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Synthesis of Annulated Pyridines by Intramolecular Inverse-Electron-Demand Hetero-Diels–Alder Reaction under Superheated Continuous Flow Conditions

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Pyrimidine alkynes can be transformed into the corresponding annulated pyridines efficiently in flow. The superheating of organic solvents far beyond their boiling point enables toxic and difficult to workup solvents such as nitrobenzene or chlorobenzene, which are usually employed for these reactions, to be replaced by less harmful ones like toluene. The relative rate of reactivity for a series of structurally close starting materials was investigated and a scalable flow process was developed, providing facile access to a series of novel annulated pyridine building blocks. The effect of thermal volume expansion of solvents under superheated conditions was found to be significant and influenced the residence times considerably. To obtain meaningful and accurate residence times, flow rates need to be corrected for volume expansion. To avoid confusion with residence times, t_R, calculated from nominal flow rates, we would propose to use for such corrected residence times the term *effective residence time*, $t_{R,eff}$.

Introduction

Flow chemistry has attracted considerable attention over recent years as an enabling and innovative technology that significantly enhances the classical process window typically accessible with standard batch laboratory equipment.[1] Flow chemical approaches have been found to be advantageous, as they allow not only for automation of operations, but also lead to better control of chemical processes due to improved heat and mass transfer.[2] Unconventional and harsh reaction conditions such as greatly elevated temperatures and pressures can be generated easily, allowing the superheating of organic solvents far beyond their boiling point in a controlled and safe manner. Therefore, toxic and difficult to workup solvents can be replaced by less harmful, environmentally benign solvents. Furthermore, reactions which were formerly avoided due to serious safety concerns can now be conducted conveniently in flow, as only small quantities of reactive materials or hazardous intermediates are within the reactor at a given time.[3] Flow chemistry thus offers an ideal opportunity to revisit challenging, difficult to operate, or dangerous reactions that have been underutilized in the past.

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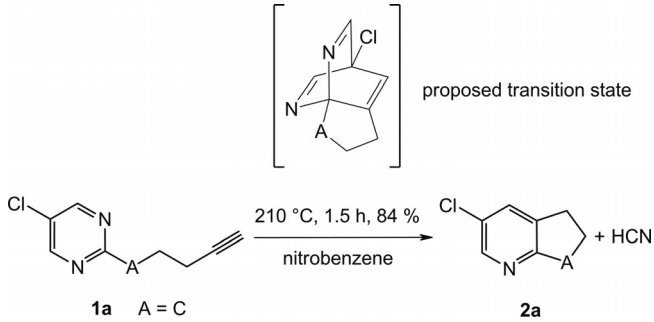
Results and Discussion

One of these "neglected reactions" that we have recently become interested in and started to reinvestigate is the transformation of pyrimidine alkynes of type **1a** to the corresponding annulated pyridine systems **2a** by an inverse-electron-demand hetero-Diels–Alder (HDA) reaction and subsequent cycloreversion reaction cascade (Scheme 1).[4] Pyridines are one of the most important heterocyclic structural motifs and are found in numerous natural products, active pharmaceuticals, and functional materials, and a number of synthetic methodologies for their preparation have been documented.[5] The HDA reaction is assumed to occur via an intermediate tricyclic adduct which results from an intramolecular [4+2] cycloaddition across the C2 and C5 position of the pyrimidine ring followed by subsequent elimination of hydrogen cyanide.[6]



Scheme 1. Classical batch synthesis of dihydro-5*H*-[1]pyridine **2a** by using nitrobenzene as solvent.[4]

Typically, these reactions are favored by strong electron-withdrawing groups on the heteroaromatic azadiene and electron-rich dienophiles, with the presumed cycloaddition reaction being the rate-determining step in this sequence.[7] In cases where A ≠ C but a heteroatom such as O or N, the reactivity of these systems is reduced due to both stereoelectronic and conformational reasons. On the one hand, heteroatoms donate additional electron density into the aza-aryl system, and on the other hand, side chains connected through heteroatoms (A ≠ C) adopt an unfavorable in-plane conformation (the N–C–A–C torsion angle shows a strong preference around 0°), which is not optimally aligned for the HDA reaction.[8] On the contrary, in cases with substituents A = C, SO_2, or NAc, a productive, perpendicular orientation of the side chain to the azadiene ring system is strongly favored, thereby allowing the reaction partners to approach one another better. As a consequence, in cases with heteroatom linkers, rather high reaction temperatures and extended reaction times are required to achieve acceptable conversion rates. Therefore these reactions have classically been conducted in high-boiling solvents such as nitrobenzene, dichlorobenzene, or diphenyl ether that are not only toxic, but also difficult to remove during workup.[4,6] Moreover, during the second retro-HDA step, hydrogen cyanide is produced in stoichiometric amounts, which poses a considerable safety risk requiring specific precautionary measures and thus further limits the scalability of this procedure within a conventional research environment.

Our initial efforts focused on the development of a stable and scalable flow process for the conversion of chloropyrimidine **1a** into the corresponding dihydro-5*H*-[1]pyridine **2a**. The Vapourtec R2+/R4 flow system equipped with a high-temperature 316 stainless steel tube flow reactor (SSTFR, 10 mL) and a 250 psi back-pressure regulator (BPR) was used to conduct this step, allowing the use of toluene as a solvent safely under superheated conditions.[9] The starting material was introduced as a 0.14 M solution through a reagent loop (1 mL) at a flow rate of 200 μL min^{-1}. The crude reaction stream was collected in an aqueous solution of sodium hydroxide and HCN was purged by a stream of nitrogen through two subsequent wash bottles equipped with a mixture of sodium hydroxide and sodium hypochlorite (bleach), which enabled this process to be run safely even on a larger scale. A schematic representation of the flow configuration is shown in Figure 1. Due to the harsh reaction conditions required in batch for this transformation we started the evaluation process at 210 °C up to the maximum temperature of 250 °C achievable in this system, varying the residence time t_R from 20 min to 50 min.

According to ^{1}H NMR spectroscopic analysis, heating of **1a** in toluene at 210 °C for 20 min resulted in the formation of the product in only 1%, which was improved considerably to 49% by increasing the heating temperature to 250 °C. Extending the residence time at the same temperature to 50 min resulted in a further significant improvement to nearly quantitative conversion of 96%. Encouraged by these optimization results we processed a 600 mg batch of **1a**, which provided, after aqueous workup and MPLC chromatography, desired product **2a** in an excellent 94% isolated yield. On the basis of these results we aimed for a further scale up to multigram quantities of **1a** by using the same equipment and identical processing parameters. By making use of both pumps of the Vapourtec R2+/R4 flow system and two SSTFR coils setup in parallel, the theoretical processing time of 54 h was reduced down to 27 h. However, after an initial processing time of 6–8 h (system pressure of about 20 bar), a gradual pressure increase was observed, which eventually led to a complete blockage of the reactor coils within 2–4 h resulting in an automated shutdown of the flow system as the maximum pressure of 50 bar was reached. Attempts to clean the reactor coils by repeated flushing with a number of different solvents of varying polarity ranging from acetone to methanol and finally water failed. In addition, dilute acids and bases were not successful in dissolving the blockage either. Repeating the flow experiment under the same reaction conditions by using a new reactor coil resulted in a similar observation with rapid internal pressure onset after a short, initially stable, processing period. To identify the cause of the obstruction, a reactor tube was cut open and the content visually inspected. A black polymer-like substance could be scratched out, which was poorly soluble in both water and organic

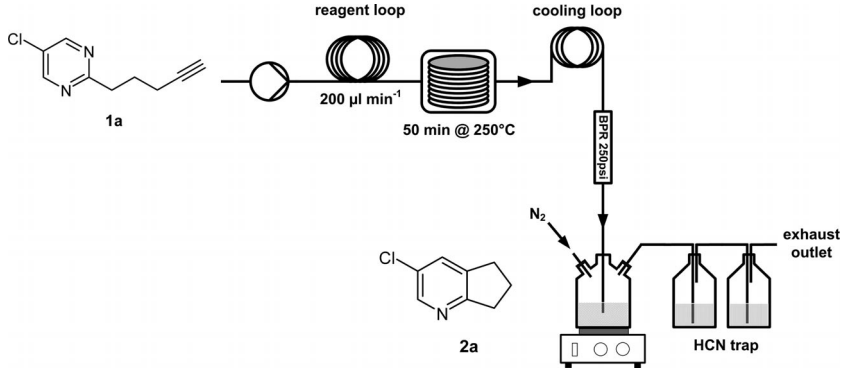


Figure 1. Illustration of the flow reactor configuration used for the transformation of pyrimidine **1a** into the corresponding annulated pyridine **2a** by employing the commercial Vapourtec R2+/R4 flow system.

solvents and most likely is the polymerization product of HCN eliminated during the retro-HDA reaction (see the Supporting Information). HCN is known to form spontaneously oligomers and polymers in nonaqueous solvents and in water even under much milder reaction conditions, a process which is known to be very difficult to control.[10] Analysis of cross- and longitudinal section cuts of the reactor revealed that the entire tube was not blocked by polymerization products, but that small plugs were formed randomly that started to aggregate and ultimately caused obstruction of the flow. Interestingly, there was no observed damage to the stainless steel surface, as trace amounts of water (toluene was not dried before use) in combination with HCN might have caused corrosion of the reactor material. Attempts to reduce polymer formation by addition of bases such as triethylamine and isopropyl ethylamine or acids like acetic acid were not successful. Moreover, introducing alternating washing cycles after 1 h processing time to rinse the reactor coil did not help considerably to diminish the gradual pressure increase or to reduce the number of blockage events. However, pentan-3-one [1% (v/v) in toluene] was finally identified as the most effective HCN trapping agent (likely by cyanohydrin adduct formation), which enabled stable, continuous processing over many hours, reliably preventing pressure increase and reactor fouling. In addition, we used a short silica plug in an OmniFit column to protect the back-pressure regulator from blockage. This slight modification to the processing conditions allowed us to keep the process stable for several hours, enabling the production of 21 g (137 mmol) of building block **2a** in a yield of 84% after MPLC purification. The structure of compound **2a** was also confirmed by single-crystal X-ray analysis (Figure 2).[11]

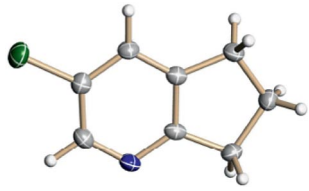
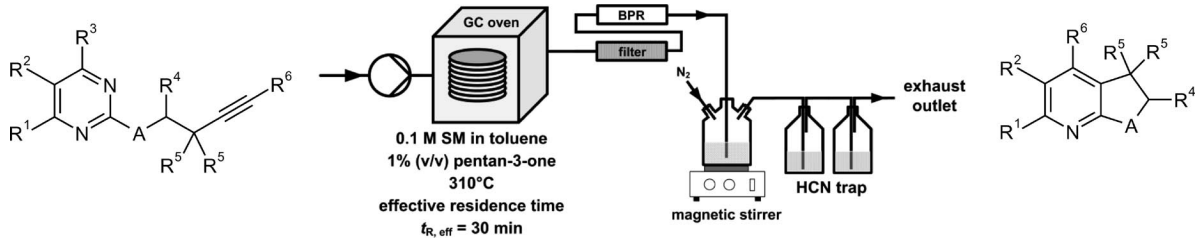


Figure 2. Single-crystal X-ray diffraction analysis of 3-chloro-6,7-dihydro-5*H*-[1]pyridine (**2a**). The ORTEP drawing depicts thermal ellipsoids at a 30% probability level.

On the basis of these encouraging results we decided to further examine the scope and limitations of this interesting transformation on a number of closely related building

Table 1. Synthesis of annulated pyridines **2a**–**u** in flow.



Entry	Starting material	Product	A	R^1	R^2	R^3	R^4	R^5	R^6	% Yield[a]
1	**1a**	**2a**	C	H	Cl	H	H	H	H	95
2	**1b**	**2b**	O	Cl	H	Cl	H	H	H	70
3	**1c**	**2c**	O	Cl	H	Cl	H	H	TMS	75
4	**1d**	**2d**	O	Cl	H	Cl	H	H	CH_3	31
5	**1e**	**2e**	O	H	H	H	H	H	H	52
6	**1f**	**2f**	O	H	F	H	H	H	H	65
7	**1g**	**2g**	O	H	Cl	H	H	H	H	60
8	**1h**	**2h**	O	H	Br	H	H	H	H	64
9	**1i**	**2i**	O	H	NO_2	H	H	H	H	60
10	**1j**	**2j**	O	H	CN	H	H	H	H	41
11	**1k**	**2k** ≡ **2b**	O	Cl	H	H	H	H	H	72[b]
12	**1l**	**2l**	O	OCH_3	H	H	H	H	H	23[b]
13	**1m**	**2m**	O	$O(CH_2)_2C{\equiv}CH$	H	H	H	H	H	16[b]
14	**1n**	**2n**	O	Ph	H	H	H	H	H	55[b]
15	**1o**	**2o**	O	CH_3	H	CH_3	H	H	H	41
16	**1p**	**2p**	O	Cl	H	Cl	CH_3	H	H	31
17	**1q**	**2q**	O	Cl	H	Cl	H	CH_3	H	59
18	**1r**	**2r**	NH	H	Cl	H	H	H	H	21
19	**1s**	**2s**	S	H	Cl	H	H	H	H	95
20	**1t**	**2t**	SO_2	H	Cl	H	H	H	H	75
21	**1u**	**2u**	NAc	H	Cl	H	H	H	H	83[c]

[a] Yield of isolated product after aqueous extraction and purification by MPLC. [b] From two possible isomers, the one following expulsion of HCN is formed exclusively. [c] Processing temperature 230 °C; at 310 °C decomposition is observed.

blocks. We were particularly interested in more challenging substrates with non-carbon-linked side chains, where rate acceleration by superheating under flow conditions would be even more important. Substrates with A = O or NH are known to be much less reactive in the HDA reaction than their carbon counterparts and often require significantly extended periods of heating to obtain acceptable yields.[12] Again, toluene was considered to be an ideal solvent for this transformation, as it allows facile superheating, easy removal during workup, and exhibits reduced toxicity. To heat toluene significantly beyond 300 °C pressures of up to 70 bar are required. Therefore, we switched from the Vapourtec R2+/R4 flow system to a self-made system consisting of a Knauer K-501 pump with internal pressure sensor (upper pressure limit of 400 bar) connected to a gas chromatography oven from a HP 6890 Series system, which allowed us to reach temperatures of up to 400 °C quickly and safely (see the Supporting Information). As a reactor coil, stainless steel tubing from Supelco with an ID of 2.1 mm and 15.2 m length was used, providing a reactor volume of 53 mL, which allows for facile upscaling.[13] The reactor outlet was equipped with a small Omnifit glass chromatography column[14] filled with a short silica plug and glass wool to protect the 750 psi back-pressure regulator, which is required to keep toluene in the liquid state under these superheated conditions.

As an ideal model compound to examine the temperature dependency of the HDA reaction at a fixed reaction time of 30 min we selected symmetrical dichloropyrimidine compound **1b** (Table 1). Due to the presence of two chlorine substituents the relative reactivity compared to the unsubstituted counterpart should be enhanced and thus compensate for the reduced activity due to the alkoxy side chain. The starting material was introduced as a 0.1 M solution [containing 1% (v/v) pentan-3-one] by passing directly through the HPLC solvent pump. To obtain a residence time of t_R = 30 min with a reactor volume of 53 mL, a theoretical, nominal flow rate of 1766 μL min^{-1} would be required. However, this simple calculation does not take into account the thermal volume expansion of toluene, which at 310 °C is significant, an estimated 31% according to literature data.[15] Our own in-house measurements of the thermal volume expansion of toluene at 310 °C by using two independent methods gave a slightly higher value of 37%.[16] In fact, expansion of the volume has a direct influence on processing time of the reactants in the heated reactor zone, which results in an effective residence time of only $t_{R,eff}$ = 22 min. Therefore, taking the thermal volume expansion effect in this case into account a corrected flow rate of 1290 μL min^{-1} (= 1766 μL min^{-1}/1.37) is obtained, which consequently was used for the following optimization study. Interestingly, the effect of volume expansion and the consequences associated with it when running high-temperature reactions seems to have been largely ignored by the flow chemistry community apart from very few exceptions.[17] Therefore, published residence times with respect to high-temperature flow chemistry should be interpreted with caution.

Using this corrected flow rate equivalent to a fixed, effective processing time of $t_{R,eff}$ = 30 min, the conversion of pyrimidine **1b** into the corresponding ring-annulated compound **2b** was assessed between a temperature range of 250 and 320 °C by using ^{1}H NMR spectroscopy (Figure 3). Whereas at 250 °C only a modest conversion of 15% to **2b** was observed, the rate of conversion increased considerably, reaching a maximum at 310 °C of 95%.

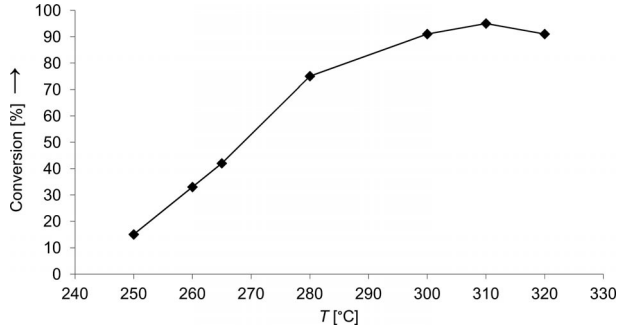


Figure 3. Temperature dependency of the HDA reaction of *O*-linked dichloropyrimidine **1b** to the corresponding annulated pyridine **2b**. Conversions of the crude reaction mixture were determined by ^{1}H NMR spectroscopic analysis after a fixed effective residence time of $t_{R,eff}$ = 30 min.

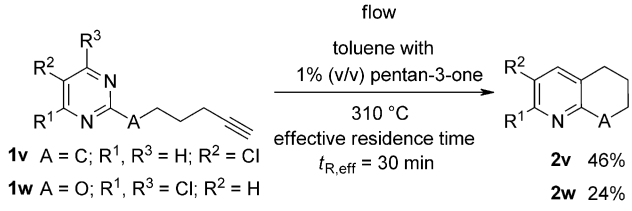
From these optimization experiments, we concluded that an effective residence time of $t_{R,eff}$ = 30 min and a temperature of 310 °C are ideal processing parameters to compare the relative rate of reactivity in a series of structurally close starting materials and to demonstrate the versatility of this procedure.

Table 1 summarizes the isolated yields in a systematic series of annulated pyridine products that were obtained by using these optimized reaction conditions. As expected, substrate **1a** with an all-carbon side chain and a chloride atom *para* to the linker atom A afforded, after MPLC purification, product **2a** in 95% yield, which is significantly better than that obtained under batch conditions.[4] Dichloropyrimidine **1b** provided **2b** in 70% isolated yield, which is somewhat lower, but given the *O*-linkage and the limited reaction time of 30 min it is an acceptable yield. Interestingly, trimethylsilyl-protected alkyne **1c** provided even slightly better results for **2c** (75%) than the corresponding free acetylene **1b**. The introduction of an alkylsilyl group at position R^6 in final product **2c** (*ortho* to the annulated ring) is of high synthetic value, as it allows further manipulation of a position that is traditionally difficult to modify with the HDA reaction. In comparison, methyl-terminated acetylene **1d** afforded rather moderate yields of **2d** (31%). Compared to unsubstituted compound **1e**, which afforded the corresponding reaction product **2e** in 52% yield, electron-withdrawing substituents *para* to the linker atom A such as fluorine, chlorine, bromine, or nitro groups are undoubtedly beneficial in boosting reactivity. This has been exemplified by **1f**–**i**, which gave product yields for the corresponding annulated products **2f**–**i** in the range of 60–65%.

Interestingly, *para*-cyano compound **1j** formed **2j** in only moderate yields of 41%, probably due to subsequent side reactions of either starting material or reaction product under these superheated conditions.

The influence of the substitution pattern on the reactivity can be evaluated by direct comparison of *para*-substituted compound **1g** with its *meta*-substituted congener **1k**, which provided the corresponding products in 60 and 72% isolated yield, respectively. Surprisingly, the presence of one or two *meta*-chlorine substituents afforded similar results when comparing **1k** (72%) with **1b** (70%). In contrast, electron-donating side chains such as alkoxy-substituted derivatives **1l** and **1m** showed significantly reduced reactivity, as evidenced by the products that were isolated in yields of 23 and 16%, respectively. Phenyl-substituted compound **1n** afforded the corresponding product in 55% yield. It should be noted that for all substrates carrying a single *meta*-substituent ($R^1 \neq H$) like **1k**–**n** only a single product was formed with retention of the substituent in the reaction products **2k**–**n**. This demonstrates that in cases of ambiguity, the expulsion of HCN from the tricyclic transition state is preferred over the loss of R^1CN ($R^1 \neq H$). However, examples bearing two symmetrical *meta*-methyl groups such as **1o** are also useful substrates, albeit providing the corresponding product **2o** in a moderate yield of 41%. The reduced yield can be rationalized with the combined unfavorable effects of the electron-donating properties of the methyl group as well as the high-energy barrier for the expulsion of acetonitrile. In the case of dichloropyrimidine **1b** we explored the influence of methyl substitution in the alkyl side chain. Whereas one methyl group at the R^4 position in **1p** leads to a rather significant reduction in yield (**2p**: 31%) compared with **1b** (**2b**: 70%), dimethylation of the R^5 position as in **1q** provided a considerable improvement in yield to 59% for **2q**, probably due to the *gem*-dialkyl (Thorpe–Ingold) effect.[7] Whereas switching of the linker atom A from C (**2a**: 95%) to O and NH resulted in a clear downward trend with respect to yields as demonstrated by 2,3-dihydrofuro[2,3-*b*]pyridine **2g** (60%) and 2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine **2r** (21%), the corresponding sulfur compound 2,3-dihydro-thieno[2,3-*b*]pyridine **2s** provided with 95% amazingly good results. To our surprise, sulfone-linked derivative **2t** was formed in slightly lower yields of 75% than its sulfur counterpart **2s**, despite the greater electron-withdrawing nature of the former. However, this might be attributed to some decomposition of reaction product **2t** due to retro-1,3-chelatotropic side reactions, resulting in the expulsion of SO_2. Compared with free aniline **1r**, acetylated derivative **1u** provided significantly enhanced yields (83%). Owing to predominant decomposition at 310 °C in this specific case, the processing temperature was reduced to 230 °C.

The HDA reaction with an unsubstituted alkyl chain was also extended to the formation of six-membered ring systems, as shown in Scheme 2. A direct comparison between **1a** and homologated analogue **1v** shows that the corresponding six-membered ring **2v** can be synthesized successfully by using the same reaction conditions, although in a reduced, unoptimized yield of 46% in comparison with its five-membered analogue **2a** (95%). As expected, switching from carbon compound **1v** to oxygen analogue **1w** resulted in a reduction in the yield for **2w** (24%) despite the presence of an additional chlorine atom. However, an increase in residence time to 1 or even 2 h should provide a significant improvement in isolable yields.



Scheme 2. Flow synthesis of dihydro-5*H*-[1]pyridines **2v** and **2w**.

Conclusions

In summary we have demonstrated that pyrimidine alkynes can be transformed in flow into the corresponding annulated pyridines in good to excellent yields by using short reaction periods through a cascade involving an inverse-electron-demand HDA reaction and subsequent cycloreversion. The use of flow technology enables organic solvents to be superheated far beyond their boiling points, and thus toxic and difficult to workup solvents such as nitrobenzene or chlorobenzene, which are typically employed for these reactions, can be replaced by less harmful ones. In addition, cyano-containing side products (generated during this transformation in stoichiometric amounts) can be trapped continuously in a controlled and safe manner, avoiding accumulation. The addition of 1% (v/v) of pentan-3-one to the toluene solvent stream was critical to prevent gradual blockage of the flow reactor coil and a key success factor in making this process scalable. We envisage that this method can be readily extended to other synthetically important building blocks requiring harsh reaction conditions, as it enables the preparation of multigram quantities of product, overcoming limitations associated with classical microwave processing. When conducting flow chemistry at such elevated temperatures, thermal volume expansion of solvents becomes significant and needs to be taken into account. The calculation of unadjusted, nominal flow rates leads to considerable errors. To obtain meaningful and accurate residence times, flow rates need to be corrected for volume expansion. To avoid confusion with residence times, t_R, calculated from nominal flow rates, we would propose to use for such corrected residence times the term *effective residence time*, $t_{R,eff}$. The prototype flow reactor system reported herein by using commercially available standard HPLC pumps, stainless steel tubing, and a cost-effective gas chromatography oven expands the ability of the synthetic chemist to perform high-temperature flow chemistry in a safe, scalable, and controlled fashion. It should allow many synthetic organic laboratories to adopt this technology and help to significantly expand their cur-

rent process window and to conduct underrepresented reactions more efficiently. It limits the risks and hazards associated with the use of traditional high-temperature and high-pressure batch equipment and enables the re-exploration of "neglected" reactions usually avoided due to lack of suitable processing tools.

Experimental Section

Experimental Setup: Knauer K-501 HPLC solvent pump, HP 6890 Series Gas Chromatography (GC) oven equipped with a 53-mL homemade reactor coil by using Supelco 304 stainless steel tubing (length × ID = 15.2 m × 2.1 mm), an Omnifit glass chromatography column [filled with a short silica plug (ca. 1 cm, silica 60 Å) and glass wool to provide a large surface for absorption of oligomeric and polymeric material] and a 750 psi back-pressure regulator.

General Flow Procedure for the Synthesis of Annulated Pyridines 2a–w: A 0.1 M solution (25 mL) of pyrimidines **1a**–**w** in toluene containing 1% (v/v) of pentan-3-one was pumped at a flow rate of 1290 μL min^{-1} (effective residence time $t_{R,eff}$ = 30 min) through the reactor coil (volume = 53 mL) heated to 310 °C. The reactant stream was collected in water containing 1 M NaOH (except for **2c** and **2u**) and gaseous cyanide side products were pushed by a gentile stream of nitrogen into two traps filled with a 1:1 mixture of 10% NaOH and sodium hypochlorite (13% active chlorine). The solution was extracted with ethyl acetate (3×), and the organic solvent was dried with anhydrous $MgSO_4$ and evaporated under reduced pressure. The crude material was purified by medium-pressure liquid chromatography (MPLC) over silica. The fume hood air space was monitored during the entire experiment by a HCN detector.

Supporting Information (see footnote on the first page of this article): Determination of the thermal volume expansion of toluene, pictures of the cross- and longitudinal section cuts of the reactor coil and the experimental setup used for meso-scale production, detailed experimental procedures, and compound characterization data.

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