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Communication

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Controlled Flow Precipitation as a Valuable Tool for Synthesis

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Supporting Information

ABSTRACT: In most standard flow process, the formation of solids represents a major problem often leading to obstruction of the flow device and reactor shutdown. However, many reactions produce solid products, and therefore finding ways to process these materials is an important area of research. In this article we demonstrate how a dynamically agitated flow reactor can be a powerful tool to facilitate workup and processing of biphasic solid−liquid flow streams at scale.

INTRODUCTION

Bromodomain containing proteins (BCPs) have recently emerged as potentially important biological targets for application in epigenetic therapies.[1] As part of an advanced stage synthesis program preparing BCP modulators for clinical testing, we required access to large quantities of the building block **1** (Figure 1). This common intermediate was then used

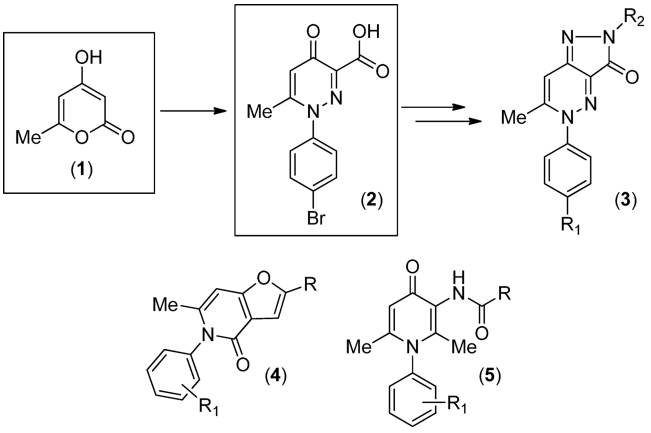

Figure 1. Target compounds selected as building block in the synthesis of BCPs modulator focused libraries.

to synthesize three related development series as highlighted by the general template structures **3**−**5**. To meet the project demands regarding short delivery times and the production of large quantities of compound, we elected to utilize continuous flow chemistry.[2]

It has been widely shown that many chemical syntheses can benefit from flow based processing procedure and the use of integrated continuous manufacturing protocols.[3] However, an issue which is repeatedly highlighted as problematic for the more general adoption of flow is the efficient manipulation of particulates and suspensions. This can be particularly restricting in synthetic chemistry where many valuable protocols specifically employ the designed precipitation of a product or dissolution of impurities as part of the reaction sequence. Such approaches may be used to constructively shift equilibrium positions or more commonly to simplify workup and purification by enabling filtration of the resulting solid products (or byproducts). A number of small scale flow reactor modifications have already been disclosed which aim to mitigate the occurrence of aggregation, sedimentation, and reactor fouling involving flow streams containing solids.[4] However, it was our belief that additional benefits could be leveraged by actively employing flow reactors specifically to instigate programmed solid formation at various stages of the sequence to promote a reaction, workup, or isolation. We wish herein to disclose an approach based upon the use of a commercial agitated reactor which proved highly valuable in the production and isolation of compound **1** and its progression into advanced structure **2**. Although this communication primarily focuses on the synthesis of compounds **1** and **2** the general techniques described are by extrapolation much more widely applicable. Indeed, we highlight that they are now regularly adopted in our laboratory to facilitate a wide range of flow chemistries.

RESULTS AND DISCUSSION

The preparation of compound **2** required a multistep sequence involving high temperature processing, the generation of several reactive intermediates and the handling of precipitates. In practice, we elected to split the synthesis into three processing sequences which could be run independently to create holding batches of material (Stages 1−3, Scheme 1).

Stage 1. Heating a xylene solution of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**6**) (0.1 M) above 90 °C (10 h) induces the loss of acetone to generate the reactive acetyl ketene **7**, which in the absence of a nucleophile undergoes dimerization via a [4 + 2] cycloaddition to yield dehydroacetic acid **8**.[5] Attempts to convert this to a flow procedure initially met with some problems as it was discovered that the elimination reaction leading to ketene **7** was reversible. Additionally, the eliminated acetone was also prone to react with ketene **7**, presumably via its enol form, to furnish 3,5-dimethyl-4-pyrone (**9**). Whereas, under batch processing conditions, the liberated acetone can be

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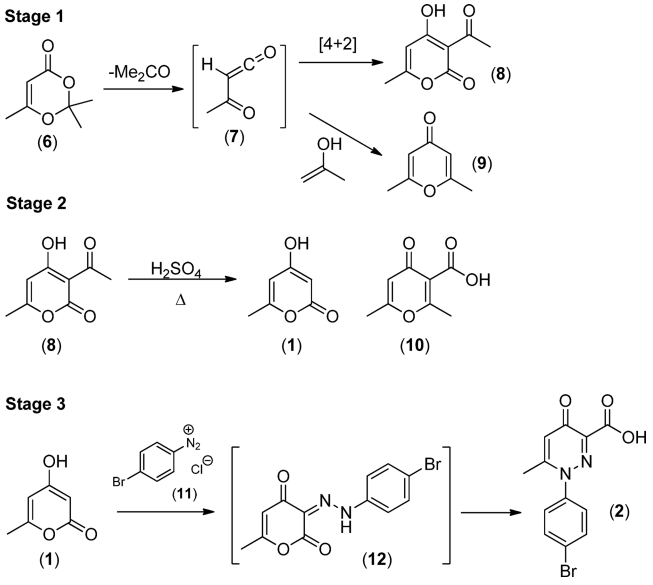
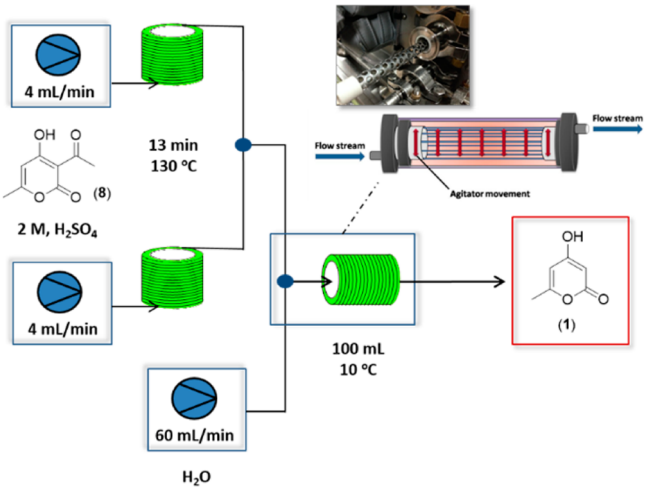
Scheme 1. Proposed Three-Stage Reaction Sequence to Key Intermediates 1−2



easily distilled off driving the equilibrium toward **7** and preventing recombination to form **9**, this is difficult to emulate in a sealed flow system. We however discovered that **8** could be successfully prepared using an elevated temperature of 180 °C and a short residence time of 8.8 min. In this process a 0.6 M stock solution of **6** in xylene was passed through a stainless steel heated flow coil (22 mL). The reactor output was rapidly cooled using a further 5 mL coil submerged in a water bath (RT) and then directed through a packed column of activated charcoal before collection. Solvent evaporation allowed the target molecule to be isolated as a pure white solid in 93% yield.

Stage 2. Having established a viable route to dehydroacetic acid (**8**), we next evaluated its deacylation. The most effective conditions involve treatment with hot (>110 °C) concentrated sulfuric acid.[6] Indeed, this worked reproducibly in batch at small scales (<10 g) with the product being isolated in 85−88%. Important to the success of the process was the careful pouring of the concentrated acidic solution onto ice prior to the rapid filtration of the resulting precipitate. Difficulties were immediately encountered in regard to isolation of lactone **1** at increased scales. Whereas the deacylation step proceeded in an identical manner (^{1}H NMR sampling), the subsequent isolation became troublesome due to a combination of the greater relative exotherm of the quenching step and the requirement for extended workup times. As a result, significant quantities of byproducts (**9** and **10**) were observed leading to a decrease in isolated yield and purity. We envisaged to potentially overcome this isolation issue by taking advantage of the enhanced heat transfer and mixing capabilities of a flow reactor enabling better regulation of the exotherm and improved processing consistency in the quench step. Consequently a reactor setup based upon the use of three commercially available flow systems[7] functioning as modular stages in an integrated sequence was assembled (Scheme 2). In the initial testing a Vaportec E-series system[7a] equipped with peristaltic pumps was used to deliver a viscous 2 M solution of dehydroacetic acid **8** in conc. H_2SO_4 to two parallel configured Polar Bear Plus Flow Synthesizers[7b] both equipped with 52 mL foil coils maintained at 130 °C. Each channel was pumped at a flow rate of 4 mL/

Scheme 2. Reactor Setup and Workflow for Preparation of Compound 1



min equating to a heated residence time of 13 min. The twin reactor outputs were combined with a quench stream of water (60 mL/min; temp: 10 °C) at the entrance to a Coflore 1 L ATR reactor[7c] (using only a single chamber of the 10 possible 100 mL reactors available, agitator frequency 4 Hz, 1.5 min residence time). To maintain the system temperature the ATR cooling jacket was fitted to a Julabo recirculating chiller which cooled the system to a set 10 °C (optimized for viscosity and product yield). The quenched reactor output comprising a thick white suspension of product **1** was directly isolated by filtration of the out-flow onto a sintered filter bed under constant vacuum suction. The solid collected was periodically removed and further dried overnight in a vacuum oven at 30 °C to yield **1** in 92%.

In additional studies, it was shown that the Coflore reactor could easily handle a higher throughput with an input of 16 mL/min of a 2 M solution of **8** and 120 mL/min of the water quench (44 s residence time). Under these optimized conditions, a throughput of 250 g/h could be achieved at steady state operation in 94% isolated yield. Of further importance to this investigation was the quality and consistency of the material isolated. The value of the flow workup can be immediately evidenced when comparisons are made against material isolated from conventional batch workup (Figure 2).

For example, quenching large quantity of **1** in H_2SO_4 as a batch workup gave the product in a variable yield of 61−80% as a pale tan colored solid after drying. It was also observed that the material produced toward the mid-quenching point became progressively discoloured, sticky, and started clumping together (more pronounced with increasing scale) making subsequent filtration and drying much more difficult and time-consuming. In contrast, the material isolated via flow (yield 94%) was consistently isolated as an off white flocculent solid which was easily filtered and rapidly dried (Figure 2). Analysis of the isolated materials identified that the product obtained via batch quenching was contaminated with varying amounts of compound **10** (8−12%), whereas the flow derived product was absent from these impurities. This clearly highlights the advantage of adopting a flow based processing sequence to maximize the yield and quality of isolated material. We consider this demonstration is highly relevant to many other transformations where the stability of the derived product is a key concern necessitating fast quenching and isolation.

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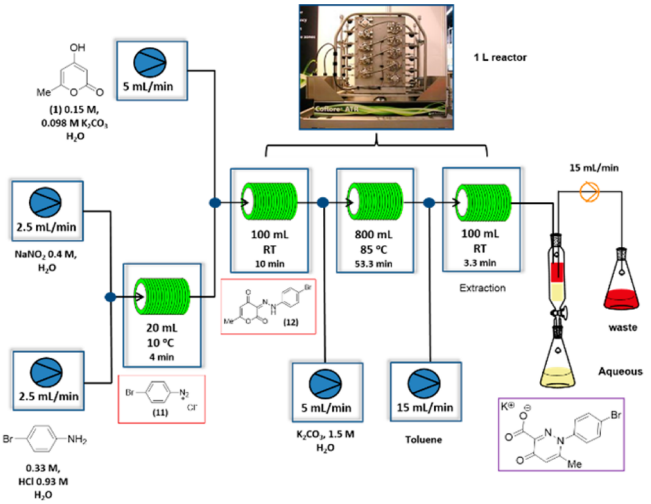
Figure 2. Qualitative comparisons among the particulates produced in flow (left) and in batch (right).

Stage 3. Encouraged by our success in preparing key building block **1**, we next devised an integrated multistep synthesis to deliver advanced intermediate **2**. This required the preparation of diazonium salt **11**, followed by its base catalyzed condensation with pyranone **1**, and finally a thermal rearrangement of the intermediate hydrazone **12** to yield **2** (Scheme 1).[8] This proposed derivatization chemistry presents several processing and handling challenges. First, the route mandates three sequential and contrasting pH changes; the diazonium forming step is strongly acidic, the rearrangement step requires basic conditions, and the isolation of the acid **2** needs again acidic pH, each change creates temperature and mixing control issues. Furthermore, the most effective base for the hydrazone generating and rearrangement steps was found to be K_2CO_3; however, this liberates copious amounts of CO_2 when added to the highly acidic diazonium salt solution creating significant foaming and problems in effective mixing. Lastly, the solubility of pyranone **1** is poor in water (see isolation above), and the resulting intermediate hydrazone **12** is almost completely insoluble in both aqueous and organic solvents compounding the foaming issue and making processing at scale challenging. To surmount these obstacles we again took advantage of the Coflore ATR reactors capabilities to aid in mixing and processing of suspensions; after a series of optimization experiments, the reactor arrangement as depicted in Scheme 3 was settled upon.

Multistep Synthesis. Two aqueous solutions, one comprising $NaNO_2$ and the other 4-bromoaniline solubilized in aqueous HCl, were combined at a T-piece mixer and then processed through a 20 mL flow coil. This simple configuration worked well at high flow rates and over a wide range of temperatures (−10 to 20 °C) rapidly forming the required diazonium salt **11**. The output was mixed with a feed of the pyranone **1** dissolved in aqueous K_2CO_3 before entering the first reaction chamber of the Coflore system (agitator frequency 4 Hz). The chamber was maintained at room temperature and

Scheme 3. Reactor Setup and Workflow for Preparation of Compound 2



resulted in the immediate generation of a thick yellow precipitate consisting of intermediate **12** which formed in almost quantitative conversion. Under mechanical agitation the material was easily progressed as a free-flowing suspension (Figure 3; solid content of 46% v/v) and was not hindered by

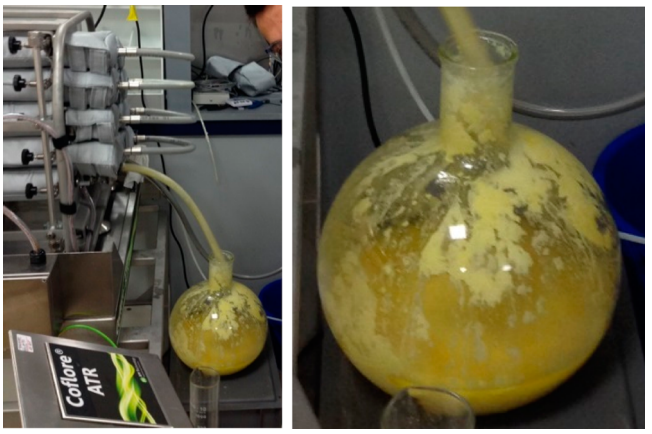


Figure 3. Collection of an analysis sample into a 10 L flask as isolated from the exit port of the first stage reactor.

the production of CO_2 resulting from the partial neutralization of the acidic diazonium stream. Indeed, the agitation facilitated the efficient degassing of the flow stream circumventing the previously encountered foaming problem.

During development we also found it highly beneficial to engineer a two-stage pH change as achieved by increasing the quantity of aqueous K_2CO_3 injected following the primary reactor (Scheme 3). Tests conducted involving higher concentrations of added K_2CO_3 either as part of the original pyranone feed or by successive injection before full conversion to the hydrazone **12** had occurred, all produced a negative outcome upon the monitored downstream conversion and purity of **2**. We concluded a combination of enhanced mixing (less foaming) leading to improved diazonium coupling and the milder reaction conditions reducing the amount of diazonium degradation (as indicated by reduced phenol formation in the reaction stream) were key factors. An additional consequence arising from the refined conditions was that a lower

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stoichiometry of the diazonium salt could be employed (1.1 equiv vs 1.8 equiv) which also beneficially impacted upon the final concentration of K_2CO_3 required in order to reached the necessary pH for the subsequent rearrangement. Under the derived basic conditions and at a temperature of 85 °C, the transformation of hydrazone **12** into the final desired pyridazone **2** proceeded efficiently. The reaction required a residence time of 50−55 min which could be easily serviced by connecting 8 of the remaining 100 mL ATR reaction chambers in series. The final ATR chamber was used to facilitate purification by extractive workup through toluene addition leading to partitioning of any organic soluble impurities. The resulting biphasic output was discharged from the ATR reactor into a settling tank which allowed the organic phase to be removed to waste and the lower aqueous layer to be drained. Isolation of the target compound **2** was achieved through acidification of the aqueous phase. In this study acidification was often performed as a batch process due to the availability of reactors; however, as a proof of concept, a test aliquot was processed in flow. The extracted aqueous solution was blended with a flow stream of conc. HCl (37% to attain pH 5.5) mixing within the Coflore ATR reactor which was regulated at 0 °C (agitator frequency 4 Hz). The flow was progressed through two sequentially linked reactor chambers and then directed onto a filtration bed set under constant vacuum suction. The pale orange solid collected was periodically removed, washed with cold water (0 °C), and dried overnight in a vacuum oven at 30 °C. The isolated material was pure as determined by NMR and HPLC analysis. For this final isolation step, no significant difference in isolated yield or purity was noted between the batch and flow processed material. Overall, this multistep sequence allowed the successful continuous processing of **2** with a productivity of over 9.6 g/h (excluding drying) of pure final product isolated in 73% yield operating at steady state.

■ CONCLUSION

Engineered flow technologies were profitably utilized to accelerate aqueous quenching and extractions as well as to facilitate the manipulation of slurries and suspensions at scale. The use of an internal mixed flow reactor allowed for a smooth and safe production of 5 kg of pure triacetic acid lactone **1**, delivering quality material with reduced time, manpower, and equipment space requirements when compared with the batch procedure. Moreover, the efficient synthesis of the advanced building block **2** has also been described. The devised flow setup, comprising three sequential synthetic steps and one in-line workup, enabled the synthesis of more than 150 g of the particular advanced target compound during a single run. Collectively these studies demonstrate that the generation of solids does not inherently represent a restriction for the general implementation of flow synthetic methodologies but could also be considered as a strategic in-line operation addressed to improve products quality and to expedite the medium-scale production of key intermediates in advanced medicinal chemistry programs.

■ EXPERIMENTAL SECTION

Materials and General Procedures. All solvents were purchased from Fisher Scientific and used without further purification. Reagents were purchased from Alfa Aesar or Sigma-Aldrich and used as received. Flow reactions were performed either on a Vaportec (R-series and E-series)[7a] or a Polar Bear Plus Flow Synthesizer[7b] or AM Technology Coflore ATR[7c] modules equipped with standard PTFE tubing (3.2 × 1.5 mm, o.d. × i.d) and connectors. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance-400 instrument and are reported relative to DMSO-d_6 (δ 2.50 ppm and δ 39.52 ppm, respectively). Data for ^{1}H NMR are reported as follows: chemical shift (δ/ ppm) (multiplicity, coupling constant, integration). Multiplicities are reported as follows: s = singlet, d = doublet, br. s = broad singlet. Data for ^{13}C NMR are reported in terms of chemical shift (δ/ ppm) and multiplicity (C, CH, CH_2, or CH_3). Data for IR spectra were obtained by use of a PerkinElmer RX1 spectrometer (neat, ATR sampling) with the intensities of the characteristic signals being reported as weak (w, < 21% of tallest signal), medium (m, 21−70% of tallest signal), or strong (s, > 71% of tallest signal). Low and high resolution mass spectrometry were performed using the indicated techniques on either Waters LCT Premier XE or Waters TQD instruments equipped with Acquity UPLC and a lock-mass electrospray ion source. For accurate mass measurements the deviation from the calculated formula is reported in mDa..

Multigram-Scale Flow Procedures. *3-Acetyl-4-hydroxy-6-methyl-2H-pyran-2-one (**8**).* Recharge stock solutions of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**6**, 1.5 mol) in *o*-xylene (2.5 L) were prepared and set to pump at 2.5 mL through a 22 mL stainless steel (SS) reactor coil heated at 180 °C. A residence time of 8.8 min gave full conversion. The material was passed directly into a 5 mL (SS) which was regulated at ambient temperature using a water bath and then directed through a packed column of activated charcoal (~250 g Spartan Series Enhanced Activated Carbon Charcoal, 50 mesh) before collection. Solvent evaporation allowed the title compound to be isolated as a pure white solid in 93% yield. During the processing the reactor was successfully run for 9 days preparing over 3 kg of product.

Mp: 111.6−112.4 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.31 (s, 1H), 2.56 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 205.15 (C), 180.93 (C), 170.66 (C), 160.94 (C), 101.43 (CH), 99.90 (C), 30.18 (CH_3), 20.57 (CH_3). IR (neat): 3086.8 (w), 1706.0 (m), 1634.4 (m), 1541.8 (s), 1447.6 (m), 1349.2 (m), 1251.6 (m), 1171.0 (w) 994.6 (s), 962.6 (m), 922.6 (m), 854.3 (s), 778.1 (m), 712.3 (m), 636.5 (w), 618.2 (w), 564.8 (m), 504.0 (w), cm^{-1}. LC-MS (ESI): 167.1 (M-H); HRMS (ESI): calculated for $C_8H_7O_4$ 167.0344, found 167.0339 (M − H, Δ = −0.5 mDa).

*4-Hydroxy-6-methyl-2H-pyran-2-one (**1**).* Two solutions of 3-acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (**8**) (2 M) were individually pumped at 4 mL/min into two parallel coil reactors (52 mL) heated at 130 °C. The combined crude outflows fed, along with a stream of water (60 mL/min), a 100 mL Coflore ATR reactor chamber cooled at 10 °C. The resulting suspension was filtered, and the pale yellow solid dried under *vacuum* obtaining the pure title compound **1** in 92% yield.

Mp: 185.6 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1H), 5.96 (s, 1H), 5,21 (s, 1H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.0 (C), 164.4 (C), 163.8 (C), 100.6 (CH), 88.6 (CH), 19.9 (CH_3). IR (neat): 2362.4 (w), 1658.1 (m), 1618.2 (m), 1538.5 (m), 1492.62 (m), 1255.2 (s), 1149.2 (m), 985.2 (s), 878.0 (m), 833.0 (s), 812.21 (s), 729.2 (m), 635.3 (m), 591.4 (s), 526.2 (s), 497.8 (s) cm^{-1}. LC-MS (ESI): 125.0 (M − H); HRMS (ESI): calculated for $C_6H_7O_3$ 127.0395, found 127.0389 (M + H, Δ = −0.6 mDa).

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*Synthesis of 1-(4-Bromophenyl)-6-methyl-4-oxo-1,4-dihydropyridazine-3-carboxylic Acid (**2**).* Two solutions pumped at 2.5 mL/min were mixed in a T-piece before entering in a coil reactor (20 mL) cooled at 10 °C: one containing $NaNO_2$ 0.4 M and the second containing 4-bromoaniline 0.33 M solubilized in aqueous HCl 0.93 M. The outflow was combined with a stream of **1** 0.15 M dissolved in $K_2CO_{3(aq)}$ 0.098 M and pumped at 5 mL/min. The resulting mixture was reacted at room temperature in the first chamber of the ATR reactor. A second stream of $K_2CO_{3(aq)}$ 1.5 M was thus injected in the reactor at 5 mL/min and main stream processed into eight 100 mL dynamically mixed pipes heated at 85 °C. As the crude mixture enters the last reactor chamber, it was mixed with a stream of toluene pumped at 15 mL/min. The biphasic solution that exited the reactor was separated. The water layer was acidified with HCl 37% and the suspension obtained filtered. The pale orange solid recovered was dried under reduced pressure obtaining the pure title compound **2** in 73% yield.

Mp: 214.0 °C (decomposed). ^{1}H NMR (400 MHz, DMSO-d_6) δ 15.55 (br. s, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.61 (d, J = 8.4 Hz, 2H), 7.12 (s, 1H), 2.25 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.3 (C), 163.1 (C), 156.0 (C), 143.0 (C), 141.5 (C), 133.1 (2CH), 129.1 (2CH), 124.0 (C), 120.6 (CH), 20.9 (CH_3). IR (neat): 1727.7 (m), 1566.3 (m), 1485.4 (s), 1337.9 (m), 1284.2 (m), 1218.8 (s), 1067.6 (s), 1015.6 (s), 909.7 (m), 839.7 (s), 794.1 (m), 738.1 (m), 641.0 (m) cm^{-1}. LC-MS (ESI): 307.1 (M − H). HRMS (ESI): calculated for $C_{12}H_{10}N_2O_3Br$ 308.9875, found 308.9882 (M + H, Δ = +0.7 mDa).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.5b00331.

Copy of NMR spectra, mass spectra, and single crystal X-ray diffraction data (PDF)

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Notes

The authors declare no competing financial interest.

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