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Synthesis of 4-Substituted Phthalazin-1(2*H*)-ones from 2-Acylbenzoic Acids: Controlling Hydrazine in a Pharmaceutical Intermediate through PAT-Guided Process Development

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Supporting Information

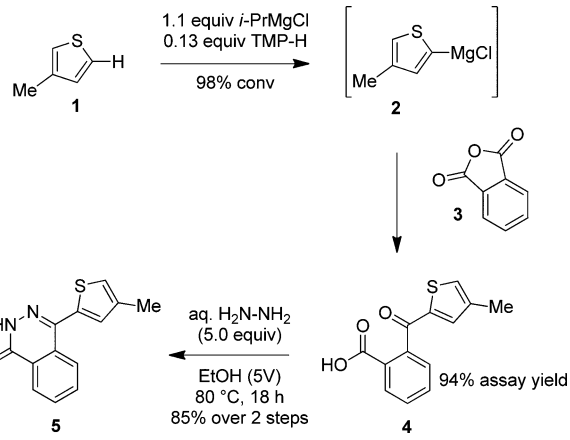
ABSTRACT: A simple one-pot, two-step process for the conversion of 2-acylbenzoic acids to phthalazin-1(2*H*)-ones was developed. A robust process was required that delivered the final isolated solid with consistently low levels of residual hydrazine, for further processing to the final drug substance. An in situ formed intermediate was critical to control reactivity and allowed for the controlled crystallization that prevented entrainment of hydrazine. Leveraging Process Analytical Technology (PAT), we investigated the reaction profile with in situ IR and Power Compensation Calorimetry (PCC) to aid development prior to a successful scale-up.

INTRODUCTION

The prevalence of phthalazin-1(2*H*)-ones have steadily increased in the pharmaceutical industry and have been components of investigational therapeutic programs for antiulcer,[1] antiasthmatic,[2] antimicrobial,[3] anti-inflammatory,[4] hypertension,[5] and obesity.[6] Literature examples for the synthesis of aryl phthalazin-1(2*H*)-ones typically begin from 2-acylbenzoic acid derivatives and rely on the use of hydrazine or substituted hydrazine derivatives as a key raw material.[7−10] In a recent development project we required a simple, scalable synthesis of phthalazin-1(2*H*)-one **5**, a key intermediate in the preparation of a clinical candidate (Scheme 1).[11] Since hydrazine is genotoxic,[12] a high degree of process control was required to ensure patient exposure would not exceed a daily exposure as defined by the staged threshold of toxicological concern (TTC).[13]

We have previously reported the preparation of 2-acylbenzoic acid **4** by reaction of the in situ-formed Grignard **2** and phthalic anhydride (**3**) (Scheme 1).[14] Subsequent elaboration of 2-acylbenzoic acid **4** with 5.0 equiv of aqueous hydrazine in 5 V (V = mL solvent/g solute) ethanol at reflux afforded phthalazin-1(2*H*)-one **5** in high yield (Scheme 1). The low solubility of **5** under the reaction conditions (1.5 mg/mL at 80 °C) led to a rapid uncontrolled crystallization and inconsistent levels of hydrazine retained in the isolated crystalline product **5** (529−3108 ppm). We hypothesized that both the superstoichiometric hydrazine and an uncontrolled reactive crystallization were the root causes of hydrazine entrainment. We looked at improving the reactivity of **4** with in situ formation of an activated intermediate and consequently

Scheme 1. Synthesis of Phthalazin-1(2*H*)-one 5 from 2-Acylbenzoic Acid



reduced hydrazine to a stoichiometric charge. Additionally, identification of a solvent system with increased solubility of **5** was required to allow for a robust isolation. This improved process achieved consistently low levels of hydrazine in isolated **5** and was characterized by in situ IR and Power Compensation Calorimetry (PCC). This process was further demonstrated in other 4-substituted phthalazin-1(2*H*)-ones.

RESULTS AND DISCUSSION

To control the level of hydrazine in the final drug substance, based on its rejection in the downstream process, we set a target of ≤110 ppm hydrazine for isolated **5**. To achieve this goal, we first investigated limiting hydrazine in the original process to a stoichiometric charge to minimize the potential for entrainment. Spontaneous crystallization occurred, however, within the first 1 h of the reaction (Scheme 2). Unfortunately, after 21 h the reaction only achieved a 66% yield of **5**. Therefore, limiting stoichiometry was not a sufficient solution so we investigated an approach that preactivated **4** as the acylimidazole.

In Situ Pre-Activation of Acylbenzoic Acid 4. We next investigated a process which involved the in situ preactivation of the starting acylbenzoic acid. The objective was to identify a

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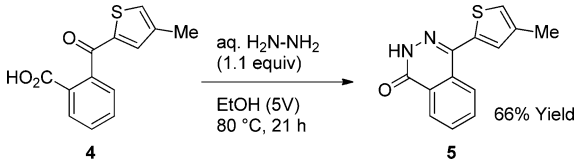
Scheme 2. Phthalazin-1(2*H*)-one Cyclization with Stoichiometric Hydrazine



reactive intermediate which rapidly reacted with stoichiometric hydrazine. 1,1-Carbonyldiimidazole (CDI) rapidly converted **4** to the intermediate acylimidazole **6**, which upon addition of hydrazine, efficiently converted to **5** (Scheme 3).[15] The reaction conditions investigated were limited to non-nucleophilic, polar aprotic solvents. When either acetonitrile (MeCN) or *N*,*N*-dimethylformamide (DMF) was employed both **4** and **6** were fully soluble; however, the solubility of product **5** differed greatly in MeCN (0.42 mg/mL at 20 °C) vs DMF (25 mg/mL at 20 °C). The low solubility of **5** in MeCN resulted in instantaneous crystallization at the beginning of the addition of hydrazine. Agglomerated crystals of **5** were observable by polarized light microscopy (PLM, Figure 1), and the final isolated product had hydrazine levels that ranged between 719 and 4275 ppm. When the reaction was performed in DMF, nucleation of **5** was not instantaneous, and crystallization was observed following completion of hydrazine addition. When **5** was isolated from the DMF crystallization, the particles were significantly less agglomerated, as observed by PLM (Figure 2), and hydrazine entrainment was consistently <110 ppm. As a result, DMF was chosen for further development.

The solubility of phthalazin-1(2*H*)-one **5** was studied in a range of pure solvents to identify a solvent combination for the crystallization conditions which would provide high product recovery and maximize the volumetric efficiency of the process. In combination with DMF, water was selected as the antisolvent because of the low solubility of **5** and the high solubility of hydrazine and imidazole in water. As shown in Figure 3, starting in 100% DMF, the addition of water to 70% DMF reduces the solubility of **5** from 25 mg/mL to 1.5 mg/mL at 20 °C.

Process Design. Our process was planned based on the hypothesis that hydrazine is rapidly consumed at an addition-controlled rate. Formation of activated acylimidazole **6** was carried out by charging 1.1 equiv of CDI in four approximately equal portions over 1 h to a solution of **4** in DMF (8 V) at 20 °C (Scheme 3). Off-gassing of CO_2 immediately followed each CDI charge, and was easily controlled by the portion-wise addition. The solution of acylimidizole was then aged for 1 h before a linear addition of 1.1 equiv of hydrazine (35 wt % aqueous). The equilibrium solubility of phthalazin-1(2*H*)-one ranged from 20−27 mg/mL and varied depending on the water activity of the end-of-reaction solution. The increased solubility

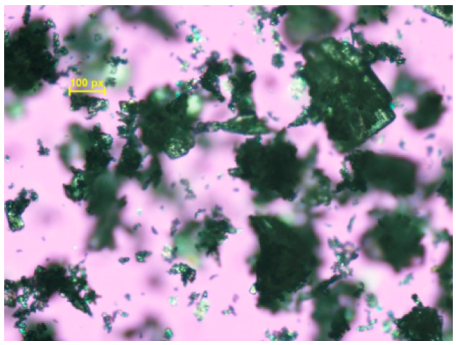


Figure 1. PLM of crystallization from MeCN (100× magnification).

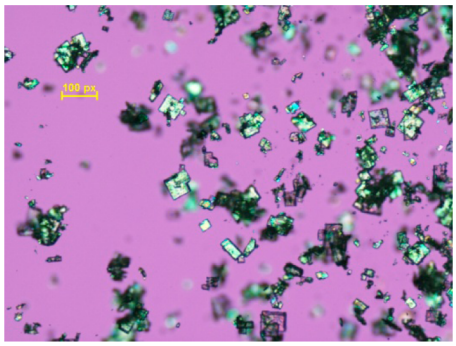


Figure 2. PLM of crystallization from DMF (100× magnification).

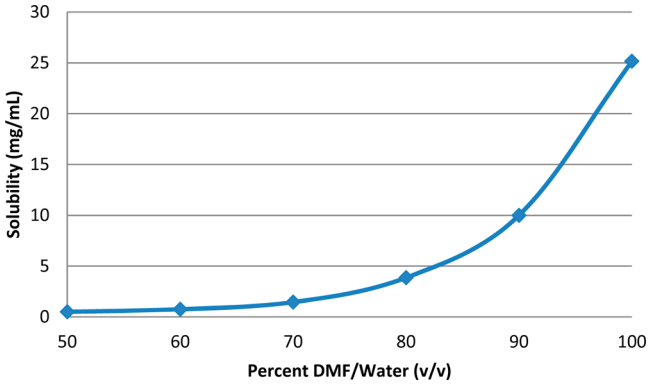
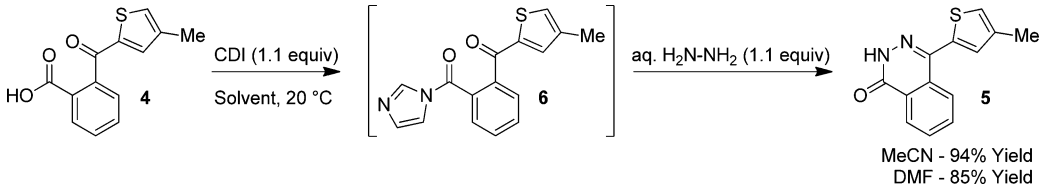


Figure 3. Solubility of **5** vs percent DMF/water (v/v).

compared to the original ethanol process ensured crystallization did not immediately occur at the initiation of hydrazine addition. Phthalazin-1(2*H*)-one **5** is in the metastable zone at the end of hydrazine addition and typically holds supersaturation until hydrazine addition is completed. Subsequent linear addition of 2.5 V water over 1.5 h lowered the supernatant concentration to <10 mg/mL furnishing product **5** in >80% isolated yield in high purity.

Scheme 3. Two-Step CDI-Meditated Phthalazin-1(2*H*)-one Formation



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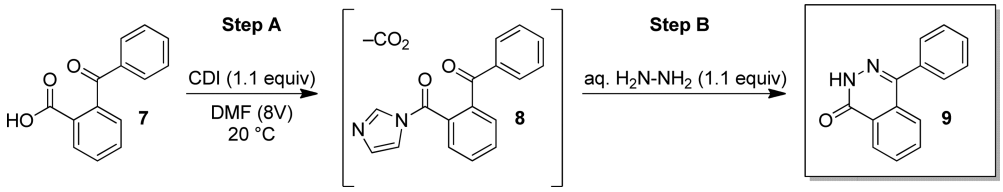
Scheme 4. CDI Mediated Phthalazin-1(2*H*)-one Synthesis



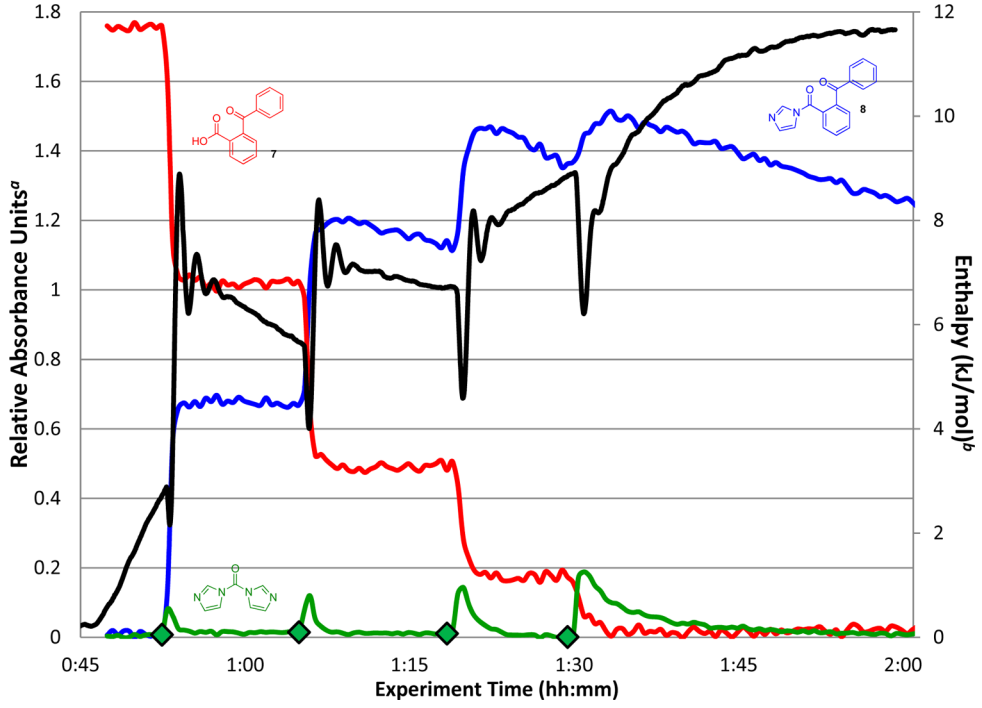


Figure 4. In situ IR and power compensation calorimetry of acylimidazole (**8**) formation, Step A[c,d]; a: left axis: red = 2-acylbenzoic acid (**7**), blue = acylimidazole (**8**); green = CDI; b: right axis: black = enthalpy uncorrected for CO_2 off-gassing; c: the symbol (green ◆) indicates charges of solid CDI; d: component trends identified using ConcIRT (Mettler-Toledo).

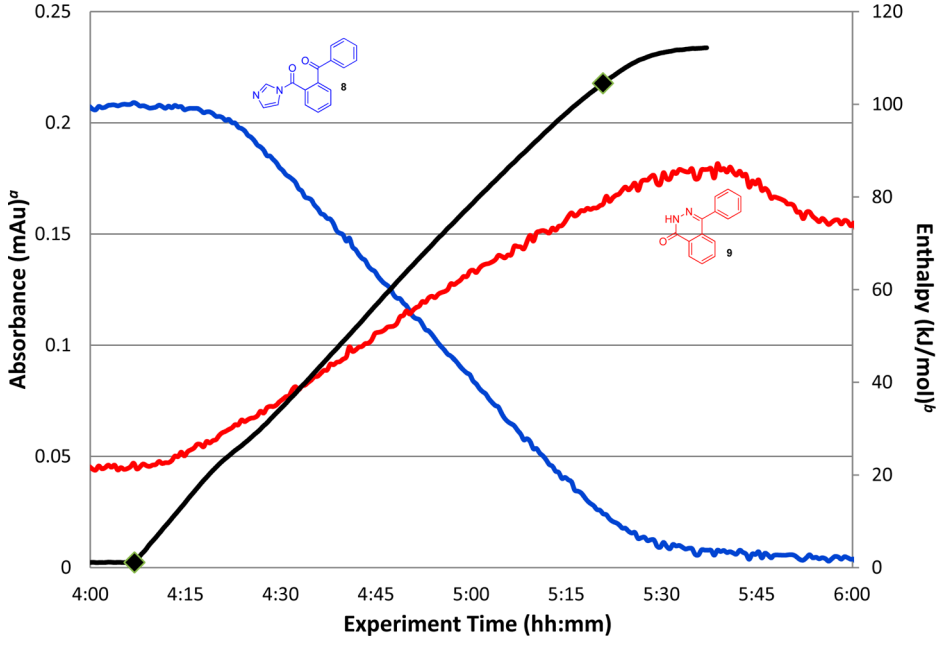


Figure 5. In situ IR and power compensation calorimetry of phthalazin-1(2*H*)-one (**9**) formation, Step B[c]; a: left axis: blue = **8** (1789 cm^{-1}, C═O), red = **9** (790 cm^{-1}, lactam N–H); b: right axis: black = enthalpy uncorrected for heat of mixing; c: the symbols (♦) indicate the duration of linear addition of hydrazine.

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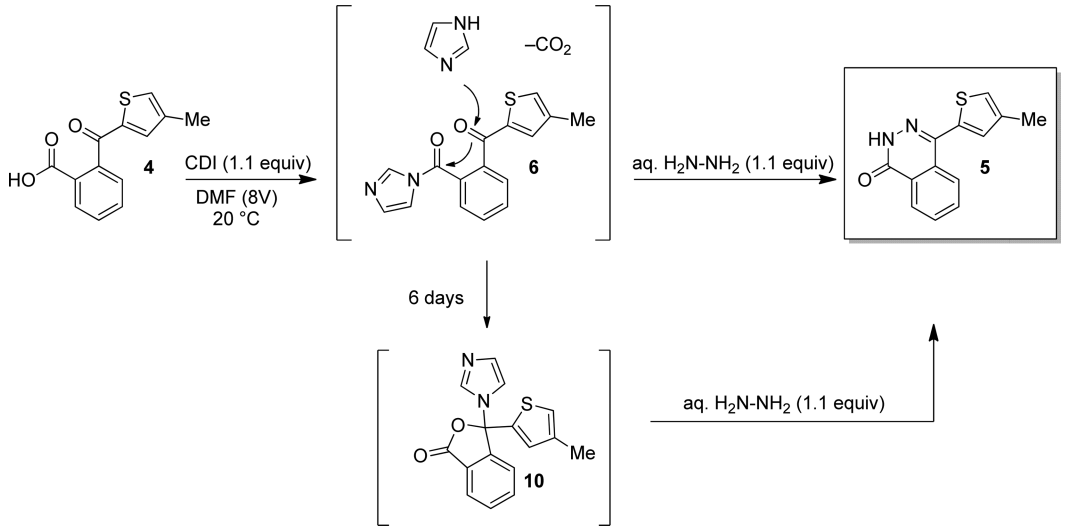
Scheme 5. Rearrangement of Acylimidazole to *N,O*-Acetal Reactive Intermediate



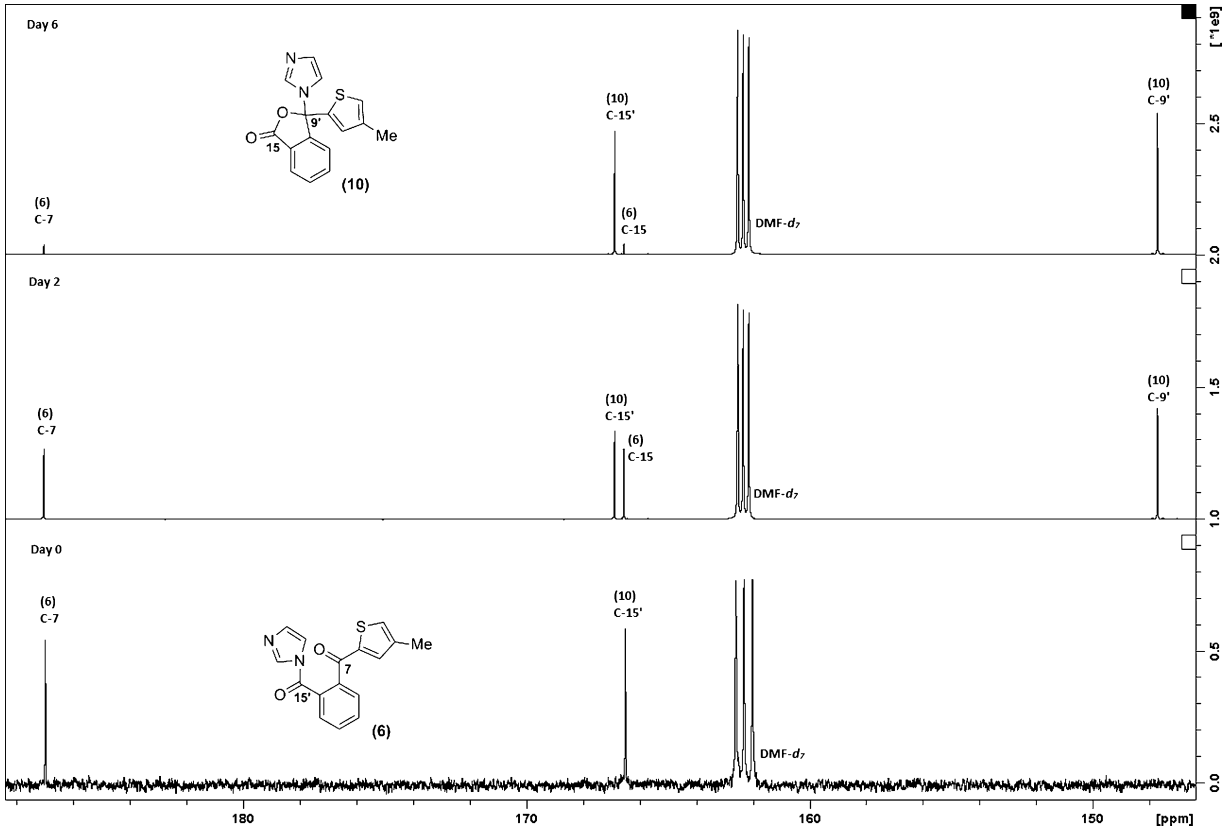


Figure 6. Rearrangement of acylimidazole to *N,O*-acetal by ^{13}C NMR (Signals are labeled with compound numbers in parentheses).

To facilitate our design, we needed to ensure hydrazine reacts at an addition-controlled rate. We leveraged in situ IR in tandem with calorimetry to understand the kinetics and thermodynamics of the two-step, one-pot chemical process and to monitor consumption of hydrazine. Phthalazin-1(2*H*)-one formation was studied in a stepwise fashion using readily available commercial 2-acylbenzoic acid **7** (Scheme 4). Experiments were monitored using a Mettler Toledo IC10 ReactIR equipped with a DiComp probe collecting 256 scans/min. Power Compensation Calorimetry (PCC)[16] experiments were performed using a Syrris Atlas Calorimeter equipped with a 250 mL vacuum jacketed reactor and a 25W heating probe; data were collected at a frequency of 1 Hz.

Acylimidiazole Formation, Step A. The ConcIRT function in the Mettler Toledo iCIR software was used to track consumption of the 2-acylbenzoic acid and CDI, and formation of acylimidazole (Figure 4). The profiles of the individual components are consistent with rapid reaction of 2-acylbenzoic acid (red) and CDI (green) to form acylimidizole (blue). The in situ IR trends are in agreement with the calorimetry data (black) collected simultaneously using PCC. Rapid heat generation was observed after each charge of solid

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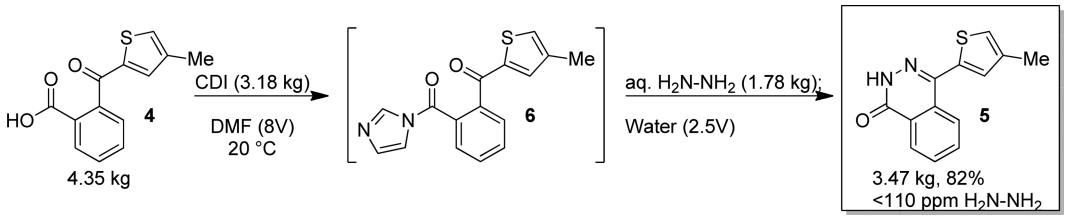
Scheme 6. Pilot-Plant Campaign



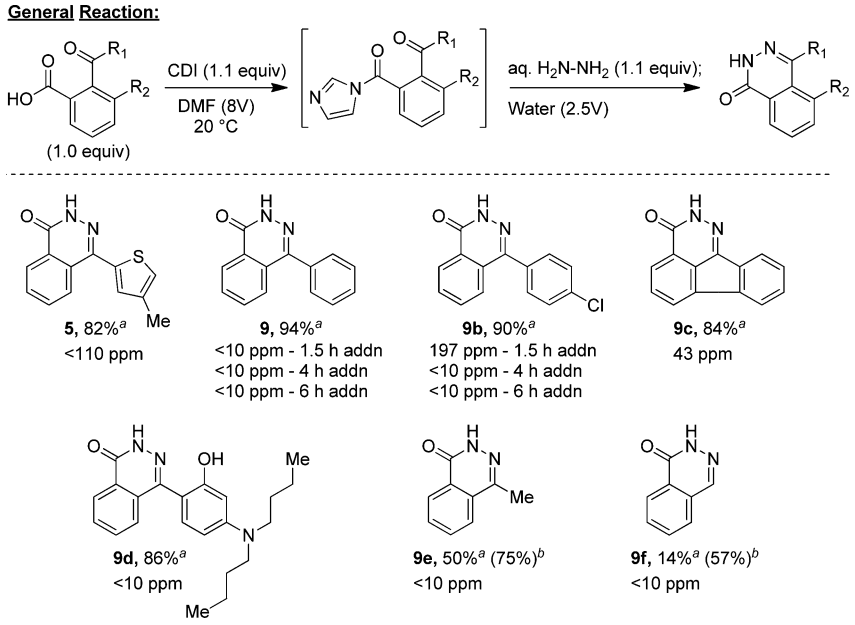


Figure 7. Substrate scope of CDI mediated synthesis of 4-substituted phthalazin-1(2*H*)-ones. (a) Isolated yield after crystallization; (b) assay yield by quantitative ^{1}H NMR.

CDI, in concert with rapid consumption of CDI. The overall enthalpy of acylimidizolide formation was 11.65 kJ/mol without correction for CO_2 liberation. Additionally, the downward sloping trend for **8** observed by in situ IR indicated that the reactive intermediate might have a stability liability that required an additional investigation (see below).

Phthalazin-1(2*H*)-one Formation, Step B. Conversion of **8** to **9** was followed by peak trending in the solvent-subtracted in situ IR (Figure 5) trace. Conversion of acylimidazole (1789 cm^{-1}) to phthalazin-1(2*H*)-one (790 cm^{-1}) was consistent with rapid consumption of hydrazine. Comparison of the calorimetry data with in situ IR trends indicated that the reaction was nearly complete at the end of the approximately 1 h hydrazine addition. The overall enthalpy of phthalazin-1(2*H*)-one formation was measured to be 112.20 kJ/mol, which was uncorrected for the heat of mixing of aqueous hydrazine and DMF.

While formation of acylimidazole **8** was facile, our study indicated potential instability of the reactive intermediate (see Figure 4). While monitoring the stability of our desired system for extended hold times, we observed the appearance of *N,O*-acetal **10** (Scheme 5).[17] We then studied the reaction of 2-acylbenzoic acid **4** and CDI in DMF-d_7 using NMR techniques to gain an understanding of *N,O*-acetal **10** formation. The extent of *N,O*-acetal formation was followed over several days, and the reaction products were completely characterized by 1-D and 2-D NMR studies (Figure 6; see Supporting Information). Data are consistent with the kinetic formation of **6** followed by rearrangement to *N,O*-acetal **10**. Examination of the downfield region of the ^{13}C spectrum allowed conversion of **6** to **10** to be tracked and required greater than 6 days at 25 °C to achieve full conversion to **10**. We then demonstrated that isolated **10** rapidly reacts with hydrazine to form phthalazin-1(2*H*)-one **5** with comparable rate and yield as **6**, which minimized the risk of a long hold time negatively impacting the batch (see Experimental Section).

Pilot Plant Campaign. With an improved understanding of the kinetic and thermodynamic profile of the phthalazin-1(2*H*)-one process, we initiated a demonstration campaign to produce the desired phthalazin-1(2*H*)-one **5** (Scheme 6). Formation of acylimidazole **6** proceeded as expected based on our development studies. Crystallization initiated at the predicted time, following complete addition of aqueous hydrazine. Phthalazin-1(2*H*)-one **5** was isolated in 82% yield (3.47 kg) as a crystalline solid, the purity was 99.7% AUC containing <110 ppm hydrazine which fell within the target for downstream processing.

Substrate Scope. The two-step CDI-mediated process was developed specifically to maximize rejection of hydrazine in the synthesis of **5**; however, we wanted to understand the synthetic limitations of the process for related phthalazin-1(2*H*)-ones. As shown in Figure 7, the process performed well to afford a variety of aryl-substituted phthalazin-1(2*H*)-ones (**5**, **9**–**9d**) tolerating a range of functional groups. Simple alkyl (**9e**) or C7–H (**9f**) phthalazin-1(2*H*)-ones would require further optimization for preparative scale; however, our process allows

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the synthesis in modest yield. The presence of a nucleophilic phenol was well-tolerated, affording **9d** in 86% isolated yield. Interestingly, the strained tetracyclic fluorenone **9c** was easily constructed and isolated in 84% yield. In all cases hydrazine was controlled to <200 ppm in the final isolated solid when a 1.5 h addition of hydrazine was employed. Compounds **9b** and **9c** both exhibit low solubility and crystallized during the 1.5 h hydrazine addition. Prolonged hydrazine addition times of 4 and 6 h were studied for compounds **9** and **9b** along with seeding and it was shown that hydrazine can be controlled to <10 ppm by minimizing the level of supersaturation for compounds with low solubility.

CONCLUSION

In summary, a safe and simple process was developed for the conversion of 2-acylbenzoic acids to phthalazin-1(2*H*)-ones using an acylimidazole as an activated intermediate. The mild conditions leveraged a fully soluble in situ-generated activated acylimidazole. The acyl imidazole was found to react with aqueous hydrazine at an addition-controlled rate which allowed hydrazine to be reduced from >5.0 equiv to 1.1 equiv. A robust crystallization was developed to control residual hydrazine levels in the isolated solid, providing a critical control point to ensure product quality and the process was successfully demonstrated on multikilogram scale.

EXPERIMENTAL SECTION

General. Reactions were conducted under an atmosphere of nitrogen with a suitable outlet to accommodate modest pressure changes. Reaction temperatures were monitored by an internal thermocouple. Reaction progress was determined by LCMS analysis of derivatized[18] reaction mixture and analysis by HPLC-MS using an XBridge C18, 3.0 mm × 50 mm, 2.5 μm column, with a 5−100% gradient method using 0.1% (v/v) formic acid/water and 0.1% (v/v) formic acid/acetonitrile as mobile phases. HRMS (ESI-TOF) spectra were obtained using Agilent 1100 systems. Melting points were determined using a TA Instruments Q200 DSC at 10 °C/min ramp. Hydrazine was monitored using a headspace GC-MS method.[19] Power compensation calorimetry (PCC) was executed in a glass-lined jacked reactor insulated with vacuum jacket. PCC temperature was maintained at a batch temperature of 20.00 ± 0.05 °C and employed a 25 W heating probe; data were collected at a frequency of 1 Hz. In situ IR experiments were conducted using a Mettler-Toledo iC10 ReactIR affixed with a DiComp probe collecting 256 scans/min.

General Procedure. Acylbenzoic acid (1.00 equiv) was charged to a reactor affixed with overhead agitation and a condenser. The reactor was inerted with nitrogen followed by the addition of 8.0 V (V = mL solvent/g acylbenzoic acid) *N,N*-dimethylformamide. The solution was agitated at 20 °C until the acylbenzoic acid was fully dissolved. Solid 1,1′-carbonyldiimidazole (1.10 equiv) was charged in 4 approximately equal portions over 20 min (CAUTION: evolution of carbon dioxide, ensure reactor is adequately vented to avoid pressure buildup). The solution was aged for approximately 0.5 h when an analytical sample was quenched into amyl amine and analyzed by LCMS to show acylbenzoic acid consumption.

A 35 wt % aqueous solution of hydrazine (1.10 equiv) was added by pump over approximately 1.5 h while maintaining the batch temperature was maintained between 20−25 °C (*CAUTION: hydrazine is acutely toxic and has a danger for cutaneous absorption. Consult the current MSDS prior to use and ensure appropriate personal protective equipment*). The slurry was aged for 12 h at 20 °C and after a 12 h hold, water (3.0 V) was added over 2 h by pump. Following a 3 h hold, the slurry was filtered by vacuum using a medium porosity sintered glass filter. The cake was washed twice with 60:40 (v/v) water: *N,N*-dimethylformamide (1.0 V) followed by a water (4.0 V) wash. The filter cake was dried on the filter by pulling dry nitrogen through the cake for 12 h whereupon phthalazin-1(2*H*)-one was isolated and characterized.

*4-Phenylphthalazin-1(2H)-one (**9**).* **9** was prepared following the general procedure employing 2-benzoylbenzoic acid (22.0 g, 97.0 mmol) as the acylbenzoic acid. 4-Phenylphthalazin-1(2H)-one (**9**) (20.29 g, 94% yield) was isolated as a colorless crystalline solid: GC-MS <10 ppm hydrazine; mp (DSC) 241.92 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ): 12.83 (s, 1H), 8.34 (t, J = 4.5 Hz, 1H), 7.88 (app t, J = 4.2 Hz, 2H), 7.66 (m, 1H), 7.59−7.52 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6, δ): 159.1, 146.3, 135.0, 133.5, 131.5, 129.2, 128.9, 128.8, 128.4, 127.9, 126.4, 126.0; HRMS-TOF (m/z): [M + H]$^+$ calcd for $C_{14}H_{11}N_2O$, 223.0866; found, 223.0873.

*4-(4-Chlorophenyl)phthalazin-1(2H)-one (**9b**).* **9b** was prepared following the general procedure employing 2-(4-chlorobenzoyl)benzoic acid (46.0 g, 176 mmol) as the acylbenzoic acid. Crystallization occurred approximately half way through the 1.5 h addition of hydrazine. 4-(4-Chlorophenyl)phthalazin-1(2*H*)-one (**9b**) (40.96 g, 90% yield) was isolated as a colorless crystalline solid: GC-MS = 197 ppm hydrazine; mp (DSC) 273.90 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ): 12.87 (s, 1H), 8.34 (m, 1H), 7.91−7.88 (m, 2H), 7.67−7.59 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6, δ): 159.1, 145.2, 133.9, 133.7, 133.6, 131.6, 131.1, 128.7, 128.5, 127.8, 126.3, 126.0; HRMS-TOF (m/z): [M + H]$^+$ calcd for $C_{14}H_{10}ClN_2O$, 257.0476; found, 257.0483.

*Indeno[1,2,3-de]phthalazin-3(2H)-one (**9c**).* **9c** was prepared following the general procedure employing 9-oxo-9H-fluorene-1-carboxylic acid (1.01 g, 4.49 mmol) as the acylbenzoic acid. Crystallization quickly occurred at the beginning of hydrazine addition. Indeno[1,2,3-de]phthalazin-3(2*H*)-one (**9c**) (0.826 g, 84% yield) was isolated as a yellow crystalline solid: GC-MS = 43 ppm hydrazine; mp (DSC) 268.13 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ): 12.73 (s, 1H), 8.18 (d, J = 7.1 Hz, 1H), 7.95 (d, J = 7.3 Hz, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.81 (app t, J = 8.2, 7.3 Hz, 1H), 7.49 (t, J = 7.2 Hz, 1H), 7.43 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ): 159.7, 146.8, 139.8, 136.0, 134.2, 133.5, 130.4, 130.2, 128.9, 125.8, 125.0, 123.9, 122.8, 121.7; HRMS-TOF (m/z): [M + H]$^+$ calcd for $C_{14}H_9N_2O$, 221.0709; found, 221.0717.

*4-(4-(Dibutylamino)-2-hydroxyphenyl)phthalazin-1(2H)-one (**9d**).* **9d** was prepared following the general procedure employing 2-(4-(dibutylamino)-2-hydroxybenzoyl) benzoic acid (20.0 g, 54.1 mmol) as the acylbenzoic acid. 4-(4-(Dibutylamino)-2-hydroxyphenyl)phthalazin-1(2*H*)-one (**9d**) containing 0.84 equiv *N,N*-dimethylformamide (19.84 g, 86% purity adjusted yield) was isolated as a yellow solid: GC-MS <10 ppm hydrazine; mp (DSC) 85.03 °C, 99.20 °C, 167.38 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ): 12.56 (s, 1H), 9.17 (s, 1H), 8.26 (m, 1H), 7.80 (ddd, J = 7.6, 5.2, 1.8 Hz, 2H), 7.50 (m, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.26−6.22 (m, 2H), 3.25 (t, J = 7.8 Hz, 4H), 1.58−1.51 (m, 4H), 1.34 (dd, J = 14.9, 7.5 Hz, 4H), 0.94 (t, J = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6, δ): 159.4, 156.1, 149.7, 145.9, 132.8, 131.4, 130.9, 130.4, 127.8,

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127.4, 125.2, 109.5, 103.0, 98.1, 50.0, 29.1, 19.7, 13.8; HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_{22}H_{28}N_3O_2$, 366.2176; found, 366.2185.

*4-Methylphthalazin-1(2H)-one (**9e**).* **9e** was prepared following the general procedure employing 2-acetylbenzoic acid (25.0 g, 152 mmol) as the acylbenzoic acid. 4-Methylphthalazin-1(2*H*)-one (**9e**) (12.3 g, 50% yield) was isolated as a colorless crystalline solid: GC-MS <10 ppm hydrazine; mp (DSC) 226.17 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ): 12.39 (s, 1H), 8.25 (d, J = 7.7 Hz, 1H), 7.94−7.81 (m, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, δ): 159.4, 143.1, 133.3, 131.3, 129.7, 127.3, 125.7, 125.4, 18.3; HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_9H_9N_2O$, 161.0709; found, 161.0713.

*Phthalazin-1(2H)-one (**9f**).* **9f** was prepared following the general procedure employing 2-formylbenzoic acid (25.0 g, 167 mmol) as the acylbenzoic acid. The final solution was partitioned with saturated aqueous ammonium chloride (200 mL, 8.0 V) and extracted with 3 × 200 mL (8.0 V) ethyl acetate. The combined organics were dried over 30 g of anhydrous magnesium sulfate and filtered. The combined organics were concentrated at 75 mmHg/40 °C to 150 g of solution whereupon 100 g heptane was charged. After 5 min, the thin slurry was again concentrated at 75 mmHg/40 °C to 150 g of slurry. After 6 h at 20 °C, the slurry was filtered by vacuum using a medium porosity sintered glass filter. The cake was washed with heptane (100 mL, 4.0 V), and the filter cake was dried in a 40 °C vacuum oven with a nitrogen bleed for 12 h.

Phthalazin-1(2*H*)-one (**9f**) (3.49 g, 14% yield) was isolated as a colorless crystalline solid along with 10.41 g (43% yield) of phthalazin-1(2*H*)-one (**9f**) lost to the mother liquor giving a combined chemical yield of 13.9 g, 57% yield. GC-MS <10 ppm hydrazine; mp (DSC) 180.30 °C; ^{1}H NMR (400 MHz, DMSO-d_6, δ): 12.63 (s, 1H), 8.35 (d, J = 0.4 Hz, 1H), 8.22 (ddd, J = 7.8, 1.0, 0.9 Hz, 1H), 7.92−7.90 (m, 2H), 7.83 (dt, J = 7.92, 4.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ): 159.5, 138.1, 133.5, 131.6, 129.9, 127.5, 126.6, 125.3; HRMS-TOF (m/z): $[M + H]^+$ calcd for $C_8H_7N_2O$, 147.0553; found, 147.0553.

*Pilot Plant Campaign: 4-(4-Methylthiophen-2-yl)-phthalazin-1(2H)-one (**5**).* 2-(4-Methylthiophene-2-carbonyl)-benzoic acid (4.35 kg, 17.66 mol) was charged to a 100 L Hastelloy reactor followed by *N,N*-dimethylformamide (25.67 kg, 27.02 L). A homogeneous solution resulted in less than 25 min after initiating agitation. Solid 1,1′-carbonyldiimidazole (3.18 kg, 19.61 mol) was charged through the man-way in four approximately equal portions over 1.25 h followed by charging a *N,N*-dimethylformamide (7.18 kg, 7.56 L) rinse. *CAUTION: carbon dioxide evolution! Ensure adequate venting is available and a rupture disk is used.* The batch was held for 1 h whereupon 2-(4-methylthiophene-2-carbonyl)benzoic acid was not detected by HPLC analysis. The batch was transferred to a 160L glass-lined steel reactor through a 10 μm inline filter followed by rinsing of the line with *N,N*-dimethylformamide (2.0 kg).

A 35 wt % aqueous solution of hydrazine (1.78 kg, 1.76 L, 19.44 mmol) was transferred over 1.5 h to the batch through a charge tank while maintaining the temperature at 16−18 °C using jacket cooling (*CAUTION: hydrazine is acutely toxic and has a danger for cutaneous absorption. Consult the current MSDS prior to use and ensure appropriate personal protective equipment*). After a 4 h hold at 20 °C, water (10.88 kg, 10.88 L) was added to the slurry through a charge tank over 1 h. The slurry was aged for 2 h at 20 °C, and HPLC analysis showed a supernatant concentration of 8 mg/mL of 4-(4-methylthiophen-2-yl)-phthalazin-1(2*H*)-one (target ≤10 mg/mL).

The slurry was transferred to a 80 L Hastelloy reactor, equipped with an agitator and a filter dryer fitted with a 25 μm polypropylene filter cloth. The cake was washed with a premade mixture of *N,N*-dimethylformamide (7.18 kg, 7.56 L) and water (1.74 kg, 1.74 L), followed by two water washes (4.35 kg, 4.35 L). The filter cake was dried under vacuum with a nitrogen sweep at ambient temperature for 13 h whereupon TGA analysis indicated LOD = 0.2% (target ≤1.0%).

4-(4-Methylthiophen-2-yl)phthalazin-1(2*H*)-one (**5**) was isolated as a colorless crystalline solid (3.47 kg, 81.5% yield). GC-MS analysis indicated the final isolated solid contained <110 ppm hydrazine. Characterization data were identical to that previously reported.[14]

*N,O-Acetal (**10**).* 2-(4-Methylthiophene-2-carbonyl)benzoic acid (**4**) (500 mg, 2.03 mol) was charged to a 4 dram vial with a magnetic stir bar. Acetonitrile (1.0 mL, 2.0 V) was added resulting in a thick paste. Solid 1,1′-carbonyldiimidazole (325 mg, 2.03 mol) was charged in one portion immediately resulting in an orange solution. *CAUTION: carbon dioxide evolution!* After 1 h, an additional solid 1,1′-carbonyldiimidazole (100 mg, 0.617 mol) was charged, and the vial was sonicated for 5 min resulting in primary nucleation. The slurry was cooled to 0 °C for 2 h and filtered by vacuum. The cake was washed with 5 mL of dry acetonitrile and dried at 40 °C in a vacuum oven with a nitrogen sweep.

N,O-Acetal (**10**) (343 mg, 57%) was isolated as a white crystalline solid: mp(DSC) 128.00 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.99 (d, J = 8.4 Hz, 1H), 7.83 (t, J = 7.5 Hz, 1H), 7.73−7.69 (m, 2H), 7.53 (s, 1H), 7.08 (m, 2H), 7.00 (s, 1H), 6.89 (t, J = 1.5 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, δ): 166.5, 147.1, 138.5, 138.2, 136.5, 135.3, 131.5, 129.9, 129.8, 126.5, 125.0, 123.5, 123.5, 118.3, 92.0, 15.6; HRMS-TOF (m/z): $[M + Na]^+$ calcd for $C_{16}H_{12}N_2O_2SNa$, 319.0517; found, 319.0533.

*Conversion of N,O-Acetal (**10**) to Phthalazin-1(2H)-one (**5**).* *N,O*-Acetal (**10**): (200 mg, 0.682 mmol) was charged to a 1 dram vial containing a magnetic stir bar. *N,N*-Dimethylformamide (0.80 mL, 4.0 V) was added resulting in a colorless solution followed by addition of 35 wt % aqueous hydrazine (0.067 mL, 0.75 mmol) (*CAUTION: hydrazine is acutely toxic and has a danger for cutaneous absorption. Consult the current MSDS prior to use and ensure appropriate personal protective equipment*). Within 5 min, primary nucleation was observed. After an 8 h hold, water (1.4 mL, 7.0 V) was added to the colorless slurry, and the slurry was aged for 12 h. It was then filtered by vacuum using a medium porosity sintered glass filter and washed with water (5 mL). The filter cake was dried in a 40 °C vacuum oven with a nitrogen bleed for 12 h.

4-(4-Methylthiophen-2-yl)phthalazin-1(2*H*)-one was isolated as a colorless crystalline solid (150 mg, 91% yield). Characterization data were identical to that previously reported.[14]

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **9**, **9b**−**9f** and **10**, 2D-HSQC NMR spectra of compounds **6** and **10**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00135.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

CDI = 1,1-carbonyldiimidazole; DMF = *N,N*-dimethylformamide; PAT = Process Analytical Technology; PCC = Power Compensation Calorimetry; PLM = polarized light microscopy; TTC = threshold of toxicological concern; V = mL solvent/g solute

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