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Flow synthesis of annulated 5-aryl-substituted pyridines by tandem intramolecular inverse-electron-demand hetero-/retro-Diels–Alder reaction

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ABSTRACT

5-Aryl-substituted annulated pyridines can be accessed directly from the corresponding acetylene substituted pyrimidines through an intramolecular *inverse-electron-demand hetero-/retro*-Diels–Alder (*ih*DA/*r*DA) reaction cascade carried out in continuous flow. Exploiting this new process, a series of cycloalka[*c*]pyridines that represent useful building blocks for medicinal chemistry were prepared in good to excellent yields with short processing times (<45 min). Importantly, utilizing the ability to superheat solvents in flow permits the replacement of typically employed high boiling solvents (e.g., nitrobenzene or chlorobenzene) with toluene.

Over the last decade flow chemistry has emerged as an innovative technology that presents a number of advantages when compared to classical batch processing.[1] For example, flow chemistry provides a means to routinely access elevated temperatures and pressures that enable superheating of organic solvents in a controlled and safe manner.[2] Other important advantages of flow chemistry are the improved mass transfer due to highly efficient mixing, as well as superior heat exchange resulting from a significantly increased surface-to-volume ratio when compared with batch reactors. For example, in a 10 mL round-bottom flask (spherical reactor) the surface-to-volume ratio is $A_s/V_s = 225\ m^{-1}$, whereas the same ratio in tubular flow reactor with the same volume increases to $4000\ m^{-1}$. This enhanced surface-to-volume ratio enables rapid heat-exchange and allows many highly exothermic or hazardous reactions to be carried out in a safe and controllable fashion. In addition, reactor volumes are typically in the low mL volume range so that at any time only small quantities of reactive materials or unstable intermediates are present providing an additional safety window.[3] Thus, flow chemistry provides unique opportunities to revisit challenging or experimentally difficult reactions that have been neglected or underutilized.

We recently reported the synthesis of annulated pyridines from 2-substituted acetylene pyrimidines under superheated continuous flow conditions by an intramolecular *inverse-electron-demand hetero-/retro*-Diels–Alder reaction (*ih*DA/*r*DA).[4,5] Using this stable and scalable flow process, a series of annulated pyridines were produced in good to excellent yields and in significantly reduced reaction times when compared to the corresponding batch process. In addition, the use of flow technology permitted replacement of high boiling point/toxic solvents that are commonly employed for this type of transformation (e.g., nitrobenzene, chlorobenzene, or diphenyl ether) with toluene. Critical to the scalability of this process was the addition of 1% (v/v) of pentan-3-one, which prevented blockage of the flow reactor coil by high-molecular weight HCN polymerization products (most likely due to formation of cyanohydrin adducts) and enabled stable, continuous processing over many hours. Another important conclusion of this work was that conducting flow chemistry at elevated reaction temperatures results in significant thermal volume expansion of organic solvents (e.g., 37% for toluene at 310 °C). This is notable, since volume expansion has a direct influence on the processing time of reactants in the heated reactor zone. Thus, in order to get to meaningful and accurate residence times, flow rates need to be corrected with respect to solvent volume expansion. To avoid confusion with residence times t_R calculated from nominal flow rates, the use of the term *effective residence time* ($t_{R,eff}$) for such corrected residence times has been proposed.[4]

Herein we describe an extension of this previously reported process for the synthesis of cycloalka[*b*]pyridines to the preparation of cycloalka[*c*]pyridines and demonstrate that aryl-substituted alkynes **1**–**3** provide the corresponding annulated

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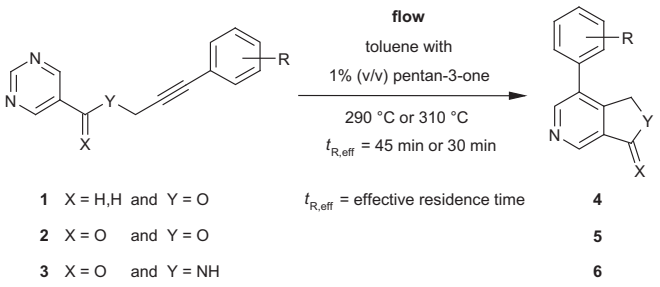


Scheme 1. Flow synthesis of 5-aryl-substituted annulated pyridines **4**–**6**.

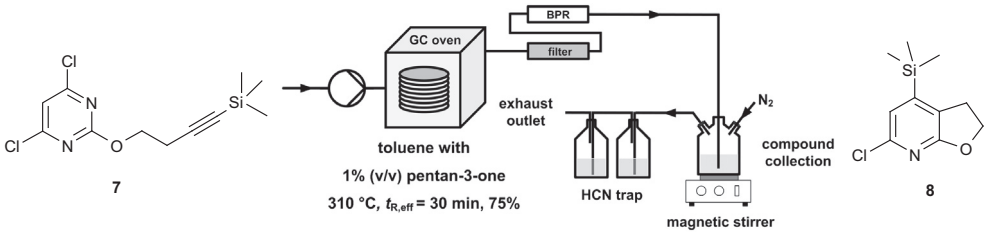
5-aryl dihydro-furan pyridines **4**, lactone pyridines **5**, and lactam pyridines **6** in good to excellent yields (Scheme 1). Despite their rather unpretentious structures, fused bicyclic pyridines are useful building blocks for medicinal chemistry and few cycloalka[*c*]pyridines are commercially available, most likely a direct consequence of the multistep reaction sequences generally required for their preparation. Direct access to these compounds, particularly for the purpose of rapid structure–activity-building activities in the lead identification phase, are thus of high importance.[6]

Our original approach to the synthesis of 5-aryl substituted annulated pyridines **4**–**6** was based on our previous demonstration that dichloropyrimidine **7** can be converted into the corresponding annulated trimethylsilyl derivative **8** in good yield using a flow process at 310 °C and an effective residence time ($t_{R,eff}$) of 30 min (Scheme 2).[4]

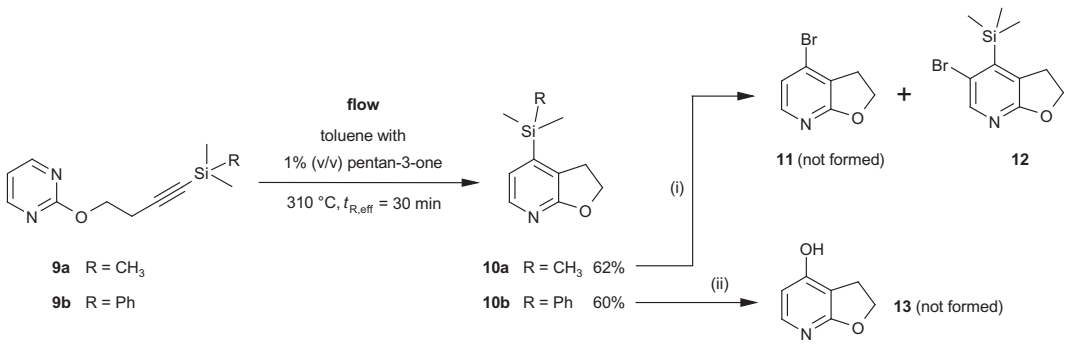
In order to provide rapid access to the desired 5-aryl-substituted pyridines **4**–**6** we intended to capitalize again on this *ih*DA/*r*DA reaction and thus aimed for the synthesis of model compound **9a** in which we could exploit the trimethylsilyl group as a synthetic handle for transition-metal mediated cross-coupling reactions (Scheme 3).

In principal, annulated pyridine **10a** can be accessed via removal of the halogen in chloropyridine **8** either by using a classical batch hydrogenation approach or by employing the flow-based H-Cube® system.[7] Alternatively, dihydropyridine **10a** is also accessible in 62% isolated yield in a more step economic approach via direct *ih*DA/*r*DA reaction from the corresponding pyrimidine precursor **9a** using our standard reaction conditions of 310 °C and $t_{R,eff}$ = 30 min, avoiding the subsequent dehalogenation step. However, bromodesilylation of pyridine **10a** proved challenging. Treatment of **10a** with bromine in CH_2Cl_2 at rt for 3 h provided the bromo derivative **12** in 43% isolated yield, without any trace of the anticipated bromopyridine **11**, in accordance with previous reports.[8] Attempted bromination of **10a** using *N*-bromosuccinimide (NBS) in CH_2Cl_2 was likewise unsuccessful under a variety of reaction conditions (−10 °C to 110 °C, 15 min to 2 h), despite literature precedent in similar systems.[9] Therefore, we prepared the dimethylphenyl-silylated derivative **10b** from **9b** using identical *ih*DA/*r*DA reaction conditions in prelude to an oxidative Fleming–Tamao desilylation (H_2O_2, KHF_2).[10] Unfortunately, reaction of **10b** under standard Fleming–Tamao conditions at both rt and elevated temperatures provided mainly a starting material accompanied by some minor decomposition products, but yet again none of the desired phenol **13**.

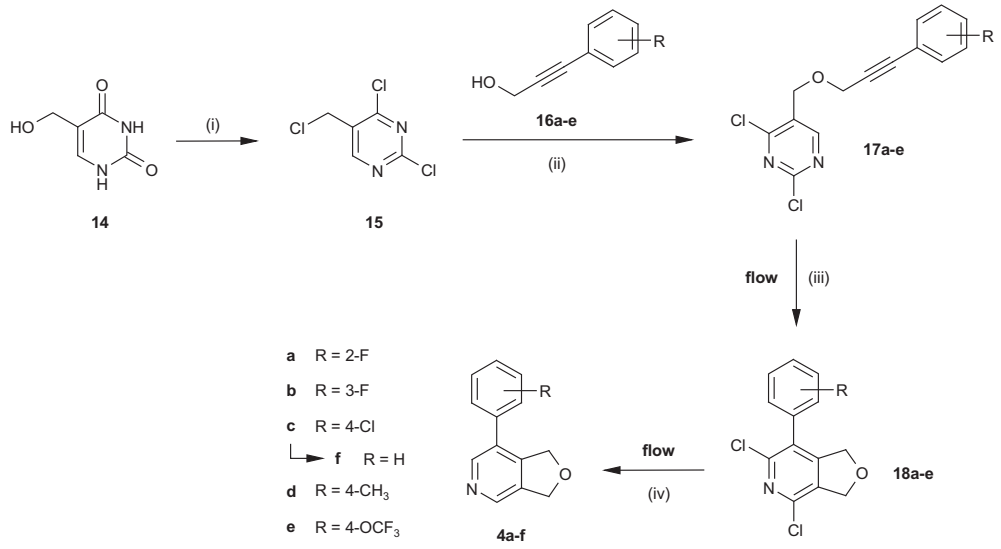
Following these disappointing results, we explored the *ih*DA/*r*DA reaction with pyrimidine acetylenes prefunctionalized with requisite terminal aryl groups. It is notable that the success of this reaction would obviate the cross-coupling reaction and provide direct access to 5-aryl substituted annulated pyridines. Despite the fact that only one related reaction has been reported, we began investigations of this route.[11] Thus, trichloropyrimidine **15** was prepared by exhaustive chlorination of commercially available hydroxyuracil (**14**) with phosphorus oxytrichloride in 67% yield. This former compound proved to be an ideal scaffold for this work, as it couples directly with propargylic alcohols **16a**–**e** and the two chlorine atoms on the pyrimidine core also function as activators for the *ih*DA reaction step (Scheme 4). Due to the reactivity of pyrimidine **15**, purification of this material was accomplished by sublimation, affording **15** as a white crystalline material. The aryl-substituted propynols **16a**–**e** were prepared by Sonogashira reaction of propargylic alcohol with appropriately substituted aryl bromides or iodides. These were then coupled with trichloropyrimidine **15** (NaH, THF) providing the *ih*DA/*r*DA substrates **17a**–**e** in good to modest yields. A notable side



Scheme 2. Illustration of the flow reactor configuration that was employed for the previously described synthesis of trimethylsily-substituted bicyclic pyridine **8** starting from 2-alkoxy substituted pyrimidine **7**.



Scheme 3. Attempted synthesis of the key building blocks bromo-pyridine **11** and pyridine phenol **13** from dihydro-pyridine model compounds **10a** and **10b**, respectively. Reagents and conditions: (i) Br_2, DCM, rt, 3 h, **12**: 43%; (ii) H_2O_2, KHF_2, MeOH, rt, 16 h or H_2O_2, KHF_2, MeOH, 55 °C, 48 h.

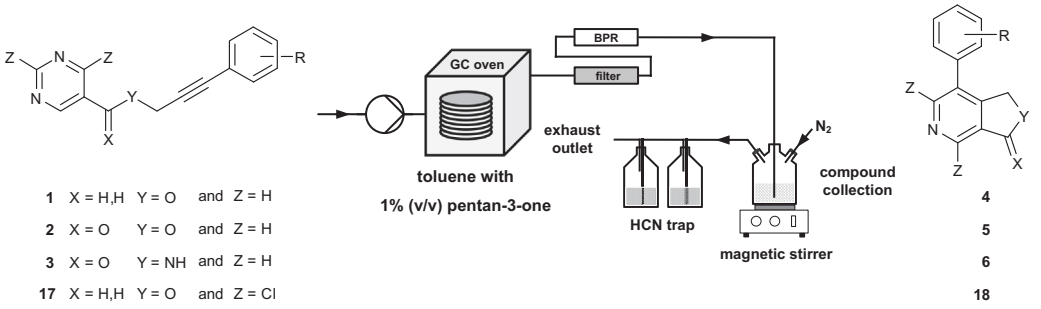


Scheme 4. Synthesis of annulated dichloro aryl pyridines **18a**–**e** in flow by *ih*DA/*r*DA reaction from pyrimidines **17a**–**e** and reduction to bicyclic pyridines **4a**–**f**. Reagents and conditions: (i) $POCl_3$, DIPEA, toluene, 0 → 125 °C, 18 h, 67%; (ii) Compounds **17a**–**e: 16a**–**e**, NaH, THF, 0 °C, 2 h, **17a**: 47%, **17b**: 31%, **17c**: 49%, **17d**: 62%; **17e**: 47%; (iii) flow synthesis, toluene with 1% (v/v) pentan-3-one, 310 °C, 30 min, **18a**: 87%, **18b**: 90%, **18c**: 69%, **18d**: 31%, **18e**: 56%; (iv) H-Cube®, full hydrogen mode, 10% Pd/C CatCart™, flow rate = 0.5 mL/min, 60 °C, ethyl acetate/ammonia (7 M in MeOH) = 9:1, **4a**: 81%, **4b**: 82%, **4c**: 25% and **4f**: 47%, **4d**: 80%, **4e**: 85%.

product of these transformations involved the reaction of phenylprop-2-yn-1-ols **16a**–**e** at position 4 on the pyrimidine ring, affording the corresponding bis-coupled side-products.

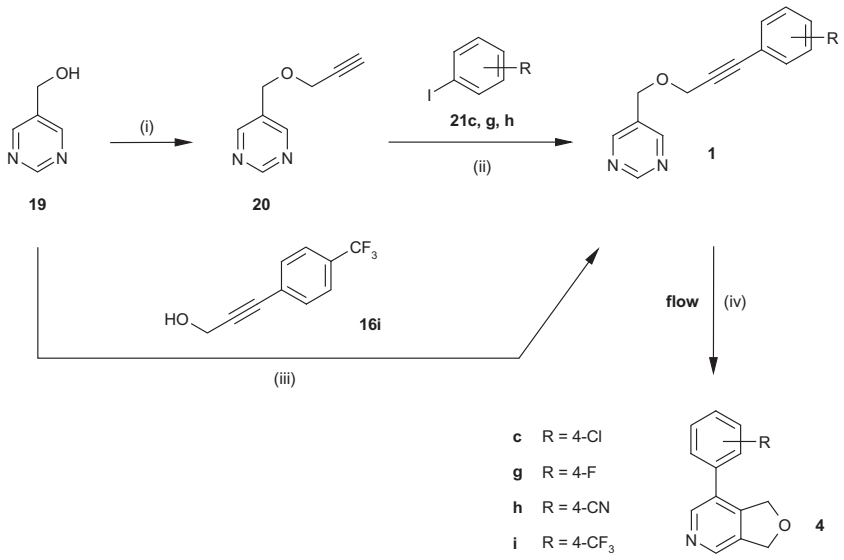
To our delight, the flow *ih*DA/*r*DA reaction of pyrimidines **17a**–**e** using our previously optimized conditions (310 °C, $t_{R,eff}$ = 30 min) delivered the annulated pyridines **18a**–**e** in good to excellent yields

Table 1
Flow synthesis of annulated dihydrofuran pyridines **4**, lactone pyridines **5**, lactam pyridines **6**, and dihydrofuran dichloropyridines **18**[a]



Entry		Starting material	Product	R	Temp (°C)	$t_{R,eff}$ (min)	Isolated yield (%)
1	Dihydrofuran dichloropyridines	**17a**	**18a**	2-F	310	30	87
2		**17b**	**18b**	3-F	310	30	90
3		**17c**	**18c**	4-Cl	310	30	69
4		**17d**	**18d**	4-CH_3	310	30	31
5		**17e**	**18e**	4-OCF_3	310	30	56
6	Dihydrofuran pyridines	**18a**	**4a**	2-F	H-cube reduction		81
7		**18b**	**4b**	3-F	H-cube reduction		82
8		**18c**	**4c**	4-Cl	H-cube reduction		25
9		**18c**	**4f**	H	H-cube reduction		47
10		**18d**	**4d**	4-CH_3	H-cube reduction		80
11		**18e**	**4e**	4-OCF_3	H-cube reduction		85
12		**1c**	**4c**	4-Cl	310	30	37
13		**1g**	**4g**	4-F	310	30	49
14		**1h**	**4h**	4-CN	310	30	89
15		**1i**	**4i**	4-CF_3	290	45	69
16	Lactone pyridines	**2c**	**5c**	4-Cl	290	45	32 (63)[b]
17		**2i**	**5i**	4-CF_3	290	45	31 (76)[b]
18		**2j**	**5j**	3-CF_3	290	45	35 (53)[b]
19	Lactam pyridines	**3c**	**6c**	4-Cl	290	45	50
20		**3i**	**6i**	4-CF_3	290	45	53
21		**3j**	**6j**	3-CF_3	290	45	84

[a] Flow conditions (temperature and residence time) have not been optimized individually for every single compound.
[b] Yields in brackets are calculated based on recovered starting material.



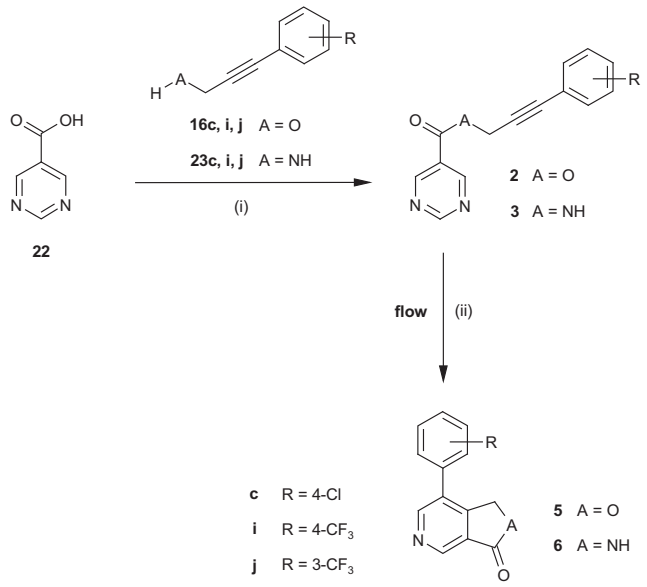
Scheme 5. Synthesis of annulated aryl pyridines **4c**, **g–i** in flow by *ih*DA/*r*DA reaction from pyrimidines **1c**, **g–i**. Reagents and conditions: (i) 3-bromo-propyne, NaH, THF, 0 → 50 °C, 21 h, 86%; (ii) Compound **1c**: **21c**, piperidine, copper(I) iodide, $PdCl_2(PPh_3)_2$, rt, 3 h, 79%; Compound **1g**: **21g**, NEt_3, copper(I) iodide, $PdCl_2(PPh_3)_2$, toluene, 50 °C, 4 h, 49%; Compound **1h**: **21h**, NEt_3, copper(I) iodide, $PdCl_2(PPh_3)_2$, toluene, rt, 18 h, 98%; (iii) Compound **1i**: (a) methane sulfonyl chloride, NEt_3, THF, 0 °C, (b) NaI, **16i**, KOtBu, THF, 0 → rt, 18 h, 21%; (iv) flow synthesis, toluene containing 1% (v/v) pentan-3-one, 310 °C, 30 min, **4c**: 37%, **4g**: 49%, **4h**: 89% and 290 °C, 45 min, **4i**: 69%.

(Table 1).[4] The influence of the substituents on the aromatic ring was not directly obvious as both 2-fluoro (**18a**) and 3-fluoro (**18b**) substituted pyrimidines provided very similar yields of the corresponding cycloalka[*c*]pyridines. However, the slightly lower yields observed for the 4-chloro (**18c**) and 4-trifluoromethoxy (**18e**) derivatives can be rationalized by the electron-withdrawing nature of these substituents, which deactivate the acetylenic dienophile.[12] The unusually low yield in the case of 4-methylphenyl substituted pyridine **18d** was most likely due to instability at elevated temperatures. It is important to note that after the initial cycloaddition, the more electronically rich moiety (in this case HCN) is extruded from the tricyclic product, giving rise exclusively to isomers **18a–e**.[4,11] All *ih*DA/*r*DA reactions were run on a home-made flow reactor system built from commercially available and cost-effective components.[13] The crude reaction stream was collected and purged by a stream of nitrogen to liberate any HCN gas through two subsequent wash bottles equipped with a mixture of sodium hydroxide and sodium hypochlorite (bleach). This procedure enabled to trap the majority of released HCN gas and to run the process safely even at a larger scale.[14] The spectator chlorine atoms in the bicyclic pyridines **18a–e** were subsequently removed by hydrogenation using an H-Cube® system, providing facile access to the targeted 5-aryl substituted dihydrofuran-annulated pyridines **4a–e**.

In order to avoid reductive removal of the two chlorine atoms in the pyridine core in example **18c**, we explored a slightly modified approach in which the *ih*DA/*r*DA reaction was conducted on pyrimidine acetylenes devoid of chlorine atoms on the heterocyclic core (Scheme 5). Thus, alkylation of pyrimidine alcohol **19** with 3-bromo-prop-1-yne yielded pyrimidine alkyne **20**.[15] Sonogashira coupling of the acetylene functionality in **20** with aryl iodide **21c** afforded the corresponding alkyne pyrimidine **1c**. Interestingly, the *ih*DA/*r*DA reaction of this substrate yielded the 4-chloropyridine **4c** in a modest yield of only 37%, and thus is comparable to the yield obtained following the two-step process depicted above. In order to evaluate the scope of this process further, we explored the *ih*DA/*r*DA reaction on additional substrates **1g–i**. Gratifyingly, the 4-fluoro (**1g**), 4-cycano (**1h**), and 4-trifluoromethyl (**1i**) pyrimidine derivatives reacted to provide the desired annulated pyridines **4g–i** in good to excellent yields. In the synthesis of 4-trifluoromethyl pyridine **4i** some decomposition was observed at 310 °C, accordingly the reaction temperature was reduced to 290 °C with concomitant extension of the reaction time to 45 min. The preparation of dihydrofuran annulated pyridines **4** from parent pyrimidines **1** is thus a viable synthetic alternative to the process depicted in Scheme 4 employing dichloropyrimidines.

After successful preparation of a number of dihydro-furan pyridines **4** we also explored the utility of this sequence in the preparation of annulated lactone **5** and lactam pyridines **6**, respectively (Scheme 6). To access the required starting materials, pyrimidine carboxylic acid **22** was coupled with phenylprop-2-yn-1-ols **16c**, **i**, and **j** to provide the pyrimidine esters **2c**, **i**, and **j**. Executing the *ih*DA/*r*DA reaction in flow on these latter substances afforded the lactone products **5c**, **i**, and **j** in fair yields of 32%, 31%, and 35%. Notably, considering the amount of starting material recovered from these reactions, the yields of **5c**, **i**, and **j** are 63%, 76%, and 53%, respectively (Table 1). The moderate outcome in terms of yield for these lactones can be ascribed to a generally lower reactivity of ester substrates in the *ih*DA/*r*DA reaction. In a similar fashion, the analogous amides **3c**, **i**, and **j** were prepared from the corresponding propynylamines **23c**, **i**, and **j**, and pyrimidine carboxylic acid **22**. Interestingly, these substrates afforded in the *ih*DA/*r*DA reaction the annulated lactam pyridines **6c**, **i**, and **j** in all cases in better yields of 50%, 53%, and 84%, respectively, compared with their lactone counterparts, demonstrating the higher reactivity of amide substrates (Table 1). The flow cyclization reactions for all lactone and lactam derivatives were conducted in dry, deoxygenated toluene at a slightly lower temperature of 290 °C and slightly increased reaction time of 45 min, both of which helped to minimize side reactions.[11]

In summary, we have developed a new advantageous process that allows the controlled continuous flow synthesis of a number of fused bicyclic 5-aryl substituted pyridine derivatives that can serve as useful building blocks in medicinal chemistry. Importantly, pressurized flow reactors enable the use of toluene as the reaction solvent, limit the risks and hazards associated with the use of traditional high-temperature and high-pressure batch equipment, and thus enabled the re-exploration of this underutilized reaction. A further important advantage of conducting these reactions in flow is the bypassing of any dangerous built-up during



Scheme 6. Synthesis of annulated lactone pyridines **5c**, **i**, and **j** and lactam pyridines **6c**, **i**, and **j** in flow by *ih*DA/*r*DA reaction from pyrimidine esters **2c**, **i**, and **j**, and pyrimidine amides **3c**, **i**, and **j**, respectively. Reagents and conditions: (i) Compound **2c**: **16c**, EDC, DMAP, DCM, rt, 2 h, 74%; Compound **2i**: **16i**, EDC, DMAP, DMF, rt, 2 h, 76%; Compound **2j**: **16j**, EDC, DMAP, DCM, rt, 2 h, 72% or Compounds **23c**, **i**, **j**, EDC, DMF, 0 → 22 °C, 18 h, **3c**: 84%, **3i**: 83%, **3j**: 90%; (ii) flow synthesis, toluene containing 1% (v/v) pentan-3-one, 290 °C, 45 min, **5c**: 32% (63%), **5i**: 31% (76%), **5j**: 35% (53%), **6c**: 50%, **6i**: 53%, **6j**: 84%. Yields in brackets are based on recovered starting material.

processing and continuous removal of highly toxic cyanide side-products that are formed in stoichiometric amounts during the cycloreversion (*r*DA) step.

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Supplementary data

Supplementary data (experimental setup, detailed experimental procedures with ^{1}H, ^{13}C, ^{19}F NMR and HRMS data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.069.

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13. Reactions were conducted on a home-made flow system consisting of a Dionex P580 pump with internal pressure sensor (upper pressure limit of 500 bar), which was connected to a gas chromatography oven from a HP 6890 Series system (upper temperature limit of 400 °C). As a reactor coil, stainless steel tubing from Supelco was used (Supelco premium grade 304 stainless steel tubing; dimensions: length × OD (ID) = 15.2 m × 3.2 mm (2.1 mm); product reference number: 2-0526-U), providing a reactor volume of 53 mL, and thus also allowing for facile up-scaling. The reactor outlet was equipped with a small stainless-steel tube (6.6 mm bore and 100 mm length) 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.
14. All flow reactions were conducted in dry and deoxygenated toluene with an addition of 1% (v/v) of pentan-3-one. This additive was identified as an effective HCN (formed in stoichiometric amounts in the *r*DA step) trapping agent (likely by cyanohydrin adduct formation). This enabled stable, continuous processing over many hours and reliably prevented gradual blockage of the flow reactor coil. For safety reasons, the airspace in the fume hood was continuously monitored during experiments with an HCN gas detector (Monitox plus, Compur Monitors. For more information, see: http://www.compur.com/).
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