JOC The Journal of Organic Chemistry

Article

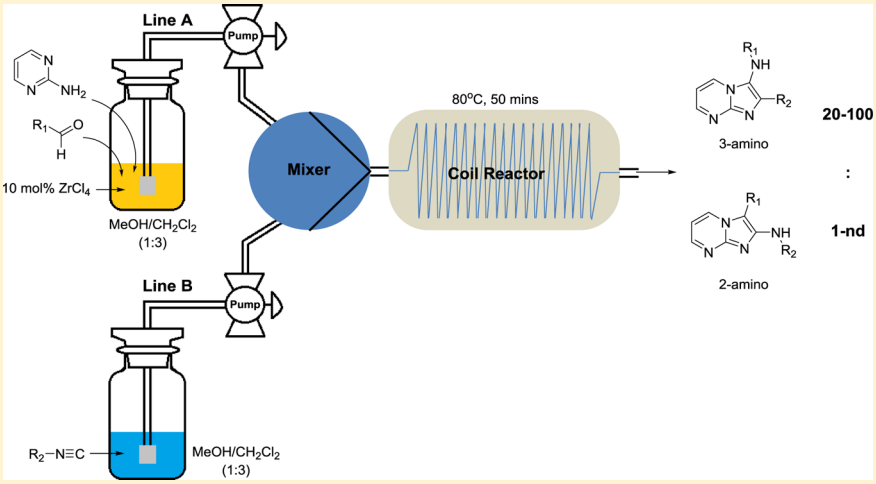
pubs.acs.org/joc

Regioselective Synthesis of 3-Aminoimidazo[1,2-*a*]-pyrimidines under Continuous Flow Conditions

Ashlie J. E. Butler, Mark J. Thompson, Patrick J. Maydom,[†] James A. Newby,[‡] Kai Guo,[§] Harry Adams, and Beining Chen*

Department of Chemistry, University of Sheffield, Dainton Building, Brook Hill, Sheffield S3 7HF, U.K.

Supporting Information



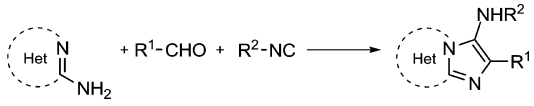
ABSTRACT: Multicomponent synthesis of 3-aminoimidazo[1,2-*a*]pyrimidines usually affords a product mixture containing varying amounts of the corresponding 2-amino regioisomer. Modified methods, particularly microwave heating, have been employed to suppress formation of this side-product, but none of the revised protocols are readily amenable to scale. A continuous flow adaptation was found to offer improved regioselectivity toward the targeted 3-amino regioisomer with significantly shorter reaction times and also widened the scope of the reaction to permit the use of aliphatic aldehyde building blocks.

INTRODUCTION

Multicomponent reactions (MCRs) have garnered increasing interest during recent years, most particularly for their utility in rapid synthesis of large chemical libraries for application in high-throughput screening efforts in drug discovery and related disciplines. One such example,[1−3] first reported in 1998 by three separate groups and now referred to as the Groebke−Blackburn reaction,[4] involves combination of a 2-aminoazine, aldehyde, and isocyanide to form a fused imidazole ring (Scheme 1).

This three-component coupling (3-CC) offers excellent atom economy and is readily applicable to preparation of extensive libraries of drug-like heterocycles. As such, it has been very widely employed in the context of drug discovery and reviewed extensively elsewhere.[5−7] The reaction is catalyzed by either Brønstead or Lewis acids but is typically performed using 2.5 mol % $Sc(OTf)_3$ in an organic solvent (methanol or methanol−dichloromethane mixtures). Although 2-aminopyridine and aminopyrazine have been employed most often as the 2-aminoazine building block due to the consistently high yields obtained, our interest primarily focuses on use of 2-aminopyrimidine as the amine starting material, yielding imidazo[1,2-*a*]pyrimidines as products. The imidazo[1,2-*a*]pyrimidine substructure is found in many compounds of potential pharmaceutical interest, including divaplon[8] **1** (Figure 1) and fasiplon[9] **2**, both being part of a large class of non-benzodiazepine agonists of $GABA_A$ receptors investigated throughout the 1980s and 1990s as potential anxiolytic and anticonvulsant agents, albeit without successful translation to clinical use.[10] It is also found in compound **3**, a potent androgen receptor antagonist with promising in vivo efficacy in

Scheme 1. Groebke−Blackburn Three-Component Approach to Fused Imidazoles



Received: August 12, 2014
Published: October 13, 2014

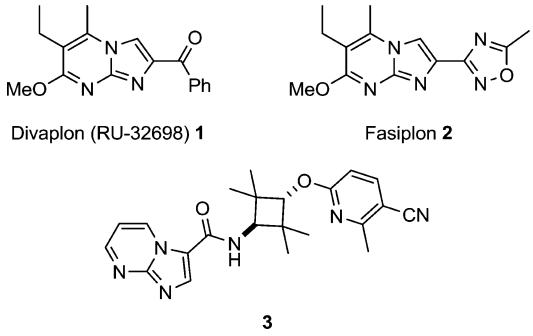
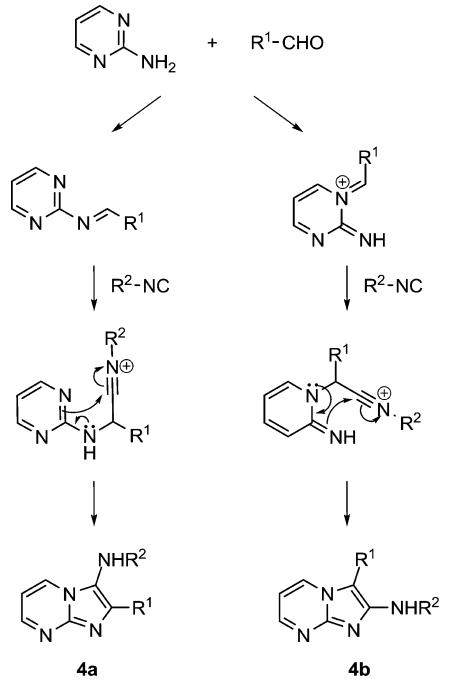


Figure 1. Examples of past or present clinical candidates containing the imidazo[1,2-*a*]pyrimidines.

animal models of castration-resistant prostate cancer,[11] which is seemingly under ongoing preclinical development.[12]

One unique feature of the Groebke–Blackburn 3-CC approach to imidazo[1,2-*a*]pyrimidines (Scheme 2) is that in addition to the expected 3-amino substituted product **4a**, the regioisomeric 2-amino compound **4b** is also formed in varying amounts, presumably via initial imine formation through one of the ring nitrogen atoms as opposed to the exocyclic amino group.[13,14] Although product distribution varies considerably with the exact nature of the aldehyde and isocyanide components, the anticipated 3-amino isomer **4a** usually predominates.[13,14] Performing the reaction in a nonpolar solvent, toluene, was found to suppress formation of **4b**,[15] supporting the assumption that this product is formed via a charged iminium intermediate as shown in Scheme 2. Alternatively, solvent-free microwave heating, in the presence of either montmorillonite K-10 clay[16] or zeolite HY[14] as a mildly acidic solid support catalyst, was found to greatly accelerate the reaction and offer significantly improved regioselectivity for **4a**.

Scheme 2. Mechanistic Rationale for the Formation of a Product Mixture in the Multicomponent Reaction of 2-Aminopyrimidine



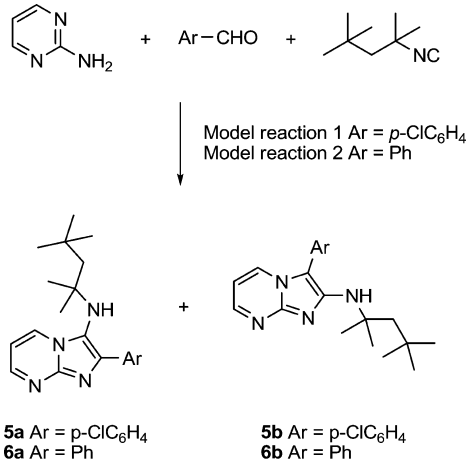
If required, the pure 2-amino isomer **4b** may be accessed by performing a Dimroth rearrangement of the initial product mixture.[17] More recently, Guchhait and Madaan intriguingly reported exclusive formation of **4b** when 10 mol % $ZrCl_4$ is used as catalyst in poly(ethylene glycol)-400 (PEG-400) at 50 °C.[18]

In the past two decades, continuous flow technology has found many applications in life science related areas such as academic research laboratories and industrial settings, with distinctive advantages of being green, efficient, and selective when compared to traditional batch processes.[19,20] In organic synthesis, it has been utilized to prepare a wide range of pharmaceutically important heterocyclic compounds.[21−23] However, this technique has never been applied to the synthesis of aminoimidazo[1,2-*a*]-pyrimidines. In this paper, we would like first to address the issue of stereochemical outcome of the synthesis of this class of heterocycles reported by Guchhait and Madaan. Then, the regioselectivity of the reaction will be explored and optimized using continuous flow techniques and the scope of the reaction demonstrated by synthesis of a small library of representative compounds.

RESULTS AND DISCUSSION

The claimed selectivity of the $ZrCl_4$/PEG-400 method for the 2-amino isomer seemed highly unprecedented because we previously demonstrated[14] preferential or even sole formation of the 3-amino product in the presence of $Sc(OTf)_3$ and would not expect the reaction to behave profoundly differently under $ZrCl_4$ catalysis, with it simply being another transition metal based Lewis acid catalyst. After closely following one of the reported examples[18] (model reaction 1, Scheme 3) and crystallizing the isolated product for X-ray analysis, it was in fact found to be 3-amino isomer **5a** (Figure S1a, Supporting Information). In the light of this apparently contradictory result, it quickly became clear that Guchhait and Madaan must have based their regiochemical assignment on the original work of Mandair et al.,[13] which erroneously designated the 3-amino product as the less polar (higher-running on TLC) and the 2-

Scheme 3. Model MCRs Used in Comparison of Sc^{3+} and Zr^{4+} Catalyst, and of Batch vs Continuous Flow Reaction Conditions



dx.doi.org/10.1021/jo501861g | J. Org. Chem. 2014, 79, 10196−10202

amino as the more polar, without additional verification, as per our subsequent report[14] which corrected this earlier error.

Because we had only previously presented example X-ray structures of the more crystalline 3-amino isomers **4a** and inferred the identity of **4b** by NOE experiments, we endeavored to also crystallize a representative 2-amino isomer for the confirmation of its absolute identity. The same model reaction as used in the earlier study,[14] between 2-aminopyrimidine, benzaldehyde, and Walborsky's reagent (1,1,3,3-tetramethylbutyl isocyanide), i.e., model reaction 2 (Scheme 3), furnished sufficient quantities of **6b** for X-ray crystallography, clearly establishing this less polar (higher-running) product as the 2-amino isomer (Figure S1b, Supporting Information). Thus, it is now confirmed beyond doubt that in the Groebke–Blackburn 3-CC of 2-aminopyrimidine, the expected 3-aminoimidazo[1,2-*a*]pyrimidine product **4a** is always the more polar (lower-running on TLC), with the corresponding 2-amino regioisomer **4b** always being higher-running.

Both Sc^{3+} and Zr^{4+} will complex to the carbonyl oxygen atom of the starting aldehyde and activate it to be attacked by 2-aminopyrimidine, although the observed product regioselectivity is unlikely to originate from this original imine formation. It more likely stems from complexation of the metal ion to the neutral imine species en route to **4a** (Scheme 2) because Zr^{4+} is a stronger Lewis acid with higher charge density and will more readily activate the imine to be attacked by the isocyanide carbanion, thus favoring formation of the 3-amino product isomer. It may also be postulated that the charged iminium intermediate ultimately leading to **4b** will not complex with either metal ion due to Coulombic repulsion. These considerations satisfactorily explain the typical selectivity of the reaction for **4a** and its enhanced preferential formation in the presence of Zr^{4+} as opposed to Sc^{3+}. Nonetheless, with the regioselectivity of the reaction now clearly resolved, the next step was to evaluate an optimal reaction yield and duration under continuous flow conditions. A coil mesofluidic reactor was employed for all continuous flow experiments.

The residence time optimization of model reaction 2 (Scheme 2) was carried out using 10 mol % $ZrCl_4$ catalyst at 70 °C and the optimum residence time maintaining a reliable flow rate was found to be 50 min, giving a yield of 37% (Figure 2a). The optimization reactions to determine the optimum temperature were carried out using the above determined optimal residence time of 50 min and a catalyst loading of 10 mol % $ZrCl_4$. At temperatures greater than 80 °C, yields began to decrease again, so it was determined that this was the optimum temperature for reaction, giving a yield of **6a** of 68%. These results are comparable to the 70% yield produced under batch conditions over 48 h (Figure 2b). The yield of **6b** was dramatically reduced in comparison to batch reactions under continuous flow conditions.

During the course of optimization experiments, it was found that the ratio of regioisomeric products in the MCR varies over time. The flow reaction to form **6a** and **6b** (Scheme 3, model reaction 2), when catalyzed by 2.5 mol % $Sc(OTf)_3$ and followed closely over short residence times, showed predominant formation of the 2-amino product **6b** in the early stages (Figure 3b). However, with a reaction duration of 10 min or above, the 3-amino isomer **6a** increasingly dominated under flow conditions. A similar phenomenon was observed when the batch synthesis of **5a** and **5b** (Scheme 3, model reaction 1) was repeated with different reaction durations in the presence of 10 mol % $ZrCl_4$. Shorter reactions led to isolation of relatively

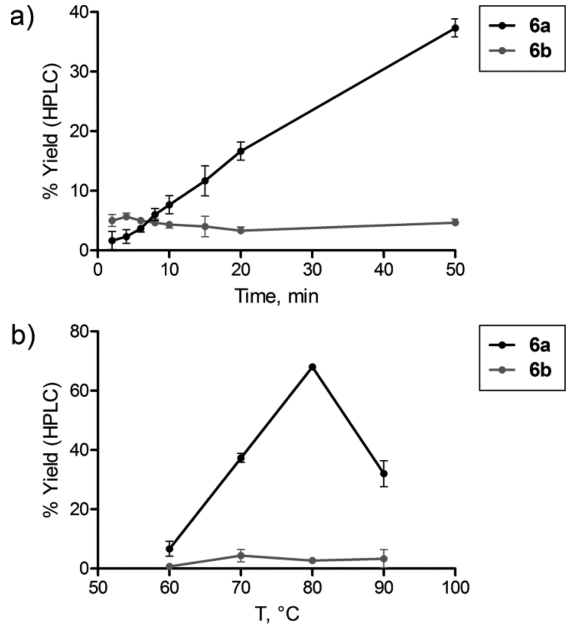


Figure 2. Results for the model reaction 2 under continuous flow conditions by varying (a) residence time (temperature was kept at 70 °C), and (b) temperature (residence time was kept at 50 min) both using 10 mol % $ZrCl_4$ as catalyst.

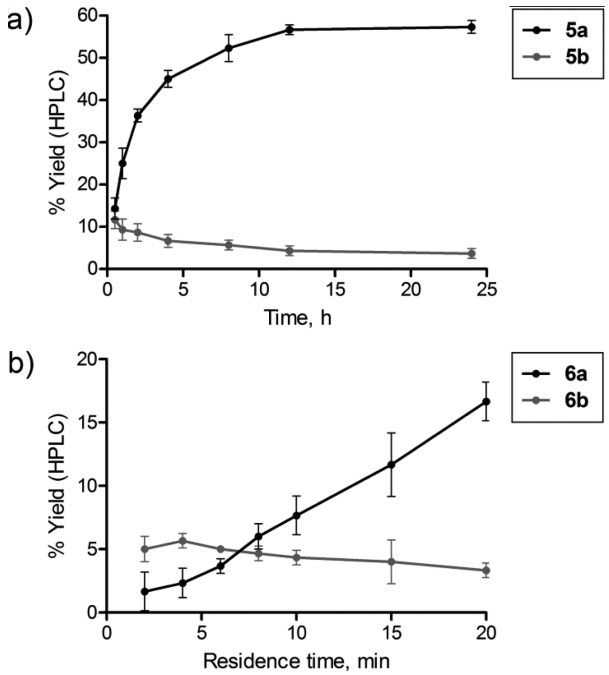


Figure 3. 2-Amino isomers were formed more rapidly during the initial stages of reaction. (a) Batch synthesis of **5a** and **5b** promoted by 10 mol % $ZrCl_4$ followed over 24 h; (b) continuous flow synthesis of **6a** and **6b** under $Sc(OTf)_3$ catalysis with varying coil residence times.

more of the 2-amino isomer **5b**, whose ratio in the product mixture decreased with prolonged heating (Figure 3a).

The foregoing observations indicate that the system is held in dynamic equilibrium, thereby implying that all steps in the proposed mechanism (Scheme 2) are reversible. These results also suggest that the 2-amino regioisomers are the kinetic product of the reaction and 3-amino regioisomers the

dx.doi.org/10.1021/jo501861g | J. Org. Chem. 2014, 79, 10196–10202

thermodynamic product, although further investigation would be necessary to confirm this supposition.

Additional reactions were performed to investigate the optimal catalyst loading and make comparisons between Zr^{4+} and Sc^{3+} as Lewis acids. The batch reactions were carried out at the reflux temperature (~45 °C) due to the low boiling point of the mixed solvents (DCM/MeOH 3:1), while under continuous flow conditions the same solvent system can be heated to 80 °C using the back pressure regulator. Comparisons with microwave irradiation were not attempted, as the solvent system used is not suitable for microwave conditions and the advantages of using this technique in synthesizing this family of compounds have been demonstrated in our previous studies.[14]

As shown in Figure 4, there is a marked improvement in regioselectivity toward the 3-aminopyrimidine product for all

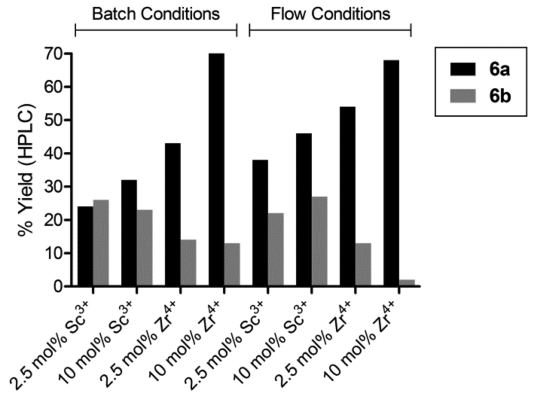


Figure 4. Outcome of model reaction 1 to form **6a** and **6b**, comparing a range of catalytic options under both batch conditions and continuous flow conditions.

reactions in continuous flow conditions compared to batch conditions, with the best yield and regioselectivity found with 10 mol % $ZrCl_4$.

To demonstrate its general application, the optimal continuous flow protocol (80 °C, 50 min residence time, 10 mol % $ZrCl_4$) was used to prepare a small library of 3-aminoimidazo[1,2-*a*]pyrimidines (Table 1). In line with earlier observations, consistently high regioselectivity was observed, with the extent of formation of the 2-amino isomer either small or undetectable. The 2-amino minor products **8b**, **9b**, **10b**, **11b**, and **13b** were detected by TLC and confirmed by ^{1}H NMR spectroscopy but were not obtained in pure form, so their presence in the mixture was confirmed by LC-MS (see Supporting Information).

In the case of the reaction to give **11a** and **11b**, unequivocal assignment of the major product was not possible based solely on ^{1}H NMR spectra and NOE experiments proved inconclusive. Subsequent crystallization and X-ray analysis identified the major product as **11a**, as anticipated (Figure S2, Supporting Information). Successful formation of **14a** and **15a** is of particular note because equivalent batch reactions gave no detectable amounts of expected products, as is typical when employing aliphatic aldehyde components. A continuous flow approach thus expands the available scope of the reaction, permitting access to a more diverse array of substituted imidazo[1,2-*a*]pyrimidines.

CONCLUSIONS

Continuous flow synthesis has steadily been gaining interest in recent years, particularly because of its ready amenability to scale up without modification of reaction parameters and its obvious safety advantages on a large scale. For these reasons among others, the pharmaceutical industry has been a key player in advancing its use,[24] and continuous flow approaches to drug-like structures of potential interest are therefore of particular appeal. We present here an optimized flow protocol to access such a class of compounds, and although a limited number of related fused imidazoles (primarily imidazo[1,2-*a*]pyridines rather than pyrimidines) have previously been prepared via continuous flow methodology,[25] this earlier work was not undertaken using the multicomponent approach outlined here, with its obvious advantages in flexibility and access to a wider diversity of products.

During the course of developing this flow protocol, we confirmed that both Sc^{3+} and Zr^{4+} Lewis acid catalysts lead to preferential formation of 3-aminoimidazo[1,2-*a*]pyrimidines over the corresponding 2-amino regioisomeric products, with Zr^{4+} offering significantly enhanced regioselectivity. Our continuous flow approach offers improved selectivity over conventional batch synthesis in considerably shorter reaction times, thus enabling rapid, scalable access to 3-aminoimidazo-[1,2-*a*]pyrimidines and was demonstrated to be equally as effective over a range of examples where the aldehyde and isocyanide components of the reaction mixture were varied.

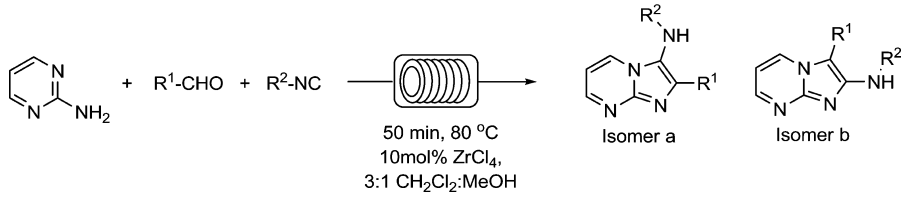
EXPERIMENTAL SECTION

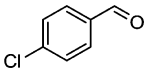
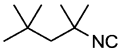
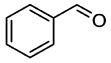
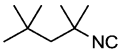
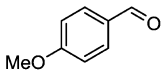
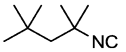
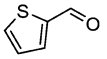
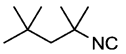
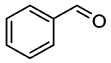
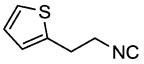
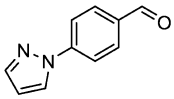
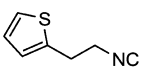
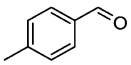
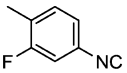
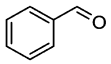
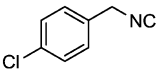
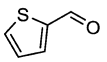
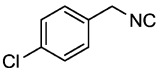
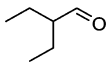
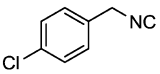
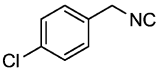
General Procedures. All solvents and reagents were obtained from commercial sources and used as supplied. Walborsky's reagent and PEG-400 are 1,1,3,3-tetramethylbutyl isocyanide and poly-(ethylene glycol)-400, respectively. *p*-Chlorobenzyl isocyanide, 2-(2-thienyl)ethyl isocyanide, 1-chloro-4-(2-isocyanoethyl)benzene, and 2-fluoro-4-isocyano-1-methylbenzene were prepared as described previously.[26] ^{1}H and ^{19}F NMR spectra were recorded at 400 and 235 MHz, respectively, and ^{13}C NMR spectra at 100 MHz with complete proton decoupling. *J* = values are reported in Hz. Electrospray mass spectra were acquired using a XE system. HPLC analysis was carried out using a C_{18} 4 μm column (4.6 mm × 150 mm); 5−95% MeCN/water over 20 min, hold 5 min; UV detection at 254 nm; flow rate 1.0 mL min^{-1}. Continuous flow reactions were performed using a flow chemistry system with two inlet pumps (designated line A and line B) operated with the supplied Flow Commander software package. The samples were injected into 2 mL injection loops and run through a 10 mL reaction coil. It was found necessary to flush the full system with solvent between reactions to prevent inconsistent results arising from cross-contamination between samples. This practice was adopted routinely and achieved using a third intake pump charged with the reaction solvent alone (1:3 MeOH−CH_2Cl_2).

2-(4-Chlorophenyl)-*N*-(2,4,4-trimethylpentan-2-yl)imidazo-[1,2-*a*]pyrimidin-3-amine 5a. *Method 1, According to Guchhait and Madaan.*[18] 2-Aminopyrimidine (190 mg, 2 mmol), *p*-chlorobenzaldehyde (281 mg, 2 mmol), and Walborsky's reagent (351 μL, 278 mg, 2 mmol) were combined in PEG-400 (2 mL), then $ZrCl_4$ (47 mg, 0.2 mmol) was added and the mixture heated at 50 °C for 1 h. Dichloromethane (50 mL) was added, and PEG-400 removed by successive extraction with water (4 × 50 mL). The organic layer was evaporated and the crude material crystallized from CH_2Cl_2/hexane, giving the title compound as a pale-yellow crystalline solid (396 mg, 56%). A portion of the product was recrystallized from the same solvent system to provide crystals suitable for structure determination by X-ray crystallography (Figure S3, Supporting Information); mp 205−212 °C; purity (HPLC) 94.2%. ν_{max} (solid/cm^{-1}): 3295, 3081, 2946, 1607, 1486, 1370, 839, 792, 763. δ_H (400

dx.doi.org/10.1021/jo501861g | J. Org. Chem. 2014, 79, 10196−10202

Table 1. Library Compounds Synthesized with the Continuous Flow Adaption of the Groebke–Blackburn Reaction with 2-Aminopyrimidine: Isolated Yields after Column Chromatography



Product	R^1-CHO	R^2-NC	% Yield Isomer A	% Yield Isomer B
5			52	2
6			61	3
7			45	2
8			60	<1[a]
9			49	<1[a]
10			55	<1[a]
11			43	<1[a]
12			46	-
13			55	<1[a]
14			27	-
15			32	-

[a]Pure products not isolated but presence of product shown by LCMS in Supporting Information.

MHz, $CDCl_3$): 1.00 (9 H, s), 1.59 (6 H, s), 1.91 (2H, s), 4.30 (1H, br s), 6.72 (1 H, dd, J = 4.5 and 6.5), 7.42 (2 H, d, J = 8.5), 7.51 (2 H, d, J = 8.5), 8.24 (1 H, dd, J = 4.5 and 2.0), 8.29 (1 H, dd, J = 6.5 and 2.0). δ_C (400 MHz, $CDCl_3$): 29.0, 31.6, 31.7, 56.8, 60.7, 107.9, 121.9, 128.2, 129.7, 131.4, 133.2, 133.4, 139.9, 145.0, 149.4. HRMS (ES-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{26}ClN_4$ 357.1846, found 357.1862.

2-(4-Chlorophenyl)-*N*-(2,4,4-trimethylpentan-2-yl)imidazo-[1,2-*a*]pyrimidin-3-amine 5a and 3-(4-Chlorophenyl)-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-*a*]pyrimidin-2-amine 5b. *Standard Batch Synthesis Method.* 2-Aminopyrimidine (380 mg, 4 mmol), *p*-chlorobenzaldehyde (562 mg, 4 mmol), and $ZrCl_4$ (93 mg, 0.4 mmol) were stirred in MeOH–CH_2Cl_2 (1:3, 50 mL) for 30 min at room temperature. After this time, Walborsky's reagent (702 μL, 556 mg, 4 mmol) was introduced to the reaction flask, and the mixture heated at 45 °C for 24 h. The solution was evaporated to dryness under reduced pressure and the crude material purified by column chromatography on basic alumina, eluted with 10 → 15 → 20 → 50% EtOAc/toluene, affording **5a** (507 mg, 36%) as a pale-yellow solid, with analytical data in agreement with those above, and **5b** (157 mg, 11%) as a bright-yellow crystalline solid: mp 62–72 °C. ν_{max} (solid/cm^{-1}): 3244, 2950, 2890, 1567, 1496, 1478, 1188, 751. δ_H (400 MHz, $CDCl_3$): 0.98 (6H, s), 1.05 (9H, s), 1.59 (2 H, s), 3.29 (1 H, s), 6.88 (1 H, dd, J = 4.0 and 7.0), 7.42 (2 H, d, J = 8.5), 7.93 (2 H, d, J = 8.5), 8.52 (2 H, dd, J = 2.0 and 4.0), 8.55 (2H, dd, J = 2.0 and 7.0). δ_C (400 MHz, $CDCl_3$): 30.1, 31.7, 31.8, 52.9, 56.2, 101.9, 107.7, 126.7, 127.5,129.1, 130.1, 133.0, 145.0, 146.6, 151.4. HRMS (ES-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{26}ClN_4$ 357.1846, found 357.1868. Repeat reactions, with different durations of heating in the final stage, were carried out and their results used to compile the graph shown in Figure 3a.

2-Phenyl-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-*a*]pyrimidin-3-amine 6a and 3-Phenyl-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-*a*]pyrimidin-2-amine 6b.[14] 2-Aminopyrimidine (951 mg, 10 mmol), benzaldehyde (1.02 mL, 1.06 g, 10 mmol), and $Sc(OTf)_3$ (123 mg, 0.25 mmol) were stirred in MeOH–CH_2Cl_2 (1:3, 100 mL) for 30 min at room temperature. Walborsky's reagent (1.75 mL, 1.39 g, 10 mmol) was then added and the mixture heated at 45 °C for 48 h. The solution was evaporated under reduced pressure and the

dx.doi.org/10.1021/jo501861g | J. Org. Chem. 2014, 79, 10196–10202

residue purified by column chromatography on basic alumina, eluted with 20 → 30 → 50% EtOAc/hexane, then CH_2Cl_2, then 1% MeOH/CH_2Cl_2, to provide **6b** (0.74 g, 23%) as a yellow crystalline solid: mp 88−94 °C; purity (HPLC) 92.6%. ν_{max} (solid/cm^{-1}): 3288, 2948, 2362, 1608, 1561, 1185, 888. δ_H (400 MHz, $CDCl_3$): 1.01 (9 H, s), 1.60 (6 H, s), 1.93 (2 H, s), 4.37 (1 H, br s), 6.71 (1 H, dd, J = 6.5 and 4.5), 7.38 (1 H, t, J = 7.5), 7.58−7.47 (3H, m), 8.24 (1 H, dd, J = 2.0 and 4.5), 8.36 (1 H, dd, J = 2.0 and 6.5). δ_C (400 MHz, $CDCl_3$): 30.2, 31.6, 31.7, 31.8, 53.1, 56.1, 107.5, 126.7, 127.5, 127.8, 128.5, 129.0, 129.8, 144.6, 151.3. m/z (ES) 322 (100%). HRMS (ES-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{27}N_4$ 323.2250, found 323.2236). **6a** (0.81 g, 25%) as a pale-yellow solid; mp 215−225 °C; purity (HPLC) 98.7%. ν_{max} (solid/cm^{-1}): 3333, 2949, 1742, 1607, 1498, 1308, 1190, 885. δ_H (400 MHz, $CDCl_3$): 0.96 (6 H, s), 1.03 (9H, s), 1.57 (2H, s), 3.33 (1H, br s), 6.84 (1H, dd, J = 4.0 and 7.0), 7.35 (1 H, t, J = 7.5), 7.45 (2H, t, J = 7.5), 7.92 (2H, t, J = 7.5), 8.49 (1H, dd, J = 2.0 and 4.0), 8.56 (1H, dd, J = 2.0 and 7.0). δ_C (400 MHz, $CDCl_3$): 29.0, 31.7, 31.8, 56.9, 60.9, 107.8, 121.8, 127.9, 128.3, 128.6, 131.2, 134.8, 141.5, 149.3. HRMS (ES-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{27}N_4$ 323.2236, found 323.2235. Both products from this reaction were used as HPLC reference standards for subsequent optimization experiments. In addition, the sample of **6b** prepared here was crystallized from toluene for use in X-ray structure determination.

Catalyst Optimization Experiments (Figure 4, Batch Conditions). 2-Aminopyrimidine (190 mg, 2 mmol), benzaldehyde (203 μL, 212 mg, 2 mmol), and the appropriate quantity of catalyst [2.5 or 10 mol % $Sc(OTf)_3$ or $ZrCl_4$] were combined in MeOH−CH_2Cl_2 (1:3, 20 mL) and stirred at room temperature for 30 min. Walborsky's reagent (351 μL, 278 mg, 2 mmol) was then added and the solution heated at 45 °C for 24 h. At this point, an aliquot of the reaction mixture was diluted 1:10 with CH_2Cl_2 then analyzed by HPLC to determine yields of **6a** and **6b**. Results are graphed in Figure 2.

Catalyst Optimization Experiments (Figure 4, Flow Conditions). Intake line A of the flow reactor was charged with a solution of 0.2 M 2-aminopyrimidine, 0.2 M benzaldehyde, and the appropriate concentration of catalyst in MeOH−CH_2Cl_2 (1:3), which had been premixed at least 30 min prior to use. Line B contained 0.2 M Walborsky's reagent in the same solvent system. The reagents were combined in the reactor coil at 80 °C for a residence time of 50 min. An aliquot of postreactor product solution from the steady-state region was drawn and analyzed as above, with the results also graphed in Figure 2.

Continuous Flow Synthesis of Imidazo[1,2-*a*]pyrimidines (Table 1) (General Procedure). Intake line A was charged with a solution of 0.2 M 2-aminopyrimidine, 0.2 M starting aldehyde, and 0.02 M $ZrCl_4$ in MeOH−CH_2Cl_2 (1:3), which had been premixed at least 30 min prior to use. Line B contained 0.2 M isocyanide in the same solvent system. The solutions were combined and passed through the reactor at 80 °C with a residence time of 50 min (or a flow rate of 0.2 mL/min). The crude product solution was collected, evaporated under reduced pressure, and then the residue purified as indicated below for each individual case. Reactions were each carried out on a 0.4 mmol scale, based on 2-aminopyrimidine, unless otherwise stated.

2-(4-Methoxyphenyl)-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-*a*]pyrimidin-3-amine 7a.[14] General procedure followed using *p*-anisaldehyde and Walborsky's reagent. Column chromatography on basic alumina, eluted with 30 → 50% EtOAc/toluene then 1% MeOH/CH_2Cl_2, yielded **7a** (0.063 g, 45%) as a yellow crystalline solid; mp 90−92 °C; purity (HPLC) 91.2%. δ_H (400 MHz, $CDCl_3$): 0.94 (6H, s), 1.01 (9H, s), 1.56 (2H, s), 3.27 (1H, s), 3.84 (3H, s), 6.80 (1H, dd, J = 4.0 and 7.0), 6.95 (2H, d, J = 9.0), 7.86 (2H, d, J = 9.0), 8.44 (1H, dd, J = 2.0 and 7.0), 8.50 (1H, dd, J = 2.0 and 7.0). δ_C (100 MHz, $CDCl_3$): 29.0, 31.7, 31.8, 55.2, 56.9, 60.8, 107.6, 113.7, 121.1, 127.3, 129.8, 131.0, 141.3, 148.9, 158.3, 159.3; HRMS (ES-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{29}N_4O$ 353.2341, found 353.2350.

2-(Thiophen-2-yl)-*N*-(2,4,4-trimethylpentan-2-yl)imidazo[1,2-*a*]pyrimidin-3-amine 8a. General procedure followed using thiophene-2-carboxaldehyde and Walborsky's reagent. Column chromatography was carried out on basic alumina, eluted with 20 → 30 → 50% EtOAc/toluene then 1% MeOH/CH_2Cl_2, after which the title compound was obtained as a dark-yellow amorphous solid (0.079 g, 60%). ν_{max} (solid/cm^{-1}): 3433, 3080, 2962, 1984, 1604, 1221, 1012, 888. δ_H (400 MHz, $CDCl_3$): 1.10 (9 H, s), 1.14 (6 H, s), 1.71 (2 H, s), 3.28 (1 H, s), 6.83 (1 H, dd, J = 4.0 and 7.0), 7.13 (1 H, dd, J = 4.0 and 5.0), 7.37 (1 H, dd, J = 1.0 and 5.0), 7.66 (1 H, dd, J = 1.0 and 4.0), 8.49 (1 H, dd, J = 2.0 and 7.0), 8.50 (1 H, dd, J = 4.0 and 2.0). δ_C (100 MHz, $CDCl_3$): 29.3, 31.8, 31.9, 57.1, 61.2, 107.8, 121.0, 125.7, 126.1, 127.3, 131.1, 136.5, 136.7, 149.5, 158.3. HRMS (ES-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{25}N_4S$ 329.1800, found 329.1816.

2-Phenyl-*N*-(2-(thiophen-2-yl)ethyl)imidazo[1,2-*a*]pyrimidin-3-amine 9a. Prepared by the general procedure, with benzaldehyde and 2-(2-thienyl)ethyl isocyanide. Column chromatography on basic alumina, using 33 → 50 → 80% EtOAc/toluene then 1% MeOH/CH_2Cl_2 as eluent, followed by a further column on silica eluted with 30 → 50 → 80% EtOAc/toluene, afforded the title compound (0.063, 49%) as a yellow amorphous solid. Purity (HPLC) 99.2%. ν_{max} (solid/cm^{-1}): 3302, 3076, 2924, 2850, 1610, 1491, 1444, 1213, 1188, 783, 761, 690. δ_H (400 MHz, DMSO-d_6): 3.02 (2H, t, J = 7.0), 3.23 (2H, q, J = 6.0), 5.11 (1H, t, J = 6.0), 6.82 (1H, dd, J = 7.0 and 4.0), 6.89 (1H, dd, J = 3.5 and 1.0), 7.01 (1H, dd, J = 5.0 and 3.5), 7.25 (1H, dd, J = 5.0 and 1.0), 7.38−7.32 (1H, m), 7.52−7.40 (2H, m), 8.02−7.94 (2H, m), 8.17 (1H, dd, J = 7.0 and 2.0), 8.50 (1H, dd, J = 2.0 and 4.0). δ_C (100 MHz, $CDCl_3$): 31.0, 49.3, 108.1, 123.9, 124.1, 125.8, 127.1, 127.3, 127.9, 128.7, 130.1, 133.4, 137.3, 141.4, 144.5, 149.2. HRMS (ES-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{17}N_4S$ 321.1174, found 321.1186.

2-(4-(1*H*-Pyrazol-1-yl)phenyl)-*N*-(2-(thiophen-2-yl)ethyl)imidazo[1,2-*a*]pyrimidin-3-amine 10a. General procedure followed using 4-(1*H*-pyrazol-1-yl)benzaldehyde and 2-(2-thienyl)ethyl isocyanide. Flash column chromatography on silica, eluted with 20 → 50 → 80% ethyl acetate/petroleum ether, afforded the title compound (0.085 g, 55%) as a yellow amorphous solid. Purity (HPLC) 98.0%. ν_{max} (solid/cm^{-1}): 3284, 3086, 2924, 2853, 1613, 1562, 1526, 1394, 1319, 1243, 1216, 1120, 1046, 1030, 935, 847. δ_H (400 MHz, DMSO-d_6): 3.05 (2H, t, J = 7.0), 3.27 (2H, q, J = 7.0), 5.15 (1H, t, J = 6.0), 6.58 (1H, t, J = 2.0), 6.87 (1H, d, J = 3.5), 6.94 (1H, dd, J = 3.5 and 5.0), 7.02 (1H, dd, J = 4.0 and 7.0), 7.33 (1H, dd, J = 1.0 and 5.0), 7.79 (1H, d, J = 1.0), 7.92 (2H, d, J = 9.0), 8.25 (2H, d, J = 9.0), 8.48 (1H, dd, J = 2.0 and 4.0), 8.37 (1H, d, J = 2.5), 8.63 (1H, dd, J = 2.0 and 7.0). δ_C (100 MHz, DMSO-d_6): 31.1, 49.7, 108.5 (d, J = 16.5), 118.8, 119.5, 124.4, 125.5, 125.8, 127.4, 128.1 (d, J = 8.2), 129.1, 131.8, 132.3, 134.7, 139.1, 141.5, 142.2, 144.2, 149.9. HRMS (ES-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}N_6S$ 387.1392, found 387.1404.

***N*-(3-Fluoro-4-methylphenyl)-2-*p*-tolylimidazo[1,2-*a*]pyrimidin-3-amine 11a.** Prepared by the general procedure with *p*-tolualdehyde and 2-fluoro-4-isocyano-1-methylbenzene. The crude material was subjected to column chromatography on silica, eluted with 0 → 1→2 → 4% MeOH/CH_2Cl_2, providing the title compound as a yellow solid (0.057 g, 43%) after further recrystallization from CH_2Cl_2/hexane: mp 89−97 °C. Purity (HPLC) 97.6%. ν_{max} (solid/cm^{-1}): 3214, 3074, 2912, 1506, 1374, 1317, 1242, 1115, 806, 765, 750. δ_H (400 MHz, DMSO-d_6): 2.06 (3H, s), 2.30 (3H, s), 6.22 (1H, d, J = 8.5), 6.28 (1H, d, J = 12.0), 6.99 (1H, t, J = 8.5), 7.03 (1H, dd, J = 4.5 and 6.5), 7.22 (2H, d, J = 8.0), 7.93 (2H, d, J = 8.0), 8.32 (1H, s), 8.39 (1H, d, J = 7.0), 8.55−8.57 (1H, m). δ_C (100 MHz, DMSO-d_6): 13.3 (d, J = 2.5), 20.8, 100.0 (d, J = 26.5), 108.8, 113.5 (d, J = 17.5), 116.7, 126.6, 129.2, 130.2, 131.26, 132.3 (d, J = 7.0), 137.4, 144.9, 145.2 (d, J = 10.0), 150.4, 160.5, 162.4. HRMS (ES-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{18}N_4F$ 333.1516, found 333.1518.

***N*-(4-Chlorobenzyl)-2-(thiophen-2-yl)imidazo[1,2-*a*]pyrimidin-3-amine 12a.** General procedure followed using thiophene-2-carboxaldehyde and *p*-chlorobenzyl isocyanide. Successive recrystallizations from EtOAc/hexane, then CH_2Cl_2/hexane, provided the title compound (0.075 g, 55%) as a dark-yellow amorphous solid. Purity (HPLC) 98.9%. ν_{max} (solid/cm^{-1}): 3275, 3049, 2978, 2856, 1610, 1490, 1198, 790, 767, 695. δ_H (400 MHz, DMSO-d_6): 4.15 (2H, d, J = 6.5), 5.46 (1H, t, J = 6.5), 6.96 (1H, dd, J = 4.0 and 7.0), 7.17 (1H, dd, J = 3.5 and 5.0), 7.32−7.39 (4H, m), 7.58 (1H, dd, J = 1.0

dx.doi.org/10.1021/jo501861g | J. Org. Chem. 2014, 79, 10196−10202

and 5.0), 7.68 (1H, dd, J = 1.0 and 3.5), 8.43 (1H, dd, J = 2.0 and 4.0), 8.52 (1H, dd, J = 2.0 and 7.0). δ_C (100 MHz, DMSO-d_6): 50.0, 108.0, 123.3, 124.5, 126.1, 127.8, 128.2, 130.1, 131.3, 131.7, 132.3, 136.7, 138.7, 143.6, 149.5. HRMS (ES-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{13}ClN_4SNa$ 363.0447, found 363.0446.

***N*-(4-Chlorobenzyl)-2-phenylimidazo[1,2-*a*]pyrimidin-3-amine 13a.** Prepared by the general procedure using benzaldehyde and 4-chlorobenzyl isocyanide. Column chromatography on basic alumina, eluted with 0 → 5→10 → 20 → 50% EtOAc/toluene, provided the title compound (0.062 g, 46%) as a yellow amorphous solid. Purity (HPLC) 98.6%. ν_{max} (solid/cm^{-1}): 3268, 3051, 2973, 2855, 1610, 1492, 793, 766, 713, 693, 662. δ_H (400 MHz, $CDCl_3$): 4.02 (1H, br s), 4.17 (2H, s), 6.80 (1H, dd, J = 4.0 and 7.0), 7.17−7.26 (4H, m), 7.34−7.40 (1H, m), 7.43−7.49 (2H, m), 8.03 (2H, d, J = 7.5), 8.32 (1H, dd, J = 2.0 and 7.0), 8.4 (1H, dd, J = 2.0 and 4.0). δ_C (100 MHz, $CDCl_3$): 51.7, 108.3, 123.8, 127.4, 128.1, 128.7, 128.8, 129.6, 130.2, 133.1, 133.5, 137.3, 137.4, 144.3, 149.6. HRMS (ES-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{16}ClN_4$ 335.1063, found 335.1061.

***N*-(4-Chlorobenzyl)-2-(2-ethylbutyl)imidazo[1,2-*a*]pyrimidin-3-amine 14a.** Prepared by the general procedure with 2-ethylbutyraldehyde and 4-chlorobenzyl isocyanide. Flash column chromatography on silica, eluted with 20 → 33 → 50 → 80% ethyl acetate/petroleum ether provided the title compound as a yellow amorphous solid (0.036 g, 27%). Purity (HPLC) 92.4%. ν_{max} (solid/cm^{-1}): 3228, 3069, 2960, 2929, 2871, 1615, 1492, 1408, 1374, 1318, 1090, 1014, 781, 732. δ_H (400 MHz, $CDCl_3$): 0.81 (6H, t, J = 7.5), 1.72−1.90 (4H, m), 2.55−2.63 (1H, m), 3.45 (1H, s), 4.13 (2H, s), 6.75 (1H, dd, J = 4.0 and 7.0), 7.27−7.32 (4H, m), 8.17 (1H, dd, J = 2.0 and 7.0), 8.41 (1H, dd, J = 2.0 and 4.0). δ_C (100 MHz, $CDCl_3$): 12.6, 27.9, 41.4, 53.0, 107.7, 124.7, 128.8, 129.6, 129.6, 133.5, 137.6, 143.9, 144.6, 148.4. HRMS (ES-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{22}ClN_4$ 329.1533, found 329.1519.

***N*-(4-Chlorobenzyl)-2-propylimidazo[1,2-*a*]pyrimidin-3-amine 15a.** Prepared by the general procedure with propionaldehyde and 4-chlorobenzyl isocyanide. Flash column chromatography on silca, eluted with 20 → 50 → 80% ethyl acetate/petroleum ether, provided the title compound as a yellow amorphous solid (0.038 g, 32%). Purity (HPLC) 92.7%. ν_{max} (solid/cm^{-1}): 3228, 2932, 2875, 1654, 1614, 1596, 1519, 1491, 1462, 1408, 1340, 1272, 1214, 1175, 1090, 1067, 1014, 800, 767. δ_H ($CDCl_3$, 400 MHz): 1.33 (3H, t, J = 7.5), 2.73 (2H, q, J = 7.5), 3.54 (1H, s), 4.14 (2H, s), 6.80 (1H, dd, J = 4.0 and 7.0), 7.21−7.31 (4H, m), 8.26 (1H, dd, J = 2.0 and 7.0), 8.44 (1H, dd, J = 2.0 and 4.0). δ_C ($CDCl_3$, 100 MHz): 13.8, 20.4, 52.7, 108.0, 128.8, 129.2, 129.7, 129.8, 133.6, 137.6, 142.5, 148.7. HRMS (ES-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{16}N_4Cl$ 287.1063, found 287.1058.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures of X-ray crystal structures, ^{1}H NMR and ^{13}C NMR for all compounds in Table 1, LC-MS data for **8b**, **9b**, **10b**, **11b**, and **13b**, and crystallographic data for compounds **5a**, **6b**, and **11a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*b.chen@sheffield.ac.uk

Present Addresses

[†]Notre Dame High School, Fulwood Road, Sheffield S10 3BT, U.K.

[‡]Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, U.K.

[§]College of Biotechnology and Pharmaceutical Engineering, Nanjing Tech University, No. 30 South Puzhu Road, Pukou District, Nanjing, Jiangsu Province, P.R. China 211816.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for funding from the UK Department of Health, The Home Office (contract no. 04-70-174), EPSRC (for a studentship to A.J.E.B.), and National Key Basic Research Program of China (973 Program) 2012CB725204 and 2011CB710803. We also thank Vapourtec for their continued technical support.

■ REFERENCES

(1) Groebke, K.; Weber, L.; Mehlin, F. *Synlett* **1998**, 661−663.

(2) Blackburn, C.; Guan, B.; Fleming, P.; Shiosaki, K.; Tsai, S. *Tetrahedron Lett.* **1998**, *39*, 3635−3638.

(3) Bienayme, H.; Bouzid, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 2234−2237.

(4) Krasavin, M.; Tsirulnikov, S.; Nikulnikov, M.; Kysil, V.; Ivachtchenko, A. *Tetrahedron Lett.* **2008**, *49*, 5241−5243.

(5) Hulme, C.; Lee, Y.-S. *Mol. Diversity* **2008**, 1−15.

(6) Alexander, D. *Chem. Rev.* **2006**, *106*, 17−89.

(7) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3168−3210.

(8) Feely, M.; Boyland, P.; Picardo, A.; Cox, A.; Gent, J. P. *Eur. J. Pharmacol.* **1989**, *164*, 377−380.

(9) Tully, W. R.; Gardner, C. R.; Gillespie, R. J.; Westwood, R. *J. Med. Chem.* **1991**, *34*, 2060−2067.

(10) Atack, J. R. *Expert Opin. Invest. Drugs* **2005**, *14*, 601−618.

(11) Guo, C.; Linton, A.; Kephart, S.; Ornelas, M.; Pairish, M.; Gonzalez, J.; Greasley, S.; Nagata, A.; Burke, B. J.; Edwards, M.; Hosea, N.; Kang, P.; Hu, W.; Engebretsen, J.; Briere, D.; Shi, M.; Gukasyan, H.; Richardson, P.; Dack, K.; Underwood, T.; Johnson, P.; Morell, A.; Felstead, R.; Kuruma, H.; Matsimoto, H.; Zoubeidi, A.; Gleave, M.; Los, G.; Fanjul, A. N. *J. Med. Chem.* **2011**, *54*, 7693−7704.

(12) Linton, A.; Kang, P.; Ornelas, M.; Kephart, S.; Hu, Q.; Pairish, M.; Jiang, Y.; Guo, C. *J. Med. Chem.* **2011**, *54*, 7705−7712.

(13) Mandair, G. S.; Light, M.; Russell, A.; Hursthouse, M.; Bradley, M. *Tetrahedron Lett.* **2002**, *43*, 4267−4269.

(14) Thompson, M. J.; Hurst, J. M.; Chen, B. *Synlett* **2008**, 3183−3187.

(15) Parchinsky, V. Z.; Shuvalova, O.; Ushakova, O.; Kravchenko, D. V.; Krasavin, M. *Tetrahedron Lett.* **2006**, *47*, 947−951.

(16) Varma, R. S.; Kumar, D. *Tetrahedron Lett.* **1999**, *40*, 7665−7669.

(17) Carballares, S.; Cifuentes, M. M.; Stephenson, G. A. *Tetrahedron Lett.* **2007**, *48*, 2041−2045.

(18) Guchhait, S.; Madaan, C. *Synlett* **2009**, 628−632.

(19) Rodrigues, T.; Schneider, P.; Schneider, G. *Angew. Chem., Int. Ed. Engl.* **2014**, *53*, 5750−5758.

(20) Elvira, K. S.; Solvas, X. C.; Wootton, R. C. R.; deMello, A. J. *Nature Chem.* **2013**, *5* (11), 905−915.

(21) Willumstad, T. P.; Haze, O.; Mak, X. Y.; Lam, T. Y.; Wang, Y.; Danheiser, R. L. *J. Org. Chem.* **2014**, *78* (22), 11450−11469.

(22) Watts, P.; Wiles, C. Synthesis of Heterocyclic Compounds Using Continuous Flow Reactors. In *Pyridines: From Lab to Production*; Best Synthetic Methods; Scriven, E. F. V., Ed.; Academic Press: New York, 2013; Chapter 9 , pp 531548.

(23) Bremner, W. S.; Organ, M. G. *J. Comb. Chem.* **2007**, *9* (1), 14016.

(24) Malet-Sanz, L.; Susanne, F. *J. Med. Chem.* **2012**, *55*, 4062−4098.

(25) Herath, A.; Dahl, R.; Cosford, N. D. P. *Org. Lett.* **2010**, *12*, 412−415.

(26) Thompson, M. J.; Chen, B. *J. Org. Chem.* **2009**, *74*, 7084−7093.