Structural Identification between Phthalazine-1,4-Diones and N-Aminophthalimides via Vilsmeier Reaction: Nitrogen Cyclization and Tautomerization Study

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Abstract: N-aminophthalimides and phthalazine 1,4-diones were synthesized from isobenzofuran-1,3-dione, isoindoline-1,3-dione, furo[3,4-b]pyrazine-5,7-dione, or 1H-pyrrolo[3,4-c]pyridine-1,3-dione with monohydrate hydrazine to carry out the 5-exo or 6-endo nitrogen cyclization under the different reaction conditions. Based on the control experimental results, 6-endo thermodynamic hydrohydrazination and kinetical 5-exo cyclization reactions were individually selective formation. Subsequently, Vilsmeier amidination derivatization was successfully developed to probe the structural divergence between N-aminophthalimide 2 and phthalazine 1,4-dione 3. On the other hand, the best tautomerization of N-aminophthalimide to diazinone was also determined under acetic acid mediated solution.

Keywords: vilsmeier reagent; phthalazine-1,4-diones; N-aminophthalimide; hydrazine

1. Introduction

Nitrogen-containing heterocyclic compounds are widely applied to the biologically active pharmaceuticals, agrochemicals, and functional materials and become more and more important [1–5]. Especially, heterocycle derivatives containing bridgehead amine and hydrazine [6,7] such as N-aminophthalimides [8] and phthalazine 1,4-diones [9] have received considerable attention. Therefore, the development of new efficient methods to synthesize N-heterocycles with structural diversity is one major interest of modern synthetic organic chemists [10–12].

Heterocycles containing phthalazine 1,4-dione moiety have been reported to possess different pharmacological properties including anti-inflammatory, cardiotoxic vasorelaxant, anticonvulsant [13], antihypertensive [14], antibacterial [15], anti-cancer [16], and carbonic anhydrase enzyme activity [17]. On the other hand, phthalimide group was conceived as a nitrogen source [18], for the direct introduction of masked amino function via the classical Gabriel protocol [19,20] as well as for the protection of amino groups [21–23]. N-aminophthalimides can be considered as phthalazine 1,4-dione tautomeric pairs. The structural arrangement of hydrazine derivatives is the mainly associated with the interconversion of imine—enamine [24,25]. Herein, we selectively synthesize N-aminophthalimide and phthalazine 1,4-dione derivatives in via the thermodynamic-kinetic control conditions. They will provide as the precursors for constructing the pharmacological heterocyclic compounds (PDE5 inhibitors) [26,27] or the chemiluminescent luminol derivatives [28].
Owing to the structural divergence between N-aminophthalimides 2 and phthalazine-1,4-diones 3, we explored the Vilsmeier amidination derivatization to identify them in this work [29–33]. Furthermore, we successfully developed the prototropic tautomeric interconversion from N-aminophthalimides to phthalazine 1,4-diones under Brønsted–Lowry acidic condition [29–35].

2. Results and Discussion

Initially, isobenzofuran-1,3-diones (1a–c), isoindoline-1,3-dione (1d), furo[3,4-b] pyrazine-5,7-dione (1e), and 1H-pyrrolo[3,4-c] pyridine-1,3-dione (1f) [34–36] were purchased or prepared as the starting materials. Reacting compounds 1a–f with monohydrate hydrazine in ethanol solution at low (at 0 °C or −20 °C) or room temperature led directly to the 5-exo cyclization N-aminophthalimide products 2a–f (81–94%) without the accumulation of hydrohydrazination products 3a–f (Table 1). On the other hand, the 6-exo cyclization of distal nitrogen instead of proximal one was exclusively observed at reflux for ~4 h, and the corresponding 6-endo phthalazine 1,4-dione products 3a–f were formed (83–91%, Table 1). Fortunately, compounds 2a–f and 3a–f can be selectively prepared via kinetic and thermodynamic control reaction with hydrazine hydrate. From the fundamental perspective, these symmetric molecules of N-aminophthalimide products 2a–f provide themselves for investigation of tautomeric conversion controlling processes as well as convenient platforms for the structural identity.

Additionally, phthalazine 1,4-diones 3a–f were used as the reference standards. Although compounds 2 and 3 were tautomeric pairs, they significantly possessed the different polarity, such as, R_f = 0.33 for N-aminophthalimide 2a and R_f = 0.41 for phthalazine 1,4-dione 3a (EA/MeOH = 9/1). All of the 2a–f and 3a–f compounds were fully characterized by spectroscopic methods. For example, compound 2a presented peaks at 3447 and 3482 cm⁻¹ for stretching of the –NH₂ group and at 1020 cm⁻¹ for stretching of the N–N group in FT-IR spectrum. For compound 3a, its IR absorption peaks were at 3461 cm⁻¹ for stretching of the –NH–NH– group and at 1051 cm⁻¹ for stretching of the N–N group. In ¹H-NMR, compounds 2 and 3 presented similar chemical shift and coupling constants, resulting in difficult structural identification of each other. For example, the ¹H-NMR spectra of compounds 2a and 3a were similar as shown in Figure 1. This observation drove us to develop a novel identification method.

On the other hand, N-aminophthalimides 2c and 2e reveal the existence of intramolecular hydrogen bonding phenomenon between carbonyl and amino group in ¹H-NMR spectra. This phenomenon leads to the different chemical shift values between H₄ and H₅ in an aromatic ring (Figure 1). However, compounds 3a–f were favorable for the free base form in DMSO-d₆ solvent. For example, the ¹H-NMR spectrum of compound 3e was presented in Figure 1. Furthermore, Compound 2c was dissolved in DMSO-d₆ and heated at ~100 °C by NMR technique. The sample was monitored in 0, 10, 20, 30, and 60 min, the timed programming result was shown in Figure 2, we found that the intramolecular hydrogen bonding phenomenon was very clearly stable.
Table 1. The thermodynamic-kinetic control synthesis of N-aminophthalimides 2a–f and phthalazine 1,4-diones 3a–f.

| Compound | Reaction Condition | Yield (%) |
|----------|--------------------|-----------|
| 1a       | NH₂NH₂ at 0 °C or -20 °C |         |
| 1b       | NH₂NH₂ at reflux |         |
| 1c       | NH₂NH₂ at reflux |         |
| 1d       | NH₂NH₂ at reflux |         |
| 1e       | NH₂NH₂ at reflux |         |
| 1f       | NH₂NH₂ at reflux |         |
| 2a       | NH₂NH₂ at 0 °C or -20 °C | 92%      |
| 2b       | NH₂NH₂ at reflux | 92%      |
| 2c       | NH₂NH₂ at reflux | 81%      |
| 2d       | NH₂NH₂ at reflux | 82%      |
| 2e       | NH₂NH₂ at reflux | 94%      |
| 2f       | NH₂NH₂ at reflux | 83%      |
| 3a       | NH₂NH₂ at 0 °C or -20 °C | 89%      |
| 3b       | NH₂NH₂ at reflux | 85%      |
| 3c       | NH₂NH₂ at reflux | 87%      |
| 3d       | NH₂NH₂ at reflux | 83%      |
| 3e       | NH₂NH₂ at reflux | 91%      |
| 3f       | NH₂NH₂ at reflux | 84%      |

* The reaction condition at -20 °C within 4h. The reaction condition at 0 °C within 4h. Compound 2f and 3f were provided and prepared from our previous work [28].
The reaction condition at –20 °C within 4h. 

b The reaction condition at 0 °C within 4h. 

c Compound 2f and 3f were provided and prepared from our previous work [28].

Figure 1. $^1$H NMR spectra of N-aminophthalimides 2a, 2c and 2e and phthalazines 1,4-dione 3a and 3e.

Figure 2. The timed programming result of N-aminophthalimides 2c of $^1$H NMR spectra (a) 0 min, (b) 10 min, (c) 20 min, (d) 30 min, (e) 60 min.

Vilsmeier amidination methodology was essentially examined for the applicable protected utilization of primary amines. The usual method was directly treating primary amines with dimethylformamide (DMF) and coupling agents including POCl$_3$, P$_2$O$_5$, PCl$_5$, (COCl)$_2$, PyBOP, SOCl$_2$, acyl chlorides, trifluoroacetic anhydride (TFAA), or sulfonyl chloride to give the corresponding amidine products [37–39]. To further probe the structural divergence, pyrazolopyridopyridazine diones 2f and N-aminopyrazolopyrrolopyridine-6,8-diones 3f were selected as model cases for the further control experiments [28]. At first, we
employed Vilsmeier reagent (halomethyleniminium salt) [29–33] to compounds 2f and 3f (Scheme 1). The reactions were individually monitored by TLC method. When compound 2f was completely consumed for 4 h at 65 °C, the corresponding acquired amidination product 4 was formed and obtained in 89% yield without producing chlorinated compound 5. The structure of compound 4 was fully characterized by spectroscopic methods and single-crystal X-ray diffraction study. Based on 1H NMR spectroscopic characterization, compound 4 possesses singlet signal of pyridine ring proton H\textsubscript{a} around 9.03 ppm, and significant amidinyl moiety signals of iminium proton H\textsubscript{b} around 7.70 ppm and two peaks of NMe\textsubscript{2} around 2.97 and 3.02 ppm (Figure 3). These results showed the free primary amine group of compound 2f was successfully converted into the amidinyl substituent. On the other hand, chlorination of compound 3f was accomplished without amidination product 4 formation by Vilsmeier reagent at reflux for 4 h, affording the corresponding product 5 with down-field proton signal H\textsubscript{c} of pyridine ring around 9.68 ppm in good yield (80%, Scheme 1 and Figure 3) [27]. Based on the above derivatization study, Vilsmeier reaction was conceived as the significant derivatization agent to identify isomers between 2f and 3f.

![Scheme 1](image)

**Scheme 1.** The results of 7-aminopyrazolopyrrolopyridine-6,8-dione 2f and pyrazolopyridopyridazine dione 3f treated with Vilsmeier reagent.

![Figure 3](image)

**Figure 3.** 1H NMR spectra of 7-amidination product 4 and dichloropyridazine 5.

For further investigation into the reactivity of Vilsmeier amidination derivatization, Vilsmeier reaction was carried out using different substrates including N-aminophthalimides 2a–e at 50 °C for 0.5 h. Various substituted reactants 2a–e were demonstrated to perform
the reactions smoothly, regardless of whether electron-donating or electron-withdrawing substituents, and the corresponding amidination products 6–10 were afforded in 74–88% yields (Table 2). All products 6–10 were fully characterized by spectroscopic methods, and they actually presented singlet peak for the significant amidinyl moiety signals of iminium proton H and two peaks of NMe2 in 1H-NMR. Subsequently, a series of phthalazine 1,4-diones 3a–e were treated with Vilsmeier reagent (POCl3/DMF) at 65 °C or 80 °C for 2–4 h. The chlorination happened smoothly to afford the desired products 11–15 in high yields (82–90%, Table 2), except for 3d (31%). Owing to the electron-rich property of nitrogen atoms on the aromatic motif of compound 3d, the complicated aromatic substitution and polyziation were proceeded. All chlorinated products 11–15 were also fully characterized by spectroscopic methods, and two peaks for the significant dione moieties were converted into −N = 13C–Cl singlet signal at δ 153–157 ppm in 13C-NMR spectrum. Therefore, Vilsmeier reagent (POCl3/DMF) was used as the derivatization reagent for the different reactive phenomenon to distinguish N-aminophthalimides 2 and phthalazine-1,4-diones 3.

Table 2. Derivatization results of N-aminophthalimides 2a–e and phthalazine 1,4-diones 3a–e with Vilsmeier reagent.

|   | Amidination | 1H NMR | Chlorination | 13C NMR |
|---|-------------|--------|--------------|---------|
| 2a | HNMe2 | 50-65 °C for 0.5-4 h | POCl3, 80 °C for 2.0 h | 11-15 |
| 6  | from 2a, 88% |  |  | 11 (from 3a, 90%) |
| 7  | from 2b, 74% |  |  | 12 (from 3b, 82%) |
| 8  | from 2c, 85% |  |  | 13 (from 3c, 84%) |
| 9  | from 2d, 88% |  |  | 14 (from 3d, 31%) |
| 10 | from 2e, 77% |  |  | 15 (from 3e, 85%) |
To explore the interconversion reactivity of the tautomerization, the solvent scope was first examined by using 7-aminopyrazolopyrrolopyridine-6,8-dione 2f. Compound 2f was screened and refluxed in the various solvents including CH$_2$Cl$_2$, THF, EtOH, MeCN, toluene, dioxane, and DMSO for 24 h. However, the reactions in CH$_2$Cl$_2$, EtOH, toluene recovered the starting material 2f without conversion happening (Table 3 entries 1–3). The use of polar THF, MeCN, dioxane, and DMSO led to lower interconversion ratios of 2f/3f from 93/7 to 88/12 (Table 3, entries 4–7). Subsequently, Brønsted–Lowry acids including acetic acid (AcOH), methanesulfonic acid (TsOH), methanesulfonic chloride (TsCl), and trifluoroacetic acid (TFA) were studied for the interconversion reaction at reflux for 4 h (Entries 8–11, Table 3). Several experimental observations are worthy to discuss: we firstly found that the conversion ratios were improved under acidic condition (Entries 8–11, Table 3). Secondly, under the strong acid such as trifluoroacetic acid (pKa = 0.30), p-toluenesulfonic acid (TsOH, pKa = −1.9), and methanesulfonic chloride (TsCl), the low conversion ratio and decomposed products were observed (Entries 8–10, Table 3).

**Table 3.** Derivatization results of N-aminophthalimides 2a–e and phthalazine 1,4-diones 3a–e with Vilsmeier reagent.

| Entry | S.M. | Solvent | Reaction Time (h) | Product | Ratio of 2f/3f$^a$ |
|-------|------|---------|------------------|---------|--------------------|
| 1     | 2f   | CH$_2$Cl$_2$ | 24               | 3f      | non-conversion     |
| 2     | 2f   | Toluene   | 24               | 3f      | non-conversion     |
| 3     | 2f   | EtOH      | 24               | 3f      | non-conversion     |
| 4     | 2f   | THF       | 24               | 3f      | 88/12              |
| 5     | 2f   | CH$_2$CN  | 24               | 3f      | 93/7               |
| 6     | 2f   | Dioxane   | 24               | 3f      | 91/9               |
| 7     | 2f   | DMSO      | 24               | 3f      | 89/11              |
| 8     | 2f   | TsOH      | 4 (pKa = −1.9)   | 3f      | 61/39              |
| 9     | 2f   | TsCl      | 4                | 3f      | 56/44              |
| 10    | 2f   | TFA       | 4 (pKa = 0.30)   | 3f      | 54/46              |
| 11    | 2f   | AcOH      | 4 (pKa = 4.76)   | 3f      | 6/94               |

$^a$ The ratio was identified by $^1$H-NMR.

For further investigations, the timed programming of the thermodynamic conversion of compound 2f was carried out under acetic acid (AcOH) solution and shown in Figure 4. The reaction mixture was sampled at 1.5, 2.3, 3.5, and 5 h and detected by the $^1$H-NMR spectroscopic method. This result showed that compound 2f was gradually converted to the thermodynamic stable product 3f (Figure 4). Finally, transformation reaction was equilibrated at reflux for more than 5 h, and the conversion ratio was obtained proximately 6/94 (2f/3f, Entry 11 of Table 4 and Figure 4). Based on the above experimental result, acetic acid was conceived as the best acidic solvent with 6/94 conversion ratio. Fortunately, 2f can be successfully and smoothly transformed to more thermodynamically stable product 3f by refluxing in acidic medium [40,41]. To further demonstrate the reliable of conversion procedure, N-aminophthalimides 2a–e were also used as starting materials at reflux for 8–9 h. Fortunately, compounds 2a–e can be smoothly transformed to give the corresponding thermodynamically pyrazolopyridopyridazine diones 3a–e under acetic acid solvent, with the ratio of 2a–e/3a–e from 6/94 to 1/99 (Table 4).
Figure 4. (a) $^1$H NMR spectrum of the beginning of the reaction ($^1$H NMR of compound 2f). (b–d) Reaction at reflux for 1.5, 2.3, and 3.5 h ($^1$H NMR of compounds 2f and 3f; the ratios of $2f/3f = \sim 72/28, 48/52, \text{and } 36/64$). (e) Reaction at reflux for 5 h ($^1$H NMR of compounds 3f; the ratios of $2f/3f = \sim 6/94$).

Table 4. The conversion results between N-aminophthalimide 2a–e and pyrazolopyridopyridazine dione 3a–e.

| Entry | S.M. | Reaction Time (h) | Product | 2a–e/3a–e$^a$ |
|-------|------|------------------|---------|----------------|
| 1     | ![2a](image) | 8                | ![3a](image) | 1/99           |
| 2     | ![2b](image) | 9                | ![3b](image) | 3/97           |
| 3     | ![2c](image) | 10               | ![3c](image) | 6/94           |
| 4     | ![2d](image) | 11               | ![3d](image) | 5/95           |
| 5     | ![2e](image) | 3                | ![3e](image) | 4/96           |

$^a$ The ratio of 2/3 was determined by crude $^1$H-NMR.
3. Experimental Section

3.1. General Procedure

All reagents were purchased commercially. All reactions were carried out under argon or nitrogen atmosphere and monitored by TLC. Flash column chromatography was carried out on silica gel (230–400 mesh). Analytical thin-layer chromatography (TLC) was performed using pre-coated plates (silica gel 60 F-254) purchased from Merck Inc. Flash column chromatography purification was carried out by gradient elution using n-hexane in ethyl acetate (EtOAc) unless otherwise stated. 1H NMR spectra were recorded at 400 or 500 MHz and 13C NMR spectra were recorded at 100 or 125 MHz, respectively, in CDCl3, DMSO-d6, or D2O solvent. The standard abbreviations s, d, t, q, and m refer to the singlet, doublet, triplet, quartet, and multiplet, respectively. Coupling constant (J), whenever discernible, has been reported in Hz. Infrared spectra (IR) were recorded in neat solutions or solids; and mass spectra were recorded using electron impact or electrospray ionization techniques. The reported wavenumbers are referenced to the polystyrene 1601 cm⁻¹ absorption. ESI-MS analyses were performed on an Applied Biosystems API 300 mass spectrometer. High-resolution mass spectra were obtained from a JEOL JMS-HX110 mass spectrometer.

3.2. Standard Procedure for Synthesis of N-Aminophthalimides 2a–f

Standard procedure for synthesis of N-aminophthalimides 2a–f. The reliable procedure involved the treatment of isobenzofuran-1,3-diones (1a–c), isoindoline-1,3-dione (1d), fur[3,4-b] pyrazine-5,7-dione (1e), or 1H-pyrrolo[3,4-c] pyridine-1,3-dione (1f, 1.0 equiv.) with monohydrate hydrazine (5.0 equiv.) in EtOH/H2O (2/1, 10 mL) at 0 °C or −20 °C to room temperature within 4 h. When the reaction was completed, the reaction mixture was added water (10 mL) for precipitation. The precipitate was filtered, washed with cold water (10 mL) and n-hexane/EA (1/2, 15 mL) to give the corresponding crude N-aminophthalimides 2a–f. The crude desired products 2a–f were recrystallized in aceton/THF (1/4) solution to obtain the pure N-aminophthalimides 2a–f in 81–94% yields. The low solubility of the compounds 2a–f made the 13C-NMR characterization of quaternary and carbonyl carbons of these substrates unclear [28].

N-Aminophthalimide (2a) [42]: White solid; 92% yield; mp 202–205 °C; 1H NMR (DMSO-d6, 400 MHz) δ 7.83 (dd, J = 5.8, 3.4 Hz, 2H, ArH), 8.05 (dd, J = 5.8, 3.4 Hz, 2H, ArH); 13C NMR (DMSO-d6, 100 MHz) δ 123.28 (2 × C), 130.53 (2 × C), 134.81 (2 × C), 167.36 (2 × C); FT-IR (KBr): 3482, 3341, 3262, 3093, 1778, 1719, 1605, 1468, 1409, 1291, 1197, 1091, 1075, 1020, 918, 800, 718, 526 cm⁻¹; EIMS m/z: 162 (M⁺, 100), 105 (12), 77 (12), 76 (26), 50 (11); HRMS (EI) m/z: [M⁺] Calcd for C8H6N2O2: 162.0429; Found: 162.0425.

N-Amino-4,5-difluorophthalimide (2b): White solid; 82% yield; mp 288–290 °C; 1H NMR (D2O, 500 MHz) δ 7.40 (t, J = 9.38 Hz, 2H, ArH); 13C NMR (D2O, 125 MHz) δ 116.43 (dd, J = 12.98, 6.09 Hz, 2 × C), 134.91 (2 × C), 148.62 (d, J = 14.78 Hz), 150.16 (d, J = 14.78 Hz), 175.06 (2 × C); FT-IR (KBr): 3358, 3290, 3072, 2593, 1658, 1597, 1495, 1372, 1182, 1094, 1090, 788, 743 cm⁻¹; EIMS m/z: 198 (M⁺, 100), 141 (24), 140 (83), 113 (14), 112 (33); HRMS (EI) m/z: [M⁺] Calcd for C8H6F2N2O2: 198.0241; Found: 198.0233.

N-Amino-4,5-dichlorophthalimide (2c): White solid; 81% yield; mp 302–305 °C; 1H NMR (DMSO-d6, 400 MHz) δ 7.72 (s, 1H, ArH), 7.84 (s, 1H, ArH); 13C NMR (DMSO-d6, 100 MHz) δ 130.36, 131.12, 132.08, 132.25, 132.57, 141.90, 164.74, 169.22; FT-IR (KBr): 3466, 3321, 3220, 3027, 2646, 1653, 1619, 1521, 1393, 1356, 1308, 1106, 1022, 930, 809, 782, 613 cm⁻¹; EIMS m/z: 232 (M⁺ + 2, 64), 230 (M⁺ + 100), 174 (46), 173 (12), 172 (72), 146 (13), 144 (19), 109 (19), 74 (17); HRMS m/z: [M⁺] Calcd for C9H6Cl2N2O2: 229.9650; found: 229.9653.

N-Amino-2,3-pyrazinedicarboxylphthalimide (2d) [42]: Brown solid; 82% yield; mp 220–222 °C; 1H NMR (D2O, 400 MHz) δ 8.59 (s, 2H, ArH); 13C NMR (D2O, 100 MHz) δ 143.28 (2 × C), 149.18 (2 × C), 172.29 (2 × C); FT-IR (KBr): 3430, 3282, 3164, 2936, 2750, 2636, 1679, 1621, 1353, 1161, 1107, 975, 825 cm⁻¹. EIMS m/z: 164 (M⁺, 36), 150 (25), 124 (40), 106 (76), 82 (31), 77 (37).
80 (100), 79 (30), 78 (56), 53 (69), 52 (95), 51 (52). HRMS m/z: [M]+ calcd for C₈H₆N₄O₂: 164.0334; found: 164.0338.

*Naphthalene-2,3-dicarboxylic hydrazide (2e):* Yellow solid; 94% yield; mp 298–300 °C; ¹H NMR (DMSO-d₆, 400 MHz) δ 7.51–7.56 (m, 2H, ArH), 7.92–7.96 (m, 2H, ArH), 8.11 (s, 1H, ArH), 8.16 (s, 1H, ArH); ¹³C NMR (DMSO-d₆, 100 MHz) δ 127.12, 127.52, 128.32, 128.48, 128.68, 128.87, 132.17, 132.32, 133.31, 137.68, 168.21, 171.85; FT-IR (KBr): 3466, 3429, 3304, 3190, 1640, 1538, 1468, 1386, 1309, 1051, 899, 809, 758, 481 cm⁻¹; EIMS m/z: 213 (14), 212 (M⁺, 100), 155 (10), 154 (45), 127 (14), 126 (39); HRMS m/z: [M]+ calcd for C₁₂H₈N₂O₂: 212.0586; found: 212.0578.

7-Amino-1,3-diphenylpyrazolo[3,4-b]pyrrolo[3,4-d]pyridine-6,8(3H,7H)-dione (2f) [28]: White solid; 83% yield; mp 170–171 °C; ¹H NMR (DMSO-d₆, 400 MHz) δ 7.82 (d, J = 8.08 Hz, 2H, ArH), 7.60–7.55 (m, 5H, ArH), 7.60–7.65 (m, 4H, ArH), 8.25 (d, J = 8.08 Hz, 2H, ArH), 8.82 (s, 1H, ArH).

3.3. Standard Procedure for Synthesis of Phthalazine 1,4-Diones 3a–f

The reliable procedure involved the treatment of isobenzofuran-1,3-diones (1a–c), isoindoline-1,3-dione (1d), furo[3,4-b]pyrazine-5,7-dione (1e), or 1H-pyrrrolo[3,4-c]pyridine-1,3-dione (1f, 1.0 equiv.) with monohydrate hydrazine (~40 equiv.) in EtOH solution (2.0 mL) at room temperature or in neat at reflux for 4 h. When the reaction was completed, the reaction mixture was added water (10 mL) for precipitation. The precipitation was filtered, washed with cold water (10 mL) and n-hexane/EA (1/2, 15 mL) to give the corresponding crude phthalazine 1,4-diones 3a–f. The crude desired products 3a–f were recrystallized in acetone/THF (1/4) solution to obtain the pure phthalazine 1,4-diones 3a–f in 83–91% yields. The low solubility of the compounds 3a–f made the ¹³C-NMR characterization of quaternary and carbonyl carbons of these substrates unclear [28].

2,3-Dihydro-phthalazine-1,4-dione (3a) [43]: White solid; 89% yield; mp 227–229 °C; ¹H NMR (DMSO-d₆, 400 MHz) δ 7.82 (dd, J = 5.93, 3.30 Hz, 2H, ArH), 8.06 (dd, J = 5.89, 3.28 Hz, 2H, ArH); ¹³C NMR (DMSO-d₆, 100 MHz) δ 125.78 (2 × C), 128.68 (2 × C), 132.35 (2 × C), 156.41 (2 × C); FT-IR (KBr): 3461, 3207, 1661, 1632, 1543, 1314, 1293, 1189, 1067, 899, 809, 758, 481 cm⁻¹; EIMS m/z: 199 (13), 198 (M⁺, 100), 141 (23), 140 (75), 113 (17), 112 (30), 63 (13); HRMS m/z: [M]+ calcd for C₈H₆N₂O₂: 198.0241; found: 198.0234.

2,3-Dihydrophthalazine-1,4-dione (3b): White solid; 85% yield; mp 220–222 °C; ¹H NMR (DMSO-d₆, 400 MHz) δ 7.99 (t, J = 9.11 Hz, 2H, ArH); ¹³C NMR (DMSO-d₆, 100 MHz) δ 114.38 (2 × C), 126.58 (2 × C), 151.48 (d, J = 16.10 Hz, 2C), 154.61 (2 × C); FT-IR (KBr): 3490, 3180, 3070, 2610, 1660, 1590, 1511, 1460, 1354, 1303, 1189, 1067, 899, 804, 565 cm⁻¹; EIMS m/z: 232 (M⁺, 229), 231 (M⁺ + 1, 17) 230 (M⁺, 100), 174 (46), 173 (12), 172 (72), 146 (13), 144 (19), 109 (19), 74 (17); HRMS m/z: [M]+ calcd for C₈H₆Cl₂N₂O₂: 229.9650; found: 229.9643.

7-Dihydropyrazino[2,3-d]pyridazine-5,8-dione (3d) [44]: Brown solid; 83% yield; mp 262–270 °C; ¹H NMR (DMSO-d₆, 400 MHz) δ 7.71 (dd, J = 6.29, 3.27 Hz, 2H, ArH), 8.25 (dd, J = 6.28, 3.28 Hz, 2H, ArH), 8.72 (s, 2H, ArH); ¹³C NMR (DMSO-d₆, 100 MHz) δ 125.13 (2 × C), 128.16 (2 × C), 128.69 (2 × C), 127.20 (2 × C), 126.49 (2 × C), 126.84 (2 × C), 129.66 (2 × C), 134.54 (2 × C), 156.22 (2 × C); FT-IR (KBr): 3461, 1663,
1,3-Diphenyl-7,8-dihydro-3H-pyrazole [4’,3’,5,6]-pyridine-6,9-dione (3f) [28]:
white solid; 84% yield; mp 292–295 °C; 1H NMR (DMSO-d$_6$, 600 MHz) δ 7.43–7.47 (m, 4H, ArH), 7.60–7.64 (m, 4H, ArH), 8.20 (d, J = 7.88 Hz, 2H, ArH), 9.43 (s, 1H, ArH).

3.4. Standard Procedure for Preparation of Amidination Products 4 and 6–10 from N-Aminophthalimides 2a–f with Vilsmeier Reagent (POCl$_3$/DMF)

The reliable procedure that involved N-aminophthalimides 2a–f (1.0 equiv.) was individually treated with ~3.0 equivalent amount of POCl$_3$ in N,N-dimethylformamide solution (DMF, 2.0 mL) at 50 °C or 65 °C for 0.5–4 h. When the reaction was completed, the reaction mixture was added to saturate sodium bicarbonate (15 mL) and extracted with dichloromethane (15 mL). The organic extracts were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residues were purified by column chromatography on silica gel to give the corresponding amidination products 4 in 89% yield and 6–10 in 74–88% yields.

N’-(6,8-Dioxo-1,3-diphenyl-6,8-dihydropyrazolo[3,4-b]pyrrolo[3,4-d]pyridin-7(3H)-yl)-N,N-dimethylformimidamide (4): Brown solid; 89% yield; mp 225–227 °C; 1H NMR (CDCl$_3$, 400 MHz) δ 2.97 (s, 3H, NMe), 3.02 (s, 3H, NMe), 7.37 (t, J = 7.36 Hz, 1H, ArH), 7.48–7.50 (m, 30, 3H, ArH), 7.54 (t, J = 7.74 Hz, 2H, ArH), 7.70 (s, 1H, ArH), 7.87 (d, J = 4.40 Hz, 2H, ArH), 8.24 (d, J = 8.00 Hz, 2H, ArH), 9.03 (s, 1H, ArH); 13C NMR (CDCl$_3$, 100 MHz) δ 33.83, 41.06, 108.85, 119.70, 122.21 (2 × C), 127.20, 127.90 (2 × C), 129.14 (2 × C), 129.37, 129.82 (2 × C), 131.52, 133.65, 138.40, 143.04, 146.08, 153.77, 161.77, 163.79, 165.45; FT-IR (KBr): 3064, 2923, 2852, 1654, 1537, 1485, 1275, 1266, 1193 cm$^{-1}$; EIMS m/z: 411 (25), 410 (M$^+$, 100), 341 (29), 340 (87), 339 (52), 268 (14), 77 (31); HRMS calcd for C$_{23}$H$_{18}$N$_2$O$_2$: 410.1491; found: 410.1482.

N’-(1,3-Dioxo-1,3-dihydro-2H-isindol-2-yl)-N,N-dimethyliminofomamide hydrochloride (6): Yellow solid; 88% yield; mp 177–179 °C; 1H NMR (CDCl$_3$, 400 MHz) δ 5.02 (s, 6H, N(CH$_3$)$_2$), 7.66 (dd, J = 5.37, 3.03, 2H, ArH), 7.75 (s, 1H), 7.79 (dd, J = 5.42, 3.09, 2H, ArH); 13C NMR (CDCl$_3$, 100 MHz) δ 34.80, 41.10, 123.01 (2 × C), 123.58 (2 × C), 130.77 (2 × C), 133.77 (2 × C), 161.52, 166.38 (2 × C); FT-IR (KBr): 3446, 2933, 1699, 1620, 1321, 1138, 706 cm$^{-1}$; EIMS m/z: 218 (12), 217 (M$^+$, 100), 148 (19), 130 (27), 105 (17), 104 (22), 90 (11), 76 (29), 71 (41), 70 (21); HRMS m/z: [M]$^+$ calcd for C$_{11}$H$_{11}$N$_2$O$_2$: 217.0851; found: 217.0842.

N’-(1,3-Dixo-5,6-difluoro-2H-isindolin-2-yl)-N,N-dimethylformimidamide (7): Light yellow solid; 74% yield; mp 183–185 °C; 1H NMR (CDCl$_3$, 400 MHz) δ 2.88 (s, 3H, NMe), 2.96 (s, 3H, NMe), 7.69 (t, J = 8.96 Hz, 2H, ArH), 8.04 (s, 1H); 13C NMR (CDCl$_3$, 100 MHz) δ 38.31, 36.98, 119.75 (dd, J = 13.4, 7.63 Hz, 2 × C), 129.46 (t, J = 4.77 Hz, 2 × C), 150.11 (d, J = 14.45 Hz), 152.68 (d, J = 14.31 Hz), 163.68, 168.39 (2 × C); FT-IR (KBr): 3048, 2919, 1695, 1620, 1450, 1355, 1148, 818 cm$^{-1}$; EIMS m/z: 254 (13), 253 (M$^+$, 100), 166 (20), 141 (25), 140 (40), 139 (16), 126 (22), 125 (12), 113 (13), 112 (52), 111 (20), 109 (16), 97 (23), 95 (17), 85 (16), 83 (21), 81 (17); HRMS m/z: [M]$^+$ calcd for C$_{11}$H$_{12}$F$_2$N$_2$O$_2$: 253.0663; found: 253.0657.

N’-(1,3-Dioxo-5,6-dichloro-2H-isindolin-2-yl)-N,N-dimethylformimidamide (8): Light orange solid; 85% yield; mp 192–194 °C; 1H NMR (CDCl$_3$, 400 MHz) δ 3.04 (s, 6H, N(CH$_3$)$_2$), 7.74 (s, 1H), 7.87 (s, 2H, ArH); 13C NMR (CDCl$_3$, 100 MHz) δ 34.80, 41.07, 125.09 (2 × C), 129.90 (2 × C), 138.54 (2 × C), 161.35, 164.42 (2 × C); FT-IR (KBr): 3092, 3024, 2926, 1773, 1705, 1624, 1345, 1145, 774 cm$^{-1}$; EIMS m/z: 287 (M$^+$ + 2, 61), 286 (M$^+$ + 1, 12), 285 (M$^+$, 100), 198 (13), 175 (12), 174 (14), 173 (22), 172 (20), 146 (16), 144 (24), 109 (11), 71 (98), 70 (36), 69 (10); HRMS m/z: [M]$^+$ calcd for C$_{11}$H$_{13}$Cl$_2$N$_2$O$_2$: 258.0072; found: 258.0064.

N’-(1,3-Dioxo-5,7-dihydro-6H-pyrrolo[3,4-b]pyrazin-6-yl)-N,N-dimethylformimidamide (9): Light yellow solid; 88% yield; mp 219–221 °C; 1H NMR (CDCl$_3$, 400 MHz) δ 3.03 (s, 3H, NMe), 3.05 (s, 3H, NMe), 7.81 (s, 1H), 8.84 (s, 2H, ArH); 13C NMR (CDCl$_3$, 100 MHz) δ 34.83, 41.18, 146.17 (2 × C), 148.52 (2 × C), 161.28, 162.31 (2 × C); FT-IR (KBr): 1654, 1289, 1545, 1293, 1104, 825 cm$^{-1}$; EIMS m/z: 220 (12), 219 (M$^+$, 56), 193 (10), 179 (13), 178 (13), 169 (12), 168
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(12), 167 (14), 165 (11), 155 (11), 152 (11), 151 (26), 150 (14), 149 (23), 147 (11), 141 (12), 139 (15), 137 (13), 135 (11), 127 (12), 125 (21), 123 (19), 121 (11), 119 (11), 115 (14), 113 (14), 112 (14), 111 (36), 110 (11), 109 (27), 107 (15), 106 (16), 105 (16), 99 (17), 98 (13), 97 (52), 96 (16), 95 (36), 93 (12), 91 (27); HRMS m/z: [M]+ calc for C₉H₆NO₂: 219.0756; found: 219.0748.

N′-(1,3-Dioxo-5,6-dihydro-2H-benzof[f]isooindol-2-yl)-N,N-dimethylformimidamide (10): Light yellow solid; 77% yield; mp 199–201 °C; ¹H NMR (CDCl₃, 400 MHz) δ 3.05 (s, 3H, NMe), 7.64–7.69 (m, 2H, ArH), 7.84 (s, 1H), 7.99–8.02 (m, 2H, ArH), 8.28 (s, 2H, ArH); ¹³C NMR (CDCl₃, 100 MHz) δ 34.89, 41.10, 124.33 (2 × C), 126.68 (2 × C), 128.99 (2 × C), 130.20 (2 × C), 135.45 (2 × C), 161.23, 166.00 (2 × C) cm⁻¹; FT-IR (KBr): 2918, 2807, 1757, 1693, 1621, 1521, 1425, 1411, 1321, 1154, 1118, 1004, 900, 754, 479 cm⁻¹; EIMS m/z: 268 (19), 267 (M⁺, 100), 225 (13), 210 (10), 198 (26), 197 (49), 180 (28), 155 (64), 154 (24), 153 (20), 152 (13), 140 (21), 127 (26), 126 (74), 71 (17), 57 (11); HRMS m/z: [M]+ calc for C₁₅H₁₃N₃O₂: 267.1008; found: 267.1015.

3.5. Standard Procedure for Preparation of Chlorination Products 5, and 11–15 from Phthalazine 1,4-Diones 3a–f with Vilsmeier Reagent (POCl₃/DMF)

The reliable procedure that involved phthalazine 1,4-diones 3a–f (1.0 equiv.) was individually treated with ~3.0 equivalent amount of POCl₃ in N,N-dimethylformamide solution (DMF, 2.0 mL) at 65 °C or 80 °C for 2–4 h. When the reaction was completed, the reaction mixture was added to saturate sodium bicarbonate (15 mL) and extracted with dichloromethane (15 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residues were purified by column chromatography on silica gel to give the corresponding chlorinated products 5 in 80% yield and 11–15 in 31–90% yields.

6,9-Dichloro-1,3-diphenyl-3H-pyrazolo[4′,3′,5,6]pyridolo[3,4-d]pyrazidine (5): Light yellow solid; 80% yield; mp 196–197 °C; ¹H NMR (CDCl₃, 500 MHz) δ 7.46 (t, J = 7.43 Hz, 1H, ArH), 7.49–7.51 (m, 3H, ArH), 7.57–7.60 (m, 4H, ArH), 8.17 (dd, J = 8.60, 1.09 Hz, 2H, ArH), 9.68 (s, 1H, ArH); ¹³C NMR (CDCl₃, 125 MHz) δ 103.92, 118.46, 123.39 (2 × C), 127.91, 127.95 (2 × C), 128.19, 129.13, 129.33 (2 × C), 130.01 (2 × C), 135.22, 137.87, 147.79, 149.88, 151.00, 152.05, 153.49; FT-IR (KBr): 3157, 3000, 2896, 2875, 1671, 1346, 1289, 1157, 993, 775, 664 cm⁻¹; EIMS m/z: 395 (12), 394 (17), 393 (M⁺ + 2, 65), 392 (36), 391 (M⁺, 99), 390 (20), 356 (20), 321 (35), 320 (60), 288 (14), 263 (12), 244 (33), 218 (17), 91 (19), 77 (100); HRMS calc. For C₂₀H₁₇Cl₂N₅: 391.0392; found: 391.0397.

1,4-Dichlorophthalazine (11): Yellow solid; 90% yield; mp 162–164 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.74–7.76 (m, 2H, ArH), 7.85–7.87 (m, 2H, ArH); ¹³C NMR (CDCl₃, 100 MHz) δ 125.86 (2 × C), 127.21 (2 × C), 134.49 (2 × C), 155.03 (2 × C); IR (KBr): 3157, 3000, 2896, 2875, 1671, 1346, 1289, 1157, 993, 775, 664 cm⁻¹; EIMS m/z: 202 (M⁺ + 4, 10), 200 (M⁺ + 2, 63), 198 (M⁺, 100), 182 (25), 180 (77), 172 (17), 170 (26), 151 (17), 135 (20), 128 (14), 125 (11), 123 (29), 102 (17), 101 (11), 99 (20), 90 (11); HRMS calc. For C₁₃H₁₁Cl₂N₂: 197.9765; found: 197.9746.

1,4-Dichloro-2,3-difluorophthalazine (12): White solid; 82% yield; mp 75–76 °C; ¹H NMR (CDCl₃, 400 MHz) δ 8.09 (t, J = 8.34 Hz, 2H, ArH); ¹³C NMR (CDCl₃, 100 MHz) δ 113.97 (dd, J = 14.25, 7.66 Hz, 2 × C), 125.19 (t, J = 5.23 Hz, 2 × C), 153.50 (d, J = 16.46 Hz), 153.68 153.50 (2 × C), 153.50 (d, J = 16.39 Hz); IR (KBr): 3143, 3068, 2836, 2782, 2781, 2611, 1625, 1571, 1539, 1511, 1389, 1218, 1161, 1104, 893, 814 cm⁻¹; EIMS m/z: 238 (M⁺ + 4, 11), 236 (M⁺ + 2, 78), 234 (M⁺, 100), 233 (30), 218 (12), 216 (36), 206 (24), 206 (18), 171 (27), 164 (30), 159 (18), 138 (11), 136 (16), 124 (10), 88 (15), 75 (11); HRMS calc. For C₁₃H₁₂Cl₂F₂: 233.9563; found: 233.9568.

1,4,6,7-Tetrachlorophthalazine (13): Light orange solid; 84% yield; mp 135–136 °C; ¹H NMR (CDCl₃, 400 MHz) δ 8.40 (s, 2H, ArH); ¹³C NMR (CDCl₃, 100 MHz) δ 126.07 (2 × C), 127.39 (2 × C), 140.2 (2 × C), 153.45 (2 × C); IR (KBr): 3094, 1596, 1535, 1453, 1501, 1380, 1268, 1242, 1130, 1035, 702, 663 cm⁻¹; EIMS m/z: 270 (M⁺ + 2, 26), 270 (M⁺ + 2, 16), 268 (M⁺, 100),
266 (77), 240 (19), 238 (14), 205 (14), 203 (14), 196 (13), 84 (10); HRMS calcd. For C₈H₂Cl₄N₂: 265.8972; found: 265.8979.

6,7-Dichloropyrazino[2,3-d]pyridazine (14) [28]: Black solid; 31% yield; mp 204–206 °C; ¹H NMR (CDCl₃, 400 MHz) δ 9.14 (s, 1H, ArH), 9.17 (s, 1H, ArH) [28].

1,4-Dichlorobenzo[g]phthalazine (15): Gray solid; 85% yield; mp 212–214 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.78–7.81 (m, 2H, ArH), 8.18–8.21 (m, 2H, ArH), 8.82 (s, 2H, ArH); ¹³C NMR (CDCl₃, 100 MHz) δ 123.23 (2 × C), 126.83 (2 × C), 129.22 (2 × C), 129.79 (2 × C), 135.46 (2 × C), 155.39 (2 × C); IR (KBr): 2961, 2932, 2857, 1739, 1725, 1461, 1282, 1264, 1121, 739 cm⁻¹; EIMS m/z: 250 (M⁺ + 2, 59), 249 (M⁺ + 1, 11), 248 (M⁺, 100), 178 (31), 152 (19), 151 (18); HRMS calcd. For C₂₃H₁₈N₆O₂: 247.9908; found: 247.9906.

4. Conclusions

N-aminophthalimides 2 and phthalazine 1,4-diones 3 were successfully and selectively synthesized from isobenzo-furan-1,3-diones (1a-c), isoindoline-1,3-dione (1d), furo[3,4-b]pyrazine-5,7-dione (1e), and 1H-pyrrolo[3,4-c]pyridine-1,3-dione (1f) with monohydrate hydrazine under the different reaction condition. The structural divergence between N-aminophthalimides 2f and phthalazine 1,4-diones 3f was effectively identified via Vilsmeier reaction methodology. Furthermore, the thermodynamically transformation from N-aminophthalimides 2a–f to phthalazine 1,4-diones 3a–f was successfully found, which provides the good conversion ratio from 6/94 to 1/99 of 2a–f / 3a–f under acetic acid mediated solution.

Supplementary Materials: The following are available online, copies of ¹H and ¹³C-NMR spectra of compounds 2a–2e, 3a–3e, and 4–15, Table S1: Crystal data and structure refinement for N'-(6,8-dioxo6,8-dihydropyrazolopyrrolo-pyridine-yl)-N,N-dimethylformimidamide 4 (CCDC No. 1954819).

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Sample Availability: Samples of the compounds are available from the authors.

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