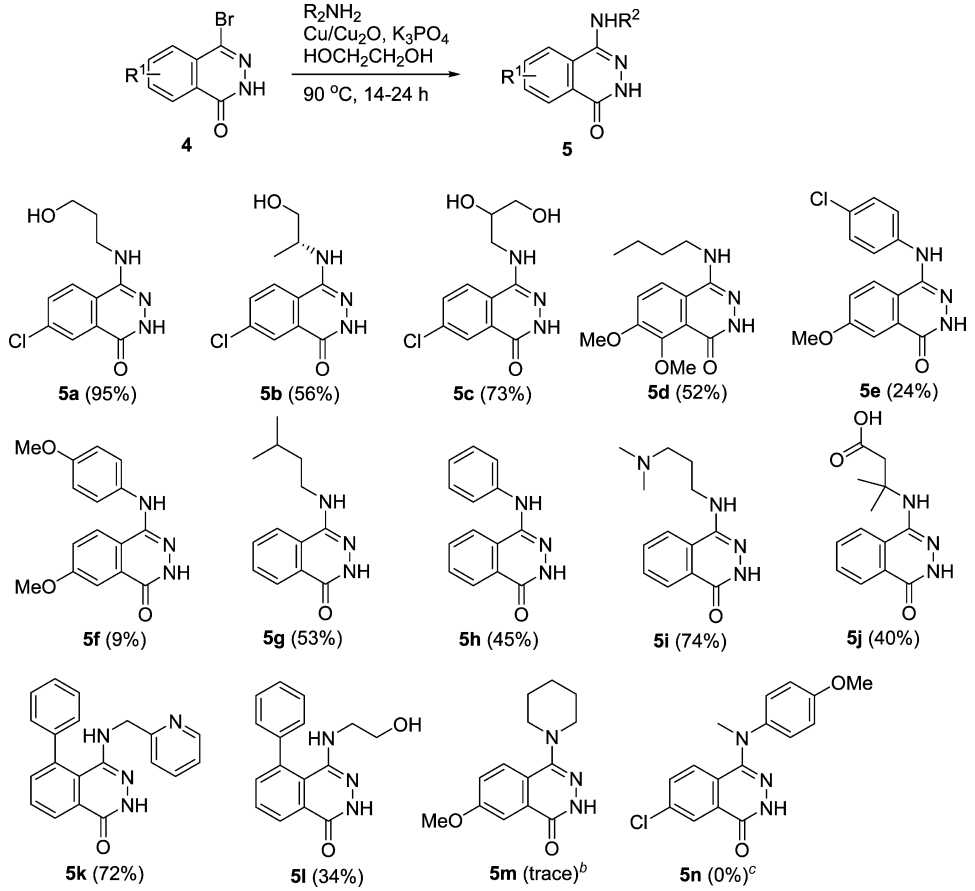
Scheme 3. C−N Coupling of 4-Bromophthalazin-1(2W)-ones 4 with Amines[a]



[a]A mixture of 4-bromo-phthalazin-1(2*H*)-one **4**, amine (3−10 equiv), potassium phosphate tribasic (3 equiv), copper powder (0.1 equiv), copper(I) oxide (0.05 equiv), and ethylene glycol was stirred at 90 °C under nitrogen for 4−20 h. Isolated yields (%) are in parentheses except for **5m−n** and were not optimized. [b]Detected by LCMS. [c]Not found by LCMS.

workers,[16] especially for 4-bromophthalazin-1(2*H*)-one derivatives **4a−4e** as studied by Kormendy and Ruff on the steric effect of the reaction of chlorophalazin-1(2*H*)-one with secondary amines at high temperature.[15] The secondary- and tertiary-substituted primary amines also worked well as illustrated with examples **5b** and **5j**.

In summary, we have developed a convenient regioselective synthesis of substituted 4-alkylamino and 4-arylaminophthalazin-1(2*H*)-ones **5** via the condensation of 2-formylbenzoic acids **1** or 3-hydroxyisobenzofuran-1(3*H*)-ones **2** with hydrazine followed by regioselective bromination of the phthalazin-1(2*H*)-ones **3** with benzyltrimethylammonium tribromide (BTMA-Br_3) and subsequent copper- and copper(I) oxide-catalyzed amination of 4-bromophthalazin-1-ols **4** with primary amines. Compounds **4** and **5** could be further functionalized to bioactive molecules as illustrated in Figure 1.

EXPERIMENTAL SECTION

All reagents were obtained commercially and used without further purification unless otherwise stated. All reactions were performed under a nitrogen atmosphere. All glassware was dried and purged with nitrogen before use. All reactions were monitored by LCMS using the following conditions: C18 column 1.7 μm 2.1 × 50 mm. Solvent: A = 100% water with 0.05% TFA; B = 100% acetonitrile with 0.05% TFA. Gradient: 2−98% B over 1.5 min. Flow: 0.8 mL/min, Wavelength: 220 nm. All ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as the solvent. HRMS were measured with electrospray ionization (ESI) and a Fourier transform mass spectrometer.

5-Bromophthalazin-1(2*H*)-one (3e). According to the literature procedure,[10] to a stirred solution of *n*-butyllithium (109 mL, 274 mmol) (2.5 M in hexanes) was added dropwise at −20 °C 2,2,6,6-tetramethylpiperidine (46.5 mL, 274 mmol) in anhydrous THF (250 mL) under N_2. After cooling to −50 °C, 3-bromobenzoic acid (25 g, 124 mmol) in THF (150 mL) was added dropwise, and then the reaction mixture was stirred for 1 h at −50 °C. *N*,*N*-Dimethylformamide (38.4 mL, 497 mmol) was added dropwise. The resulting reaction mixture was allowed to warm to rt. Water (200 mL) was added slowly at rt, and the aqueous layer was washed with ether (500 mL) and acidified with 1 N HCl. The acidic mixture was extracted with ether (1 L), and the organic layer was separated, dried with Na_2SO_4, filtered, and concentrated in vacuo to give the crude product 4-bromo-3-hydroxyisobenzofuran-1(3*H*)-one (**2**) (16.7 g, 72.9 mmol, 58.6% yield), which was used in the next step without further purification.

To a 1 L, three-necked round-bottom flask was added 4-bromo-3-hydroxyisobenzofuran-1(3*H*)-one (**2**) (16.7 g, 72.9 mmol) and ethanol (250 mL). To the resulting solution was added hydrazine (19.7 mL, 406 mmol) over 4 min. The reaction mixture was heated with stirring at 80 °C for 2 h. The reaction mixture was cooled to rt and then vacuum filtered. The filter cake was rinsed with 100 mL of ethanol and then dried by vacuum suction to give product 5-bromophthalazin-1(2*H*)-one (**3e**) (7.3 g, 44% yield) as white needles. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.94 (br s, 1H), 8.42 (s, 1H), 8.26−8.19 (m, 2H), 7.76 (t, J = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.0, 138.0, 136.5, 133.4, 130.0, 129.0, 126.0, 120.5.

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HRMS (ESI-FTMS): m/z calcd for $C_8H_6BrN_2O$ $[M + H]^+$, 224.9658; found, 224.9655.

5-Phenylphthalazin-1(2*H*)-one (3f). To a N_2 flushed round-bottom flask were added 5-bromophthalazin-1(2*H*)-one (**3e**) (8.3 g, 36.9 mmol), phenylboronic acid (5.40 g, 44.3 mmol), sodium carbonate monohydrate (13.72 g, 111 mmol), dioxane (400 mL), and water (100 mL). The suspension was bubbled with N_2 for 5 min. $PdCl_2$(dppf) (1.35 g, 1.84 mmol) was added. It was then heated at 90 °C under nitrogen for 1.5 h. After it was cooled to rt, the dark reaction mixture was concentrated to yield a gray semisolid. This semisolid was partitioned between water (500 mL) and DCM (500 mL). The organic layer was separated, and the aqueous layer was extracted with DCM (250 mL). The combined DCM layers were washed with brine (500 mL), dried with Na_2SO_4, and concentrated to give the crude product, which was purified by column chromatography using EtOAc and hexane as the eluents to give pure 5-phenylphthalazin-1(2*H*)-one (**3f**) (6.72 g, 82% yield) as a white solid. Mp: 203−205 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.77 (s, 1H), 8.29 (dq, J = 7.8, 0.7 Hz, 1H), 8.08−8.05 (m, 1H), 7.94−7.82 (m, 2H), 7.59−7.48 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.9, 140.1, 137.8, 136.1, 134.9, 131.9, 130.3, 129.2, 128.9, 128.7, 127.6, 125.4. HRMS (ESI-FTMS): m/z calcd for $C_{14}H_{11}N_2O$ $[M + H]^+$, 223.0866; found, 223.0862.

General Procedure for the Synthesis of 3. To a three necked round-bottom flask was added 2-formylbenzoic acid **2** (1 equiv) and ethanol (15 mL/g). To the resulting solution was added hydrazine (5 equiv) over several mins. The reaction mixture was heated with stirring at 70−80 °C for 2 h. The reaction mixture was cooled to rt and then vacuum filtered. The filter cake was rinsed with ethanol and then dried by vacuum suction to give the product phthalazin-1(2*H*)-one **3**.

7-Chlorophthalazin-1(2*H*)-one (3a). 5-Chloro-2-formylbenzoic acid (**1a**, 2.5g) gave 2.09 g of product **3a** as a white solid in 90% yield. Mp: 246−247 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.81 (br s, 1H), 8.40 (d, J = 0.4 Hz, 1H), 8.16 (s, 1H), 7.99 (d, J = 1.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.0, 138.1, 137.0, 134.4, 129.7, 129.5, 129.0, 125.1. HRMS (ESI): m/z calcd for $C_8H_6ClN_2O$ $[M + H]^+$, 181.0163; found, 181.0160.

7,8-Dimethoxyphthalazin-1(2*H*)-one (3b). 6-Formyl-2,3-dimethoxybenzoic acid (**1b**, 4.7 g) gave 4.4 g of product **3b** as a white solid in 95% yield. Mp: 165−167 °C (lit.[17] mp 162−164 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.17 (s, 1H), 8.15 (s, 1H), 7.70−7.65 (m, 2H), 3.93 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.4, 155.3, 147.6, 138.2, 125.3, 124.1, 122.2, 119.5, 61.7, 56.8. HRMS (ESI-FTMS): m/z calcd for $C_{10}H_{11}N_2O_3$ $[M + H]^+$, 207.0764; found, 207.0761.

7-Methoxyphthalazin-1(2*H*)-one (3c). 2-Formyl-5-methoxybenzoic acid (**1c**, 1.0 g) gave 1.24 g of product **3c** as an off white solid in 85% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.57 (br s, 1H), 8.29 (s, 1H), 7.89 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 2.7 Hz, 1H), 7.51 (dd, J = 8.7, 2.7 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.2, 160.0, 138.3, 130.0, 129.4, 124.5, 123.4, 106.5, 56.3. HRMS (ESI-FTMS): m/z calcd for $C_9H_9N_2O_2$ $[M + H]^+$, 177.0659; found, 177.0658.

General Procedure for the Synthesis of 4. To a solution of phthalazin-1(2*H*)-one **3** (1 equiv) in DMF (10 mL/g) was added potassium carbonate (2 equiv). After the mixture was stirred for 5 min, benzyl trimethylammonium tribromide (BTMA-Br_3) (2 equiv) was added. The reaction mixture was stirred at 40 °C for 5 h. After cooling to rt, the mixture was vacuum filtered through a Celite pad. To the filtrate were added water and DCM. The organic layer was washed with water three times and brine once, dried over Na_2SO_4, and concentrated. The residue was purified by trituration with an appropriate solvent or column chromatography.

4-Bromo-7-chlorophthalazin-1(2*H*)-one (4a). 7-Chlorophthalazin-1(2*H*)-one (**3a**, 0.63 g) gave 0.498 g of product **4a** as an off white solid in 55% yield after purification by column chromatography using 0−50% EtOAc in hexane as the eluent. Mp: 221−223 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.08 (s, 1H), 8.23−8.19 (m, 1H), 8.08 (dd, J = 8.7, 2.2 Hz, 1H), 7.97−7.93 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.5, 138.3, 135.2, 130.5, 130.0, 129.1, 129.1, 126.1. HRMS(ESI-FTMS): m/z calcd for $C_8H_5ClBrN_2O$ $[M + H]^+$, 258.9268; found, 258.9265.

4-Bromo-7,8-dimethoxyphthalazin-1(2*H*)-one (4b). 7,8-Dimethoxyphthalazin-1(2*H*)-one (**3b**, 1.5 g) gave 1.52 g of product **4b** as an off white solid in 73% yield after purification by trituration with a mixture MeOH and heptane (1:10). Mp: 250−253 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.46 (s, 1H), 7.79−7.69 (m, 2H), 3.97 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.8, 156.3, 148.3, 129.2, 125.2, 124.2, 122.5, 119.6, 61.8, 56.9. Anal. Calcd for $C_{10}H_9BrN_2O_3$: C, 42.13; H, 3.18; N, 9.83. Found: C, 42.16; H, 2.95; N, 9.69.

4-Bromo-7-methoxyphthalazin-1(2*H*)-one (4c). 7-Methoxyphthalazin-1(2*H*)-one (**3c**, 0.50 g) gave 0.403 g of product **4c** as a light yellow solid in 56% yield after purification by column chromatography using 0−100% EtOAc/hexanes as the eluent. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.85 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.65 (d, J = 2.7 Hz, 1H), 7.58 (dd, J = 8.9, 2.8 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.1, 159.4, 130.6, 130.3, 129.5, 124.0, 123.9, 107.9, 56.6. Anal. Calcd for $C_9H_7BrN_2O_2$: C, 42.38; H, 2.77; N, 10.98. Found: C, 42.53; H, 2.80; N, 11.02.

4-Bromophthalazin-1(2*H*)-one (4d).[5] Phthalazin-1(2*H*)-one (**3d**, 5.0 g) gave 6.05 g of the product as an off white solid in 79% yield after purification by trituration with a mixture of DCM and heptane (1:1). Mp: 277−279 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.93 (br s., 1H), 8.29−8.22 (m, 1H), 8.08−7.99 (m, 1H), 7.97−7.91 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.5, 135.1, 133.7, 130.3, 129.8, 128.7, 128.0, 126.9. HRMS (ESI-FTMS): m/z calcd for $C_8H_6BrN_2O$ $[M + H]^+$, 224.9658; found, 224.9659.

4-Bromo-5-phenylphthalazin-1(2*H*)-one (4e). Phthalazin-1(2*H*)-one (**3e**, 6.5 g) gave 7.0 g of product **4e** as a white solid in 80% yield after purification by trituration with a mixture ethyl acetate and heptane (2:5). Mp: 229−231 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.02 (br s, 1H), 8.38 (dd, J = 7.9, 1.4 Hz, 1H), 7.97−7.90 (m, 1H), 7.81 (dd, J = 7.5, 1.5 Hz, 1H), 7.49−7.42 (m, 3H), 7.39−7.31 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.3, 141.1, 140.0, 138.0, 132.1, 130.5, 129.9, 128.5, 128.3, 127.4, 126.7, 126.3. Anal. Calcd for $C_{14}H_9BrN_2O$: C, 55.84; H, 3.01; N, 9.30. Found: C, 55.77; H, 2.92; N, 9.27.

General Procedure for the Synthesis of 5. A mixture of 4-bromo-phthalazin-1(2*H*)-one derivative **4** (1 equiv, 300 mg, 0.996 mmol), an appropriate amine (3−10 equiv), ethylene glycol (10 mL/g), potassium phosphate tribasic (2.2 equiv), copper powder (0.1 equiv), and copper(I) oxide (0.05 equiv) was stirred at 90 °C for 4−20 h. EtOAc or DCM (10-fold volume of ethylene glycol) was added. The mixture was stirred at rt for 5 min and filtered through a Celite pad. The resulting filtrate was washed with water three times and brine once, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography using 0−20% of MeOH in DCM as the eluent to give product **5**.

7-Chloro-4-((3-hydroxypropyl)amino)phthalazin-1(2*H*)-one (5a). White solid, 193 mg, 95% yield. Mp: >198 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.72 (s, 1H), 8.23−8.11 (m, 2H), 7.97 (dd, J = 8.7, 2.3 Hz, 1H), 6.64 (t, J = 5.1 Hz, 1H), 4.47 (t, J = 5.1 Hz, 1H), 3.55−3.48 (m, 2H), 3.30−3.23 (m, 2H), 1.78 (q, J = 6.7 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.1, 145.0, 136.5, 133.4, 130.2, 126.2, 126.0, 124.2, 59.4, 39.1, 32.1. HRMS (ESI-FTMS): m/z calcd for $C_{11}H_{13}ClN_3O_2$ $[M + H]^+$, 254.0691; found, 254.0688.

(*R*)-7-Chloro-4-((1-hydroxypropan-2-yl)amino)phthalazin-1(2*H*)-one (5b). Off white solid, 165 mg, 56% yield. Mp: 244−246 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.71 (s, 1H), 8.25 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 2.3 Hz, 1H), 7.98 (dd, J = 8.7, 2.4 Hz, 1H), 6.25 (d, J = 7.3 Hz, 1H), 4.66 (t, J = 5.7 Hz, 1H), 3.89 (dq, J = 12.7, 6.5 Hz, 1H), 3.55 (dt, J = 10.6, 5.3 Hz, 1H), 3.39 (dt, J = 10.5, 6.1 Hz, 1H), 1.19 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.0, 144.4, 136.5, 133.3, 130.3, 126.4, 125.9, 124.3, 64.5, 48.7, 17.6. HRMS (ESI-FTMS): m/z calcd for $C_{11}H_{13}ClN_3O_2$ $[M + H]^+$, 254.0691; found, 254.0686.

3-(6-Chloro-4-hydroxyphthalazin-1-yl)amino)propane-1,2-diol (5c). White solid, 228 mg, 73% yield. Mp: >231 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.73 (s, 1H), 8.22 (d, J = 8.7 Hz,

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J. Org. Chem. XXXX, XXX, XXX−XXX

1H), 8.15 (d, J = 2.3 Hz, 1H), 7.98 (dd, J = 8.7, 2.3 Hz, 1H), 6.62 (t, J = 5.3 Hz, 1H), 4.79 (d, J = 4.3 Hz, 1H), 4.57 (t, J = 5.6 Hz, 1H), 3.80 (d, J = 2.9 Hz, 1H), 3.46−3.35 (m, 3H), 3.20−3.10 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 157.1, 145.1, 136.6, 133.4, 130.2, 126.3, 126.0, 124.2, 70.0, 64.7, 45.4. HRMS (ESI-FTMS): m/z calcd for $C_{11}H_{13}ClN_3O_3$ $[M + H]^+$, 270.0640; found, 270.0637.

4-(Butylamino)-7,8-dimethoxyphthalazin-1(2*H*)-one (5d). White solid, 152 mg, 52% yield. Mp: 195−197 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.13 (s, 1H), 7.85 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 9.0 Hz, 1H), 6.45−6.14 (m, 1H), 3.92 (s, 3H), 3.75 (s, 3H), 3.25−3.07 (m, 2H), 1.67−1.52 (m, 2H), 1.47−1.26 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 156.8, 155.0, 148.4, 144.9, 122.8, 120.2, 120.1, 118.2, 61.5, 56.7, 41.6, 31.1, 20.5, 14.4. HRMS (ESI-FTMS): m/z calcd for $C_{14}H_{20}N_3O_3$ $[M + H]^+$, 278.1499; found, 278.1496.

4-((4-Chlorophenyl)amino)-7-methoxyphthalazin-1(2*H*)-one (5e). Off white solid, 86 mg, 24% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.89 (s, 1H), 8.67 (s, 1H), 8.27 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 2.8 Hz, 1H), 7.66−7.60 (m, 2H), 7.55 (dd, J = 9.0, 2.8 Hz, 1H), 7.35−7.29 (m, 2H), 3.95 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.1, 158.5, 142.2, 141.2, 131.0, 128.7, 126.3, 124.6, 122.3, 120.8, 119.5, 107.9, 56.3. HRMS (ESI-FTMS): m/z calcd for $C_{15}H_{13}ClN_3O_2$ $[M + H]^+$, 302.0691; found, 302.0692.

7-Methoxy-4-((4-methoxyphenyl)amino)phthalazin-1(2*H*)-one (5f). Off white solid, 31 mg, 9% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.70 (s, 1H), 8.33 (s, 1H), 8.28 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 2.8 Hz, 1H), 7.53−7.47 (m, 3H), 6.90−6.86 (m, 2H), 3.95 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.9, 158.4, 154.6, 143.1, 135.0, 131.0, 126.2, 122.2, 122.1, 119.4, 114.2, 107.9, 56.2, 55.7. HRMS (ESI-FTMS): m/z calcd for $C_{16}H_{16}N_3O_3$ $[M + H]^+$, 298.1186; found, 298.1185.

4-(Isopentylamino)phthalazin-1(2*H*)-one (5g). Yellow solid, 162 mg, 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.18 (br s, 1H), 8.57−8.43 (m, 1H), 7.86−7.74 (m, 2H), 7.70−7.62 (m, 1H), 4.41 (br s, 1H), 3.48−3.30 (m, 2H), 1.83−1.71 (m, 1H), 1.67−1.53 (m, 2H), 1.00 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 145.4, 133.0, 131.1, 128.5, 127.6, 125.3, 121.2, 40.4, 38.3, 26.2, 22.6. HRMS (ESI-FTMS): m/z calcd for $C_{13}H_{18}N_3O$ $[M + H]^+$, 232.1444; found, 232.1444.

4-(Phenylamino)phthalazin-1(2*H*)-one (5h). Off white solid, 143 mg, 45% yield. Mp: 246−251 °C (lit.[15] mp 257−258 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.88 (s, 1H), 8.58 (s, 1H), 8.35 (d, J = 8.1 Hz, 1H), 8.29 (dd, J = 7.9, 1.0 Hz, 1H), 7.99 (td, J = 7.6, 1.5 Hz, 1H), 7.92−7.87 (m, 1H), 7.63−7.58 (m, 2H), 7.32−7.26 (m, 2H), 6.97−6.90 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.6, 142.5, 142.1, 133.5, 132.0, 129.3, 129.098, 128.9, 126.8, 126.0, 124.1, 121.5, 119.7, 119.6. HRMS (ESI-FTMS): m/z calcd for $C_{14}H_{12}N_3O$ $[M + H]^+$, 238.0975; found, 238.0971.

4-((3-(Dimethylamino)propyl)amino)phthalazin-1(2*H*)-one (5i). Colorless liquid, 242 mg, 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.32 (br s, 1H), 8.49−8.43 (m, 1H), 7.82−7.75 (m, 2H), 7.61−7.57 (m, 1H), 7.17 (br s, 1H), 3.48−3.43 (m, 2H), 2.59−2.54 (m, 2H), 2.37 (s, 6H), 1.89 (dt, J = 11.8, 6.0 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.6, 145.8, 133.7, 131.9, 129.1, 127.2, 126.0, 123.8, 63.7, 58.3, 46.1, 27.1. HRMS (ESI-FTMS): m/z calcd for $C_{13}H_{19}N_4O$ $[M + H]^+$, 247.1553; found, 247.1551.

3-((4-Hydroxyphthalazin-1-yl)amino)-3-methylbutanoic Acid (5j). Off white solid, 140 mg, 40% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.60 (s, 1H), 8.21 (dd, J = 7.8, 1.2 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H), 7.90−7.84 (m, 1H), 7.83−7.76 (m, 1H), 5.90 (br s, 1H), 2.86 (s, 2H), 1.51 (s, 6H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 158.0, 144.2, 133.2, 131.5, 128.8, 126.6, 126.2, 123.8, 52.6, 43.5, 27.5. HRMS (ESI-FTMS): m/z calcd for $C_{13}H_{16}N_3O_3$ $[M + H]^+$, 262.1186; found, 262.1184.

5-Phenyl-4-((pyridin-2-ylmethyl)amino)phthalazin-1(2*H*)-one (5k). Off white solid, 352 mg, 72% yield. Mp: 204−206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.66−8.53 (m, 1H), 8.27 (dt, J = 4.1, 0.7 Hz, 1H), 7.80−7.73 (m, 1H), 7.61 (dd, J = 7.5, 1.5 Hz, 1H), 7.56 (td, J = 7.6, 1.7 Hz, 1H), 7.50−7.42 (m, 5H), 7.13−7.03 (m, 2H), 5.36 (t, J = 4.1 Hz, 1H), 4.40 (d, J = 4.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.0, 156.9, 148.6, 145.4, 140.1, 139.0, 136.6, 136.2, 130.1, 129.5, 129.4, 128.8, 128.3, 127.2, 122.8, 121.7, 121.4, 47.3. Anal. Calcd for $C_{20}H_{16}N_4O$: C, 73.15; H, 4.91; N, 17.06. Found: C, 72.85; H, 4.88; N, 17.13.

4-((2-Hydroxyethyl)amino)-5-phenylphthalazin-1(2*H*)-one (5l). Yellow-white solid, 95 mg, 34% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.73 (s, 1H), 8.35 (dd, J = 7.9, 1.4 Hz, 1H), 7.89−7.77 (m, 1H), 7.70−7.60 (m, 1H), 7.55−7.48 (m, 3H), 7.46−7.38 (m, 2H), 4.30 (t, J = 5.0 Hz, 1H), 4.12 (t, J = 5.0 Hz, 1H), 3.17 (q, J = 5.5 Hz, 2H), 2.99 (q, J = 5.6 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.2, 144.8, 140.2, 139.0, 136.5, 130.8, 129.9, 129.5, 129.1, 129.0, 126.8, 122.7, 59.2, 44.6. HRMS (ESI-FTMS): m/z calcd for $C_{16}H_{16}N_3O_2$ $[M + H]^+$, 282.1237; found, 282.1239.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02652.

^{1}H and ^{13}C NMR spectra of compounds **3**−**5** (PDF)

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Notes

The authors declare no competing financial interest.

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