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Palladium-Catalyzed Annulation of Arynes by *o*-Halobenzamides: Synthesis of Phenanthridinones

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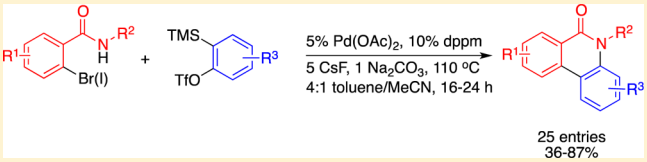
Supporting Information

ABSTRACT: The palladium-catalyzed annulation of arynes by substituted *o*-halobenzamides produces *N*-substituted phenanthridinones in good yields. This methodology provides this important heterocyclic ring system in a single step by simultaneous C−C and C−N bond formation, under relatively mild reaction conditions, and tolerates a variety of functional groups.



INTRODUCTION

Phenanthridinones are important subunits found in many compounds possessing interesting biological and pharmaceutical activities. They have been used as PARP inhibitor anticancer drugs[1] and as neurotrophin activity enhancers for the treatment of nerve diseases.[2] One of the traditional approaches for the synthesis of phenanthridinones is through reductive cyclization of the corresponding nitrocarbonylbiphenyls.[3] However, traditional preparations of the starting nitrocarbonylbiaryls by Ullmann coupling or the nitration of biaryls[4] require either harsh reaction conditions or exotic functionalized arenes, significantly limiting the broad application of this approach. Other common approaches to phenanthridinones include the Schmidt/Beckmann rearrangement of fluorenone derivatives that are not all that readily available[4g,5] and the photochemical rearrangement of 2-halobenzamides.[6] There are also reports of phenanthridinone synthesis involving aryne generation under harsh basic conditions and subsequent intramolecular cyclization.[7]

Transition-metal-catalyzed annulation reactions are tremendously valuable in organic synthesis.[8] Among such processes, palladium-mediated reactions are by far the most powerful in constructing carbocycles and heterocycles,[9] due to the high efficiency with which they construct C−C and C−X (X = O, N) bonds[10] and their high compatibility with functional groups. For example, some phenanthridinone derivatives have been synthesized by palladium-catalyzed intramolecular or intermolecular cyclization processes of aryl halides and amides[11] or by oxidative ortho arylation of benzanilides.[12]

Since a convenient approach to aryne generation by the fluoride-induced 1,2-elimination of *o*-(trimethylsilyl)aryl triflates was first reported,[13] arynes have attracted considerable attention.[14] The high electrophilicity of arynes has been used extensively in the construction of many heteroaromatic structures via annulation reactions.[15] To take further advantage of aryne chemistry, many metal-catalyzed coupling[16] and annulation reactions[17] of arynes have been explored. In our group, we have been especially interested in the palladium-catalyzed annulation of arynes.[18]

Herein, we report the palladium-catalyzed annulation of arynes by substituted *o*-halobenzamides to produce *N*-substituted phenanthridinones in good yields. In this reaction, C−C and C−N bonds are formed simultaneously to generate this important heterocyclic ring system.

RESULTS AND DISCUSSION

Optimization Studies. We attempted to optimize the reaction of *N*-ethyl-2-bromobenzamide (**1a**) and the benzyne precursor *o*-(trimethylsilyl)phenyl trifluoromethanesulfonate (**2a**) in 4/1 toluene/acetonitrile with CsF as the fluoride source (Table 1). In all cases, the cyclotrimerization side product **4a**[19] and the desired benzyne annulation product **3a** were observed.

Optimization work was conducted with respect to different palladium catalysts, ligands, solvent ratios, and temperatures (Table 1). Without any ligand, palladium black precipitated out very quickly with only a trace amount of the desired product being formed and the aryl halide **1a** was left in large amounts (entry 1). The simple triphenylphosphine ligand did not improve the yield (entry 2). Both tri-*o*-tolylphosphine and *o*-(dicyclohexylphosphino)biphenyl ligands increased the yield to ∼50% (entries 3 and 7). Several bidentate ligands have also been examined (entries 4−6). Among them, dppm proved the most efficient, producing lactam **3a** in 66% yield, although 10 mol % of ligand seemed necessary to obtain a decent yield (entry 8). In addition to examining the effect of the ligand on the yield, several bases have also been tested in this reaction (entries 9−12). The results indicate that, with 1.0 equiv of Na_2CO_3, a 73% yield of the desired product can be achieved (entry 9). Other bases gave lower yields (entries 10 and 11). On the basis of our previous experience, the solvent can often prove critical for palladium-catalyzed aryne reactions, mostly

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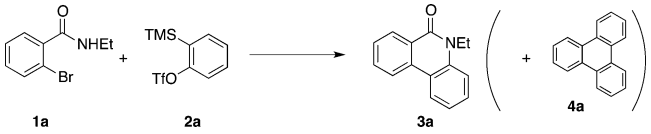
Table 1. Optimization of the Pd-Catalyzed Annulation of Benzyne[a]



entry	ligand (amt (mol %))	additive (amt (equiv))	solvent ratio (toluene/MeCN)	% yield of **3a**[b]
1			4/1	10
2	PPh_3 (10)		4/1	13
3	P(*o*-tolyl)$_3$ (10)		4/1	50
4	dppm (10)		4/1	66
5	dppe (10)		4/1	30
6	dppf (10)		4/1	25
7	L (10)[c]		4/1	56
8	dppm (5)		4/1	53
9	**dppm (10)**	**Na_2CO_3 (1)**	**4/1**	**73**
10	dppm (10)	K_2CO_3 (1)	4/1	70
11	dppm (10)	Cs_2CO_3 (1)	4/1	67
12	dppm (10)	Na_2CO_3 (2)	4/1	57
13	dppm (10)	Na_2CO_3 (1)	3/1	52
14	dppm (10)	Na_2CO_3 (1)	6/1	49
15	dppm (10)	Na_2CO_3 (1)	4/1	50[d]
16	dppm (10)	Na_2CO_3 (1)	4/1	60[e]

[a]All reactions were run using substrate **1a** (0.25 mmol), 5 mol % of $Pd(OAc)_2$, 2.0 equiv of **2a**, 5.0 equiv of CsF, 5 mL of solvent at 110 °C for 16−24 h, unless otherwise specified. [b]Isolated yield. [c]*o*-(Dicyclohexylphosphino)biphenyl. [d]The reaction was conducted at 90 °C for 12 h, at which time the Pd had precipitated out. [e]1.6 equiv of **2a** and 4.0 equiv of CsF were employed.

because the aryne is generated at substantially different rates in different solvents.[17] With a toluene/acetonitrile mixed solvent and CsF as the fluoride source, benzyne is generated more slowly in mixtures with less acetonitrile, because CsF has a lower solubility in toluene. Thus, the solvent ratio was examined and 4/1 toluene/acetonitrile afforded the best result (compare entries 9, 13, and 14). With a 3/1 ratio, more of the trimer **4a** is formed; with a 6/1 ratio, the benzyne is generated too slowly, giving a lower yield of the desired product.

An effort was made to lower the temperature and the benzyne precursor loading (entries 15 and 16), but it appears that 110 °C and 2 equiv of the benzyne precursor, plus 5 equiv of CsF, are necessary in order to obtain a high yield. Several other palladium catalysts, including $PdCl_2(MeCN)_2$ (63%), $Pd(dba)_2$ (65%), and $Pd(PPh_3)_4$ (61%), have also been examined in this process, but none proved better than $Pd(OAc)_2$. We have chosen the reaction conditions reported in entry 9 of Table 1 as our optimal conditions.

On the basis of our experimental results and previous experience with related processes,[18] we propose that this phenanthridinone synthesis proceeds through either of the possible pathways shown in Scheme 1.

One possible pathway proceeds by the oxidative cyclization of Pd(0) with the aryne generated from the silyl triflate to form the palladacycle **I** (path a).[20] Oxidative addition of **1a** to this palladacycle forms the Pd(IV) intermediate **II**. Reductive elimination gives rise to the arylpalladium(II) intermediate **III**. However, we cannot rule out the possibility that Pd(0) inserts directly into the C−Br bond of **1a** to form the intermediate **IV**, which then undergoes carbopalladation of the aryne to give rise to intermediate **III**[21] (path b). Regardless of how the intermediate **III** is formed, under the basic conditions, it is expected to cyclize to the intermediate **V**. Finally, through reductive elimination the desired product **3a** can be generated, alongside Pd(0), which can reenter the catalytic cycle. There does not appear to be any particular evidence favoring either of these pathways.

Reaction Scope and Limitations. To test the scope and limitations of this reaction, we have examined a variety of substituted 2-halobenzamides, and the results are summarized in Table 2. Different amide nitrogen substituents, including alkyl (entries 1−4), allyl (entry 5), phenyl (entry 6), and benzyl groups (entries 7−10), have been examined. Among them, excellent yields were achieved for *N*-primary and *N*-secondary alkyl (entries 1−3) substituted amides, as well as *N*-benzyl substituted amides (entries 7−10). The analogous amide with

Scheme 1. Tentative Mechanisms

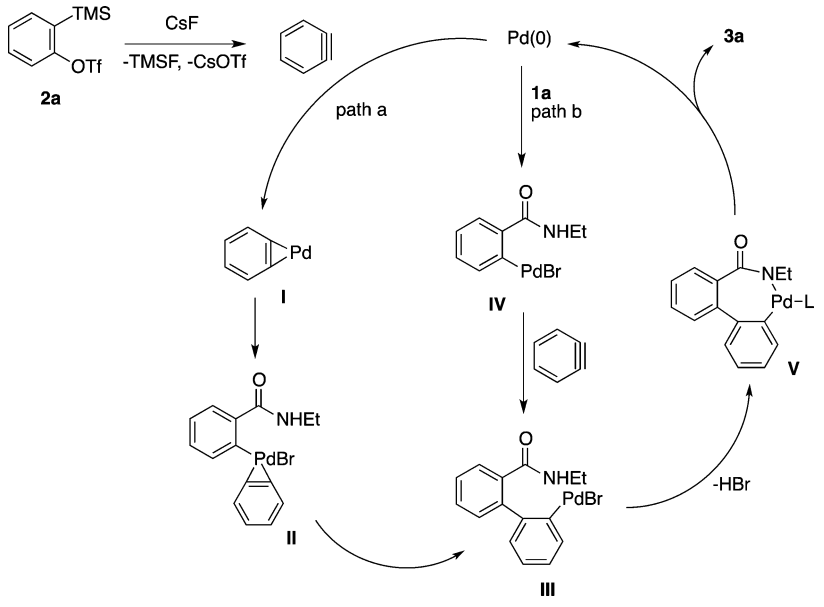


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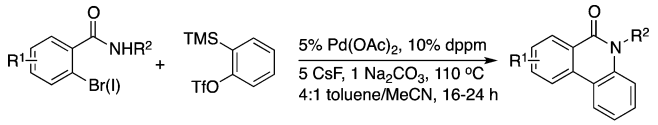
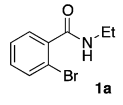
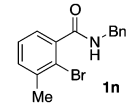
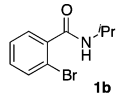
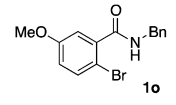
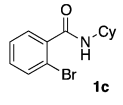
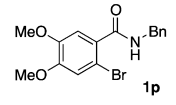
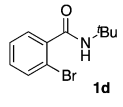
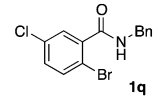
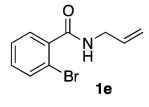
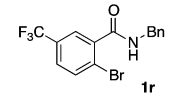
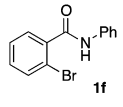
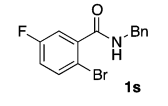
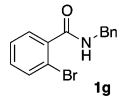
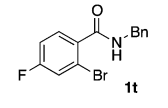
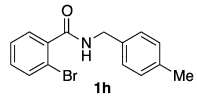
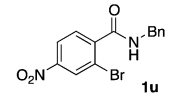
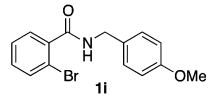
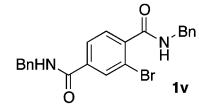
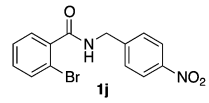
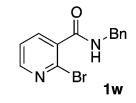
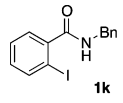
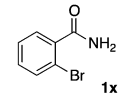
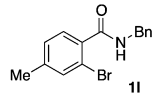
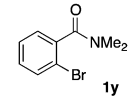
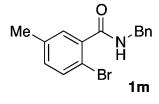
Table 2. Pd-Catalyzed Annulation of Benzyne 2a[a]



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

entry	substrate	% yield of **3**[b]	entry	substrate	% yield of **3**[b]
1	 **1a**	(**3a**) 73	14	 **1n**	(**3n**) 74
2	 **1b**	(**3b**) 70	15	 **1o**	(**3o**) 74
3	 **1c**	(**3c**) 87	16	 **1p**	(**3p**) 70
4	 **1d**	(**3d**) 64	17	 **1q**	(**3q**) 67
5	 **1e**	(**3e**) 65	18	 **1r**	(**3r**) 52
6	 **1f**	(**3f**) --[c]	19	 **1s**	(**3s**) 65
7	 **1g**	(**3g**) 82	20	 **1t**	(**3t**) 79
8	 **1h**	(**3h**) 77	21	 **1u**	(**3u**) 70
9	 **1i**	(**3i**) 75	22	 **1v**	(**3v**) 55
10	 **1j**	(**3j**) 83	23	 **1w**	(**3w**) 36
11	 **1k**	(**3g**) 38	24	 **1x**	(**3x**) 0
12	 **1l**	(**3l**) 84	25	 **1y**	(**3y**) 0
13	 **1m**	(**3m**) 79			

[a]Representative procedure: **1** (0.25 mmol), 2.0 equiv of **2**, 5.0 equiv of CsF, 5 mol % of $Pd(OAc)_2$, 10 mol % of dppm, 1.0 equiv of Na_2CO_3 in 5 mL of 4/1 toluene/MeCN at 110 °C for 16−24 h. [b]Isolated yield. [c]An unknown mixture was generated with products overlapping with the starting material **1d** on the TLC plate.

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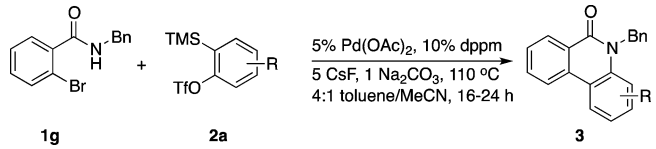
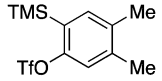
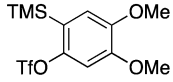
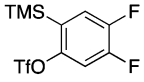
Table 3. Investigation of Different Arynes in the Pd-Catalyzed Annulation of *o*-Halobenzamide 1g[a]



1g 2a 3

entry	aryne	% yield of **3**[b]
1	 **2b**	(**3gb**) 50
2	 **2c**	(**3gc**) 46
3	 **2d**	(**3gd**) 43

[a]Representative procedure: **1g** (0.25 mmol), 2.0 equiv of **2**, 5.0 equiv of CsF, 5 mol % of $Pd(OAc)_2$, 10 mol % of dppm, 1.0 equiv of Na_2CO_3 in 5 mL of 4/1 toluene/MeCN at 110 °C for 16−24 h. [b]Isolated yield.

N-^{t}Bu (entry 4) afforded a lower yield, presumably due to the steric hindrance of the ^{t}Bu group. The presence of an *N*-allyl group (entry 5) also caused complications—the reaction looked messier on the TLC plate than did the parent system (**1a**) with a resulting lower yield. Aryl-substituted amide **1f** produced some uncharacterized products, which overlapped with the starting amide left on the TLC plate (entry 6). The reaction was also performed using 2-iodobenzamide (**1k**; entry 11), where a much lower yield was obtained than was the case for the corresponding bromobenzamide **1g**. Although for most palladium-catalyzed reactions of aryl halides aryl iodides provide better results than the corresponding aryl bromides, because the oxidative addition of Pd(0) to the aryl halide is easier and faster (see the later mechanistic discussion), there are several publications where the same halide effect that is seen here has been reported and mechanistic studies on such reactions have been conducted.[22] The reason for this halogen effect is not clear. However, we have observed that palladium precipitates out more quickly with a lower conversion and more side products in the reaction of **1k** than in the reaction of **1g**.

To further test the scope and limitations of the reaction, we examined a variety of 2-bromobenzamides with various functional groups (entries 12−22). Amides with slightly electron donating methyl groups at the 3- (entry 14), 4- (entry 12), and 5-positions (entry 13) generally afforded excellent yields of above 70%, although **1n** provided a slightly lower yield than the others, presumably due mainly to the steric hindrance of the methyl group during oxidative addition of the carbon−halogen bond to the palladium catalyst. Strongly electron donating methoxy groups also did not lower the yield significantly, and yields above 70% were generated from **1o**,**p**, which suggested that the oxidative addition of the aryl bromide to Pd(0) is not very difficult under these reaction conditions. Halogens, such as F (entries 19 and 20) and Cl (entry 17), were well tolerated in these reactions, providing good yields of the corresponding amides.

o-Bromobenzamides with electron-withdrawing groups, including CF_3 (entry 18), NO_2 (entry 21), and an amide group (entry 22), were also tested, and lower yields were obtained in comparison to **1g**. The reason for this decrease can be explained as follows. Although the electron-withdrawing nature of these functional groups facilitates oxidative addition of the carbon−bromine bond in the amide to Pd(0), it at the same time decreases the nucleophilic nature of the nitrogen in the amide, which is critical for the cyclization step (see the later mechanistic discussion).

In addition to these *N*-benzyl-2-bromobenzamide derivatives, the pyridine-derived amide **1w** has also been examined, but only a 36% yield of the desired product was isolated, which may be caused by deactivation of the Pd catalyst through strong coordination of the nitrogen in the pyridine to Pd.

This reaction was also applied to 2-bromobenzamide (**1x**, entry 24) and *N*,*N*-dimethyl-2-bromobenzamide (**1y**, entry 25). Amides **1x** and **1y** both remained in the reaction system in very large amounts after the reaction, and neither of the desired products was observed. The reasons for the failure of these two reactions may not, however, be the same. In the reaction of amide **1x**, strong coordination of the NH_2 group with the Pd in either complex **III** or **IV** (see Scheme 1) may inhibit the cyclization, while in amide **1y** two methyl groups on the nitrogen prohibit nucleophilic attack of the nitrogen on the Pd in complex **III** (see the step from **III** to **V** in Scheme 1).

In addition to the silylphenyl triflate **2a**, other aryne precursors have also been examined as an annulation partner in our methodology (Table 3). The 4,5-dimethylbenzyne precursor **2b**, the 4,5-dimethoxybenzyne precursor **2c**, and the 4,5-difluorobenzyne precursor **2d** have all been examined under our annulation conditions. They formed the expected annulation products **3gb**, **3gc**, and **3gd**, respectively, not surprisingly with lower yields in comparison to that for benzyne precursor **2a** (Table 2, entries 1−3). This may be due to either the slower rate of generation of the arynes or the lack of stability of these arynes, as has been suggested by earlier work in our group.[18d,e]

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CONCLUSIONS

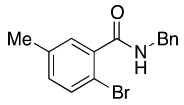
In summary, we have developed a novel synthesis of phenanthridinones, which involves the palladium-catalyzed annulation of arynes by 2-halobenzamides. This method provides an efficient synthesis of substituted phenanthridinones from readily available starting materials. Our process has been shown to be tolerant of a wide variety of functional groups, which makes further elaboration possible.

EXPERIMENTAL SECTION

General Considerations. The ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. All melting points are uncorrected. High-resolution mass spectra (HRMS) were obtained using EI at 70 eV (TOF) or using an Agilent QTOF 6540 mass spectrometer (APCI at 70 eV). All reagents were used directly as obtained commercially unless otherwise noted. All reactions were carried out in oven-dried glassware and monitored by thin-layer chromatography (SiO_2, hexanes or hexanes/EtOAc). THF was distilled over Na. The silylaryl triflate **2a,** CsF, TBAF solution (1 M in THF), and acetonitrile were purchased from Sigma-Aldrich Co. The 4,5-dimethyl-substituted silylaryl triflate **2b**, the 4,5-dimethoxy-substituted silylaryl triflate **2c**, and the 4,5-difluoro-substituted silylaryl triflate **2d** were prepared according to a previous literature procedure.[18e,23]

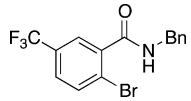
Noncommercially Available Compounds. Noncommercially available starting materials were prepared according to literature procedures.[24]

*N-Benzyl-2-bromo-5-methylbenzamide (**1m**).* White solid: mp 133−135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41−7.21 (m, 7H),



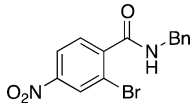
7.04 (dd, J = 9.0, 3.0 Hz, 1H), 6.47 (s, 1H), 4.59 (d, J = 3.0 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 167.8, 137.8, 137.7, 137.4, 133.2, 132.2, 130.3, 128.8, 128.1, 127.7, 115.9, 44.2, 20.9; HRMS (EI) calcd for $C_{15}H_{14}NOBr$ 303.0259, found 303.0265.

*N-Benzyl-2-bromo-5-(trifluoromethyl)benzamide (**1r**).* White solid: mp 148−150 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 9.17 (t,



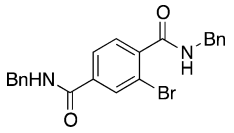
J = 6.0 Hz, 1H), 7.93 (d, J = 9.0 Hz, 1H), 7.80 (s, 1H), 7.74 (dd, J = 9.0, 3.0 Hz, 1H), 7.42−7.25 (m, 5H), 4.50 (d, J = 6.0 Hz, 2H); ^{13}C NMR (300 MHz, d_6-DMSO) δ 166.0, 139.9, 138.7, 134.1, 128.4, 127.4, 127.4, 127.0, 125.5, 125.4, 123.9, 121.9, 42.7; HRMS (EI) calcd for $C_{15}H_{11}NOBrF_3$ 356.9976, found 356.9973.

*N-Benzyl-2-bromo-4-nitrobenzamide (**1u**).* White solid: mp 148−150 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.17 (dd, J = 9.0,



3.0 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.37−7.26 (m, 5H), 6.39 (br s, 1H), 4.63 (d, J = 6.0 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.9, 148.7, 143.5, 137.1, 130.3, 129.1, 128.6, 128.2, 128.2, 122.7, 120.2, 44.6; HRMS (EI) calcd for $C_{14}H_{11}N_2O_3Br$ 333.9953, found 334.9960.

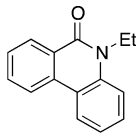
*N,N′-Dibenzyl-2-bromo-1,4-benzenedicarboxamide (**1v**).* White solid: mp 219−221 °C; ^{1}H NMR (300 MHz, d_6-DMSO) δ 9.28 (t, J = 6.0 Hz, 1H), 9.09 (t, J = 6.0 Hz, 1H), 8.18 (s, 1H), 7.95 (d, J = 9.0 Hz, 1H), 7.55 (d, J = 9.0 Hz, 1H), 7.41−7.25 (m, 10H), 4.49 (d, J = 6.0 Hz, 2H); ^{13}C NMR (300 MHz, d_6-DMSO) δ 168.9, 164.2, 141.4, 139.3, 139.0, 136.3, 131.4, 128.8, 128.4, 128.4, 127.3, 126.9, 126.9,



126.6, 119.0, 42.8, 42.5; HRMS (EI) calcd for $C_{22}H_{19}N_2O_2Br$ 422.0630, found 422.0625.

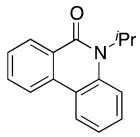
General Procedure for the Palladium-Catalyzed Synthesis of Phenanthridinones. The 2-bromobenzamide (**1a**; 0.25 mmol), the 2-(trimethylsilyl)aryl triflate (2.0 equiv), CsF (5.0 equiv), Na_2CO_3 (1.0 equiv), $Pd(OAc)_2$ (5 mol %), dppm (10 mol %), 4 mL of toluene, and 1 mL of MeCN were placed in a 4 dram vial, and the vial was sealed. The reaction mixture was stirred first at room temperature for 1 min and then heated to 110 °C for 16−24 h. The mixture was cooled to room temperature, diluted with ethyl acetate, washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel using hexanes/EtOAc as the eluent.

*5-Ethylphenanthridin-6(5H)-one (**3a**).* White solid (41.0 mg, 73%): mp 98−99 °C (lit.[25] mp 87−90 °C); ^{1}H NMR (300 MHz,



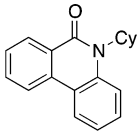
d_6-acetone) δ 8.48−8.44 (m, 3H), 7.82 (td, J = 9.0, 3.0 Hz, 1H), 7.65−7.59 (m, 3H), 7.35−7.30 (m, 1H), 4.46 (q, J = 6.0 Hz, 2H), 1.35 (t, J = 6.0 Hz, 3H); ^{13}C NMR (300 MHz, d_6-acetone) δ 160.4, 137.3, 133.8, 132.6, 130.0, 128.5, 128.0, 125.9, 123.9, 122.4, 122.2, 119.3, 115.7, 37.3, 12.4; HRMS (EI) calcd for $C_{15}H_{13}NO$ 223.0997, found 223.0995. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[26]

*5-Isopropylphenanthridin-6(5H)-one (**3b**).* White solid (41.4 mg, 70%): mp 99−101 °C; ^{1}H NMR (300 MHz, d_6-acetone) δ 8.44 (dd, J



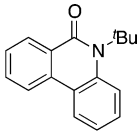
= 9.0, 3.0 Hz, 3H), 7.84−7.76 (m, 2H), 7.64−7.54 (m, 2H), 7.32 (t, J = 9.0 Hz, 1H), 5.42 (m, 1H), 1.68 (d, J = 9.0 Hz, 6H); ^{13}C NMR (300 MHz, d_6-acetone) δ 162.5, 135.1, 133.8, 130.8, 129.6, 129.2, 128.0, 125.3, 123.5, 123.3, 121.1, 117.2, 49.1, 20.5; HRMS (EI) calcd for $C_{16}H_{15}NO$ 237.1154, found 237.1152.

*5-Cyclohexylphenanthridin-6(5H)-one (**3c**).* White solid (60.1 mg, 87%): mp 117−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J =



7.8 Hz, 1H), 8.23 (dd, J = 10.0, 7.5 Hz, 2H), 7.74−7.45 (m, 4H), 7.26 (t, J = 7.2 Hz, 1H), 2.72 (m, 2H), 2.00−1.76 (m, 6H), 1.56−1.36 (m, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.2, 138.1, 133.7, 132.3, 129.1, 128.7, 128.0, 126.8, 123.7, 122.2, 121.5, 120.3, 115.9, 57.9, 29.3, 26.9, 25.7; HRMS (EI) calcd for $C_{19}H_{19}NO$ 277.1467, found 277.1465.

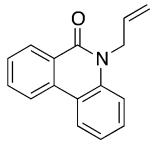
*5-tert-Butylphenanthridin-6(5H)-one (**3d**).* White solid (40.3 mg, 64%): mp 128−130 °C; ^{1}H NMR (300 MHz, d_6-acetone) δ 8.30−8.21



dx.doi.org/10.1021/jo3016192 | J. Org. Chem. 2012, 77, 8648−8656

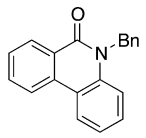
(m, 3H), 7.76−7.72 (m, 2H), 7.56 (t, J = 9.0 Hz, 1H), 7.42 (t, J = 9.0 Hz, 1H), 7.25 (td, J = 9.0, 3.0 Hz, 1H), 1.79 (s, 9H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 165.6, 138.1, 133.9, 132.1, 129.6, 127.9, 127.7, 126.8, 123.8, 122.7, 122.2, 121.5, 120.8, 60.7, 30.7; HRMS (EI) calcd for $C_{17}H_{17}NO$ 251.1310, found 251.1311.

*5-Allylphenanthridin-6(5H)-one (**3e**).* White solid (38.4 mg, 65%): mp 97−98 °C (lit.[27] mp 99 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60



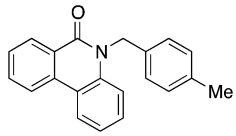
(d, J = 8.0 Hz, 1H), 8.33 (dd, J = 8.3, 3.7 Hz, 2H), 7.81 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 6.12−5.98 (m, 1H), 5.27 (d, J = 10.5 Hz, 1H), 5.20 (d, J = 17.3 Hz, 1H), 5.10 (d, J = 4.7 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.4, 137.3, 133.7, 132.6, 132.0, 129.5, 129.0, 128.0, 125.5, 123.3, 122.5, 121.7, 119.5, 117.0, 115.8, 45.1; HRMS (APCI) calcd for $C_{16}H_{14}NO$ $[M + H]^+$ 236.1070, found 236.1073.

*5-Benzylphenanthridin-6(5H)-one (**3g**).* Pale yellow solid (from **1g**, 58.5 mg, 82%; from **1k**, 27.4 mg, 38%): mp 126−129 °C (lit.[28] mp



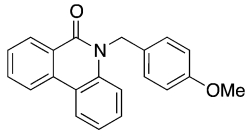
112−113 °C); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (d, J = 8.7 Hz, 1H), 8.35−8.27 (m, 2H), 7.82 (t, J = 7.6 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.41 (t, J = 8.4 Hz, 1H), 7.36−7.23 (m, 7H), 5.70 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.0, 137.3, 136.6, 133.9, 132.8, 129.6, 129.2, 128.8, 128.1, 127.2, 126.6, 125.4, 123.3, 122.6, 121.7, 119.6, 116.1, 46.5; HRMS (APCI) calcd for $C_{20}H_{16}NO$ $[M + H]^+$ 286.1226, found 286.1232. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[29]

*5-(4-Methylbenzyl)phenanthridin-6(5H)-one (**3h**).* White solid (57.7 mg, 77%): mp 106−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ

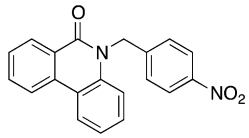


8.62 (d, J = 8.1 Hz, 1H), 8.27 (t, J = 6.3 Hz, 1H), 7.77 (t, J = 7.2 Hz, 1H), 7.60 (t, J = 7.2 Hz, 1H), 7.36−7.07 (m, 8H), 5.61 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.1, 137.6, 137.0, 134.0, 133.7, 132.8, 129.7, 129.6, 129.3, 128.2, 126.7, 125.6, 123.4, 122.7, 121.9, 119.7, 116.2, 46.4, 21.3; HRMS (EI) calcd for $C_{21}H_{17}NO$ 299.1310, found 299.1307.

*5-(4-Methoxybenzyl)phenanthridin-6(5H)-one (**3i**).* Pale brown glassy solid (59.4 mg, 75%): mp 136−137 °C; ^{1}H NMR (600 MHz,

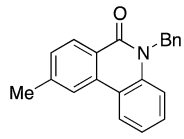


$CDCl_3$) δ 8.66 (d, J = 8.0 Hz, 1H), 8.31 (t, J = 9.1 Hz, 2H), 7.81 (t, J = 8.3 Hz, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.43 (t, J = 8.4 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 8.0 Hz, 1H), 7.25 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.63 (s, 2H), 3.78 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.9, 158.8, 137.4, 133.8, 132.7, 129.6, 129.2, 128.7, 128.1, 127.9, 125.5, 123.3, 122.6, 121.7, 119.5, 116.1, 114.2, 55.3, 46.0; HRMS (APCI) calcd for $C_{21}H_{18}NO_2$ $[M + H]^+$ 316.1332, found 316.1322. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[29]



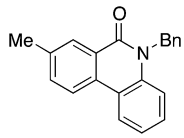
*5-(4-Nitrobenzyl)phenanthridin-6(5H)-one (**3j**).* White solid (68.5 mg, 83%): mp 235−237 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 9.0 Hz, 1H), 8.36 (d, J = 9.0 Hz, 2H), 8.25 (dd, J = 6.0, 3.0 Hz, 1H), 7.85 (t, J = 9.0 Hz, 1H), 7.65 (t, J = 9.0 Hz, 1H), 7.42−7.27 (m, 4H), 7.09 (d, J = 9.0 Hz, 1H), 6.99 (dd, J = 6.0, 3.0 Hz, 1H), 6.05 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.6, 137.3, 134.4, 133.3, 132.6, 130.1, 129.4, 128.5, 128.4, 127.7, 125.9, 125.4, 123.8, 123.3, 122.1, 119.9, 115.7, 45.1; HRMS (EI) calcd for $C_{20}H_{14}N_2O_3$ 330.1004, found 330.1011.

*5-Benzyl-9-methylphenanthridin-6(5H)-one (**3l**).* White solid (62.6 mg, 84%): mp 173−175 °C; ^{1}H NMR (300 MHz, d_6-acetone)



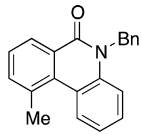
δ 8.47 (d, J = 6.0 Hz, 1H), 8.42 (d, J = 6.0 Hz, 1H), 8.35 (s, 1H), 7.51 (d, J = 9.0 Hz, 1H), 7.43 (dd, J = 6.0, 3.0 Hz, 2H), 7.31−7.23 (m, 6H), 5.70 (s, 2H), 2.59 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.1, 143.4, 137.7, 136.9, 134.0, 129.7, 129.6, 129.4, 129.0, 127.3, 126.7, 123.4, 122.6, 121.9, 119.7, 116.2, 46.6, 22.4; HRMS (EI) calcd for $C_{21}H_{17}NO$ 299.1310, found 299.1304.

*5-Benzyl-8-methylphenanthridin-6(5H)-one (**3m**).* White solid (59.0 mg, 79%): mp 173−175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ



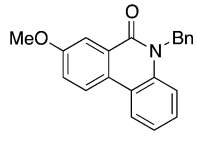
8.43 (s, 1H), 8.25 (d, J = 7.8 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.61 (dd, J = 8.1, 1.8 Hz, 1H), 7.38−7.21 (m, 8H), 5.67 (s, 2H), 2.54 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.2, 138.4, 137.2, 136.9, 134.2, 131.6, 129.2, 129.1, 129.0, 127.3, 126.7, 125.5, 123.2, 122.7, 121.9, 119.8, 116.1, 46.6, 21.6; HRMS (EI) calcd for $C_{21}H_{17}NO$ 299.1310, found 299.1306.

*5-Benzyl-10-methylphenanthridin-6(5H)-one (**3n**).* White solid (55.1 mg, 74%): mp 122−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ



8.62 (d, J = 9.0 Hz, 1H), 8.46 (d, J = 6.0 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.52 (t, J = 9.0 Hz, 1H), 7.38−7.23 (m, 8H), 5.67 (s, 2H), 2.97 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.4, 137.7, 137.4, 136.8, 134.7, 133.5, 129.0, 128.8, 128.1, 127.8, 127.5, 127.3, 126.7, 121.9, 121.3, 116.0, 47.0, 26.3; HRMS (EI) calcd for $C_{21}H_{17}NO$ 299.1310, found 299.1303.

*5-Benzyl-8-methoxyphenanthridin-6(5H)-one (**3o**).* White solid (58.3 mg, 74%): mp 133−135 °C; ^{1}H NMR (300 MHz, d_6-acetone) δ



8.42 (d, J = 9.0 Hz, 1H), 8.36 (d, J = 6.0 Hz, 1H), 7.96 (d, J = 3.0 Hz, 1H), 7.46−7.24 (m, 9H), 5.71 (s, 2H), 3.98 (s, 3H); ^{13}C NMR (300 MHz, d_6-acetone) δ 162.3, 161.2, 138.8, 137.8, 130.1, 129.9, 128.7,

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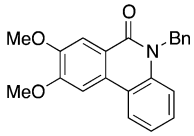
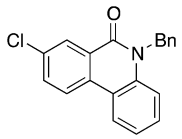
128.4, 128.3, 128.0, 125.5, 124.3, 123.9, 123.3, 120.8, 117.4, 110.9, 56.5, 47.1; HRMS (EI) calcd for $C_{21}H_{17}NO_2$ 315.1259, found 315.1259.

*5-Benzyl-8,9-dimethoxyphenanthridin-6(5H)-one (**3p**).* White solid (60.2 mg, 70%): mp 210−212 °C; ^{1}H NMR (300 MHz,



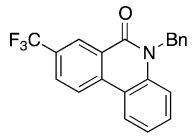
$CDCl_3$) δ 8.13 (d, J = 7.8 Hz, 1H), 7.98 (s, 1H), 7.59 (s, 1H), 7.38−7.21 (m, 8H), 5.65 (s, 2H), 4.09 (s, 3H), 4.04 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 161.5, 153.6, 150.0, 137.0, 137.0, 128.9, 128.8, 128.8, 127.3, 126.7, 122.8, 122.5, 119.5, 119.5, 116.2, 109.4, 102.7, 56.4, 56.3, 46.6; HRMS (EI) calcd for $C_{22}H_{19}NO_3$ 345.1365, found 345.1370.

*5-Benzyl-8-chlorophenanthridin-6(5H)-one (**3q**).* White solid (53.5 mg, 67%): mp 155−157 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ



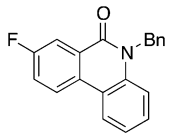
8.59 (d, J = 2.1 Hz, 1H), 8.23 (d, J = 9.0 Hz, 1H), 8.22 (d, J = 8.1 Hz, 1H), 7.73 (dd, J = 8.1, 2.4 Hz, 1H), 7.41 (m, 1H), 7.32−7.24 (m, 7H), 5.65 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 161.1, 137.4, 136.5, 134.5, 133.2, 132.5, 130.1, 129.1, 128.9, 127.5, 126.9, 126.7, 123.7, 123.5, 123.0, 119.0, 116.4, 46.8; HRMS (EI) calcd for $C_{20}H_{14}NOCl$ 319.0764, found 319.0756.

*5-Benzyl-8-(trifluoromethyl)phenanthridin-6(5H)-one (**3r**).* White solid (45.7 mg, 52%): mp 186−188 °C; ^{1}H NMR (300 MHz, $CDCl_3$)



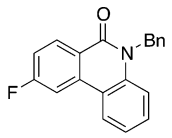
δ 8.92 (s, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.30 (dd, J = 8.1, 1.5 Hz, 1H), 7.99 (dd, J = 8.7, 1.8 Hz, 1H), 7.47 (m, 1H), 7.36−7.24 (m, 7H), 5.67 (m, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 161.3, 138.1, 136.3, 131.1, 129.1, 129.0, 129.0, 127.6, 127.1, 127.0, 126.7, 125.7, 124.1, 123.2, 122.9, 118.6, 116.5, 46.9; HRMS (EI) calcd for $C_{21}H_{14}NOF_3$ 353.1027, found 353.1035.

*5-Benzyl-8-fluorophenanthridin-6(5H)-one (**3s**).* Pale solid (49.3 mg, 65%): mp 164−166 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33−



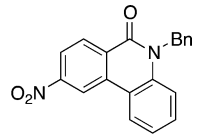
8.29 (m, 2H), 8.24 (d, J = 7.9 Hz, 1H), 7.54 (td, J = 8.4, 2.9 Hz, 1H), 7.43 (t, J = 8.4 Hz, 1H), 7.38−7.24 (m, 7H), 5.68 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.0, 137.3, 136.6, 133.9, 132.8, 129.6, 129.2, 128.8, 128.1, 127.2, 126.6, 125.4, 123.3, 122.6, 121.7, 119.6, 116.1, 46.5 (extra peaks due to C−F coupling); ^{19}F NMR (600 MHz, $CDCl_3$) δ −112.0; HRMS (APCI) calcd for $C_{20}H_{15}FNO$ $[M + H]^+$ 304.1132, found 304.1136.

*5-Benzyl-9-fluorophenanthridin-6(5H)-one (**3t**).* Pale white solid (60.1 mg, 79%): mp 155−158 °C (lit.[28] mp 157−158 °C); ^{1}H NMR



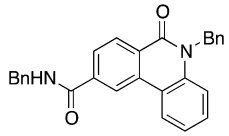
(600 MHz, $CDCl_3$) δ 8.67 (dd, J = 8.9, 5.9 Hz, 1H), 8.19 (d, J = 7.3 Hz, 1H), 7.94 (dd, J = 10.3, 2.4 Hz, 1H), 7.46 (t, J = 8.5 Hz, 1H), 7.37−7.25 (m, 8H), 5.68 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.7, 165.0, 161.3, 137.8, 136.5, 136.5, 136.4, 132.5, 132.4, 130.3, 129.6, 128.9, 127.3, 126.5, 123.6, 122.7, 122.0, 122.0, 118.8, 118.8, 116.4, 116.3, 116.2, 115.4, 107.8, 107.6, 46.5 (extra peaks due to C−F coupling); ^{19}F NMR (600 MHz, $CDCl_3$) δ −105.4; HRMS (APCI) calcd for $C_{20}H_{15}FNO$ $[M + H]^+$ 304.1132, found 304.1136. The ^{1}H and ^{13}C NMR spectral data are in good agreement with the literature data.[28]

*5-Benzyl-9-nitrophenanthridin-6(5H)-one (**3u**).* Yellow solid (58.0 mg, 70%): decomposes above 300 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ



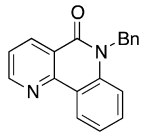
9.18 (d, J = 2.1 Hz, 1H), 8.80 (d, J = 8.7 Hz, 1H), 8.41−8.36 (m, 2H), 7.56−7.50 (m, 2H), 7.40−7.27 (m, 6H), 5.69 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 160.4, 147.2, 139.1, 138.4, 136.8, 132.3, 129.0, 127.5, 127.0, 126.9, 125.8, 125.5, 125.1, 124.2, 123.7, 118.0, 116.9, 46.2; HRMS (EI) calcd for $C_{20}H_{14}N_2O_3$ 330.1004, found 330.1001.

*5-Benzyl-9-[(benzylamino)carbonyl]phenanthridin-6(5H)-one (**3v**).* White solid (57.9 mg, 55%): mp 197−200 °C; ^{1}H NMR (300



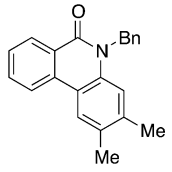
MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.58 (d, J = 8.1 Hz, 1H), 8.30 (d, J = 7.8 Hz, 1H), 7.85 (dd, J = 8.4, 1.5 Hz, 1H), 7.33−7.22 (m, 13H), 6.88 (s, 1H), 5.61 (s, 2H), 4.72 (d, J = 5.7 Hz, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 166.8, 161.4, 138.1, 138.0, 136.4, 134.3, 130.3, 129.8, 129.0, 129.0, 128.2, 127.9, 127.4, 126.6, 125.3, 123.8, 123.0, 121.9, 119.2, 116.2, 46.7, 44.6; HRMS (EI) calcd for $C_{28}H_{22}N_2O_2$ 418.1681, found 418.1689.

*6-Benzylbenzo-1,6-naphthyridin-5-one (**3w**).* White solid (25.7 mg, 36%): mp 129−131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (dd,



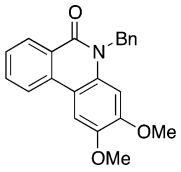
J = 6.0, 3.0 Hz, 1H), 8.90 (d, J = 9.0 Hz, 1H), 8.83 (dd, J = 9.0, 3.0 Hz, 1H), 7.57−7.47 (m, 2H), 7.37−7.24 (m, 7H), 5.66 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.1, 154.2, 138.8, 137.2, 136.4, 131.5, 129.1, 127.6, 126.7, 125.5, 123.3, 123.2, 121.1, 115.7, 46.7; HRMS (EI) calcd for $C_{19}H_{14}N_2O$ 286.1106, found 286.1098.

*5-Benzyl-2,3-dimethylphenanthridin-6(5H)-one (**3gb**).* White solid (39.0 mg, 50%): mp 155−157 °C; ^{1}H NMR (300 MHz,



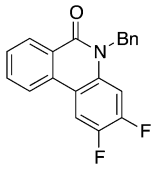
$CDCl_3$) δ 8.64−8.58 (m, 1H), 8.32−8.25 (m, 1H), 8.01 (s, 1H), 7.78−7.73 (m, 1H), 7.65−7.54 (m, 1H), 7.32−7.25 (m, 3H), 7.09 (s, 1H), 6.87 (d, J = 12.0 Hz, 2H), 5.64 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.1, 138.9, 137.1, 132.9, 132.7, 129.8, 129.4, 129.0, 129.0, 128.2, 127.3, 126.7, 123.5, 121.9, 116.2, 46.6, 20.7, 19.6; HRMS (EI) calcd for $C_{22}H_{19}NO$ 313.1467, found 313.1470.

dx.doi.org/10.1021/jo3016192 | J. Org. Chem. 2012, 77, 8648−8656



*5-Benzyl-2,3-dimethoxyphenanthridin-6(5H)-one (**3gc**).* White solid (39.6 mg, 46%): mp 153−155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (dd, J = 8.1, 1.5 Hz, 1H), 8.14 (d, J = 8.1, 1H), 7.76 (td, J = 8.1, 1.5 Hz, 1H), 7.64 (s, 1H), 7.56 (t, J = 8.1 Hz, 1H), 7.30−7.23 (m, 5H), 6.79 (s, 1H), 5.66 (s, 2H), 3.99 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 162.2, 150.8, 145.3, 137.1, 134.0, 132.8, 132.4, 129.5, 129.1, 127.5, 127.2, 126.8, 124.7, 121.3, 112.4, 105.4, 100.1, 56.5, 56.1, 47.1; HRMS (EI) calcd for $C_{22}H_{19}NO_3$ 345.1365, found 345.1370.

*5-Benzyl-2,3-difluorophenanthridin-6(5H)-one (**3gd**).* White solid (34.7 mg, 43%): mp 187−189 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ



8.61 (d, J = 9.0 Hz, 1H), 8.05 (m, 1H), 7.82 (t, J = 9.0 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.35−7.08 (m, 7H), 5.60 (s, 2H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 161.9, 152.7, 148.1, 136.8, 135.9, 133.3, 129.6, 129.2, 129.0, 128.7, 128.3, 127.8, 127.4, 126.7, 116.3, 111.8, 105.6, 47.2; HRMS (EI) calcd for $C_{20}H_{13}NOF_2$ 321.0965, found 321.0973.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures giving ^{1}H and ^{13}C NMR data for the compounds. 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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