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The Kondrat'eva Reaction in Flow: Direct Access to Annulated Pyridines

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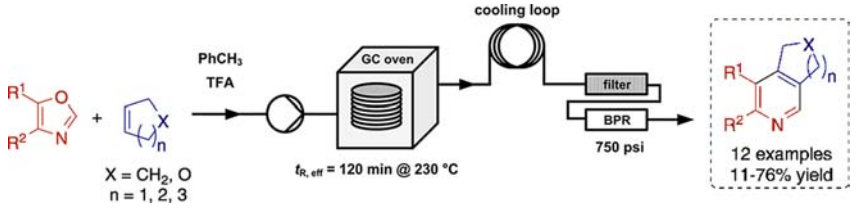
ABSTRACT



A continuous flow *inverse-electron-demand* Kondrat'eva reaction has been developed that provides direct access to cycloalka[*c*]pyridines from unactivated oxazoles and cycloalkenes. Annulated pyridines obtained by this one-step process are valuable scaffolds for medicinal chemistry.

Annulated pyridines are common scaffolds in medicinal chemistry and are present in many drug leads.[1] For example, the dihydro-5*H*-cyclopenta[*b*]pyridine **1** (Figure 1) is a low nM agonist for the serotonin receptor 5HT2c,[2] the 4-aza analogue of ramelteon **2** is a potent melatonin receptor agonist,[3] and the naturally occurring alkaloid sinensine (**3**) has demonstrated potentially useful cytoprotective activity.[4] Recently, Martin et al. reported a process for the synthesis of cycloalka[*b*]pyridines (e.g., **5**) in continuous flow by means of an intramolecular *inverse-electron-demand hetero*/*retro*-Diels–Alder (*ih*DA/*r*DA) reaction cascade involving pyrimidine alkynes (e.g., **4**).[5] To support several ongoing drug discovery programs, access to the corresponding cycloalka[*c*]pyridines, such as those constituting the structural core of alkaloids **2** and **3**, was also required. In order to efficiently sample the chemical space surrounding this scaffold,[6] we sought a concise and modular approach that permits the incorporation of functional or diversifiable groups on the pyridine moiety (e.g., carboxyl or haloaryl) and provides access to annulated pyridines of differing ring size (e.g., cyclopenta-, cyclohexa-, and cycloheptа[*c*]-pyridines). As described below, these efforts led to the development of a continuous flow *inverse-electron-demand* Kondrat'eva (*ied*K) reaction[7] that is capable of producing a wide array of oxacycloalka- and cycloalka[*c*]pyridines directly from unactivated cycloalkenes and substituted oxazoles. Notably, this work constitutes the first Kondrat'eva reactions of cycloalkenes and the first examples of this reaction in continuous flow.

The Kondrat'eva reaction[7−9] involves a [4 + 2] cycloaddition between an oxazole (e.g., **6**) and an alkene (e.g., **7**), followed by dehydration of the cycloadduct (e.g., **8**)

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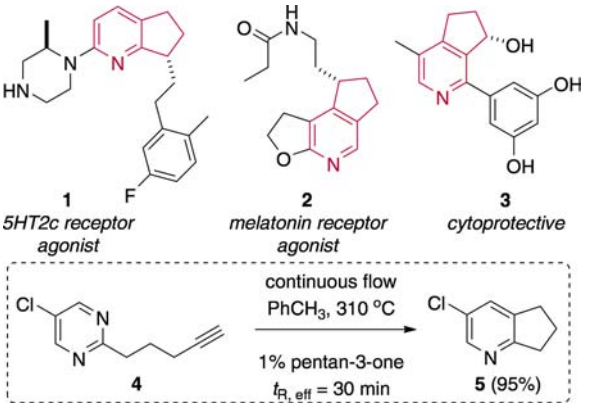
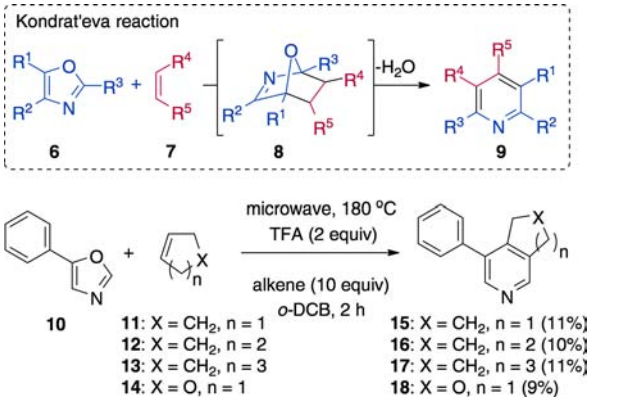


Figure 1. Annulated pyridines in drug discovery and a continuous flow process for cycloalka[*b*]pyridines.

to afford functionalized pyridines (e.g., **9**, Scheme 1). This reaction has been employed to great effect in the synthesis of natural products[10] and pharmaceuticals and was classically demonstrated in the production of pyridoxine (vitamin B_6) by researchers at Merck & Co. in 1962.[11] In general, the Kondrat'eva reaction is facilitated by electron-donating groups on the oxazole, with 5-alkoxy- and 5-aminooxazoles displaying similar cycloaddition reactivity to all-carbon dienes.[8f] In fact, the preponderance of examples of this reaction involve activated 5-alkoxyoxazoles.[9] Conversely, the presence of aryl groups at oxazole positions C2 or C5 is reported to inhibit reactions with dienophiles, possibly due to a deconjugative effect or steric crowding in the transition structure (e.g., **6**, R^1 or R^3 = Ph).[9h] In order to promote reactions of unactivated oxazoles (e.g., those lacking a 5-alkoxy or 5-amino group), the reactive partners can be tethered, in which case the cycloaddition can occur spontaneously.[10] Considering that the most direct route to the annulated pyridines would involve a Kondrat'eva reaction between a cycloalkene and an oxazole,[12] and thus avoid tethering of reactants, our investigations began by exploring the microwave promoted reaction of cyclopentene with 5-phenyloxazole (**10**) (Scheme 1). While cognizant that the phenyl substituent at C5 in **10** may inhibit the desired reaction (*vide supra*) and that cycloalkenes have not demonstrated utility as dieneophiles in Kondrat'eva reactions, the corresponding annulated 3-arylpyridine **15** is an attractive scaffold for medicinal chemistry. Moreover, conditions that promote this difficult reaction should prove general for the synthesis cycloalka[*c*]pyridines.

Scheme 1. The Kondrat'eva Reaction and Microwave Promoted Reactions of 5-Phenyloxazole with Cycloalkenes



Initial attempts to effect the reaction of 5-phenyloxazole (**10**) with cyclopentene (**11**) involved use of excess **11** (10 equiv) in *o*-dichlorobenzene (*o*-DCB) at temperatures ranging from 120 to 210 °C in a microwave reactor[13] and provided none of the dihydro-5*H*-cyclopenta[*c*]pyridine **15**. Considering the reversible nature of the [4 + 2]-cycloaddition, the reaction was repeated with the addition of DBU to promote dehydration of the intermediate cycloadduct.[10e] Unfortunately, these modified conditions also failed to provide detectable quantities of the annulated pyridine **15**. Finally, we explored the use of Brønsted acids in an effort to activate the oxazole by protonation and effect an *ied*K reaction.[14] While very little product (< 2%) was detected with the addition of HOAc, trichloroacetic acid, *p*-TsOH, or *p*-nitrobezoic acid, addition of either H_2SO_4 or trifluoroacetic acid (TFA) led to the production of small amounts of the annulated pyridine **15**. As depicted in Scheme 1, when 5-phenyloxazole (**10**) was heated with an excess of cyclopentene and 2 equiv of TFA, yields of up to 11% of **15** were realized. Likewise, the TFA-promoted reaction of dihydrofuran (**14**) and other cycloalkenes (e.g., **12** and **13**) with 5-phenyloxazole afforded the corresponding annulated pyridines **16**–**18** in similar yields. Despite the fact that considerable amounts of 5-phenyloxazole were recovered from these reactions, we were not able to

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(10) For use of intramolecular Kondrat'eva reactions in total synthesis, see: (a) Chughtai, M.; Eagan, J. M.; Padwa, A. *Synlett* **2011**, 215. (b) Ohba, M.; Natsutani, I.; Sakuma, T. *Tetrahedron* **2007**, *63*, 10337. (c) Ohba, M.; Izuta, R.; Shimizu, E. *Tetrahedron Lett.* **2000**, *41*, 10251. (d) Subramanyam, C.; Noguchi, M.; Weinreb, S. M. *J. Org. Chem.* **1989**, *54*, 5580. (e) Levin, J. I.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 4325. (f) Levin, J. I.; Weinreb, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 1397.

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(12) The cycloaddition of dihydrofuran with an activated, 5-alkoxy oxazole in an autoclave has been reported; see: Sharif, S.; Schagen, D.; Toney, M. D.; Limbach, H.-H. *J. Am. Chem. Soc.* **2007**, *129*, 4440.

(13) See Supporting Information for full experimental details.

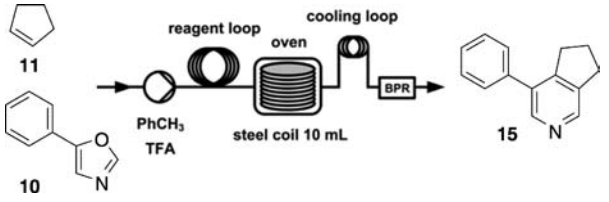
(14) Firestone, R. A.; Harris, E. E.; Reuter, W. *Tetrahedron* **1967**, *23*, 943.

improve the conversion due to high-pressure (>200 psi) shutdown of the microwave instrument and leakage of the volatile alkenes (e.g., bp **11** = 44–46 °C) from the crimped (Teflon seal) vials. Bearing these complications in mind, we initiated investigations of this process under flow conditions,[15] where high temperatures and pressures can be more safely managed, providing a novel process space.[16]

As summarized in Table 1, repetition of the batch reaction depicted in Scheme 1 between 5-phenyloxazole (**10**) and cyclopentene (**11**) in continuous flow at 210 °C in toluene afforded the annulated pyridine **15** in a slightly improved yield (17%, entry 1).[17] Increasing the system pressure to 500 psi resulted in a significant increase in yield (entry 2), while further increases in reaction pressure (e.g., 750 psi) did not noticeably improve the process. As highlighted in entries 2–5, 230 °C proved to be the optimal temperature for this reaction. Several experiments were also conducted in an effort to minimize the amount of cyclopentene required, as byproducts most likely formed from the acid promoted decomposition and/or polymerization of cyclopentene, and insolubility of both the starting material and pyridine product in cyclopentene often complicated the continuous flow process. Ultimately, as indicated in entry 6, injection of a solution of the reagents in a 1:1 mixture of toluene–cyclopentene proved most favorable. Following evaluation of several effective residence times (e.g., entries 6–8), a reaction time of 2 h in the heated chamber provided the annulated pyridine **15** in good yield (75%). Finally, using this optimized set of continuous flow parameters, the equivalents of TFA were adjusted (e.g., entries 8–10), and it was found that although very small amounts of product were produced without TFA (<10%), increases beyond 2 equiv of TFA (e.g., 3 or 4 equiv) had little effect on the yield of **15**. Thus, the reaction conditions described in entry 8 were considered optimal for the production of the annulated pyridine **15** and a significant improvement over the corresponding microwave batch reaction (Scheme 1).

Having identified this optimized set of reaction conditions (Table 1, entry 8), we next evaluated the scope of the continuous flow process using a customized system and flow tube reactors with slightly larger bore sizes than the system employed for optimization purposes (Table 1).[18–20] As highlighted in Figure 2, several cycloalkenes and commercially available substituted oxazoles were combined to rapidly prepare a small collection of annulated pyridines **15**–**26** in modest to good yield.[21] Not surprisingly,[22] the reactions involving cyclohexene and cycloheptene (i.e., formation of **16** and **17**) compared with cyclopentene

Table 1. Optimization of *ied*K Reaction in Continuous Flow[a]



entry	temp (°C)	$t_{R,\,eff}$[b] (min)	PhMe:**11**	psi[c]	TFA (equiv)	**15** (%)[d]
1	210	60	1:3	250	2	17
2	210	60	1:3	500	2	45
3	190	60	1:3	500	2	42
4	230	60	1:3	500	2	58
5	250	60	1:3	500	2	53
6	230	60	1:1	500	2	61
7	230	90	1:1	500	2	67
8	230	120	1:1	500	2	75
9	230	120	1:1	500	0	9
10	230	120	1:1	500	4	75

[a] Reaction optimization experiments were conducted on a Vaportec R2+/R4 flow system equipped with a high temperature 316 stainless steel tube flow reactor (SSTFR, 10 mL) and a 250 or 500 psi back-pressure regulator (BPR). [b] Effective residence time (corrected for volume expansion, which for toluene at 210 °C is approximately 23%).[5] [c] Pressure controlled by use of BPR. [d] Percent yield based on HPLC-MS analysis with internal standard.

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(17) TFA is known to decompose at temp >180 °C, producing (among other byproducts) HF, CF_3H, CO_2 ($t_{1/2}$ at 275 °C = 15 min); see: Jollie, D. M.; Harrison, P. G. *J. Chem. Soc., Perkin Trans. 2* **1997**, 1571. As a precautionary measure, the products of all flow reactions were collected directly into a flask containing triethylamine.

(18) Reactions were performed on a customized flow system consisting of a Dionex P580 pump (internal pressure sensor) connected to an oven from an HP 6890 Series GC. As a reactor coil, premium grade 304 stainless steel tubing was used (Supelco, dimensions: length × OD (ID) = 15.2 m × 3.2 mm (2.1 mm), reactor volume = 53 mL). 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 BPR required to keep toluene in the liquid state under superheated conditions.

(19) The nominal, volume expansion unadjusted flow rate for a reactor coil volume of 53 mL and 2 h residence time is 0.44 mL min^{-1}. However, considering the volume expansion of toluene at 210 °C is 23%, and at 230 °C is 26%, the corrected flow rate is 0.36 mL min^{-1}.

(20) Typical experimental procedure: cyclopentene (10 equiv) was added to 5-phenyloxazole (1 equiv), and the mixture was diluted with toluene. Trifluoroacetic acid (2 equiv) was then added, and the reaction mixture was applied to the flow coil buffered by 1 mL of a mixture of cyclopentene (10 equiv) and trifluoroacetic acid (2 equiv) in toluene before and after injection to mitigate diffusion. The residence time of the reaction mixture was adjusted such that it remained in the heated area (230 °C) for 2 h, factoring in volume expansion of the solvent (see ref 5). The crude product was collected into a vial containing triethylamine. The flow-coil was cooled to 100 °C and flushed with 1 column volume (53 mL) of MeOH, which was also collected and combined with crude product. Solvents were removed under reduced pressure, and the crude product was purified by flash chromatography.

(21) The annulated pyridines depicted in Figure 2 proved challenging to purify by flash chromatography due to limited solubility during sample loading and are often partitioned between aqueous and organic phases during reaction workup. Consequently, the isolated yields presented in Figure 2 are lower than the percentage yield calculated from HPLC-MS analysis of the crude reaction mixtures using internal standards.

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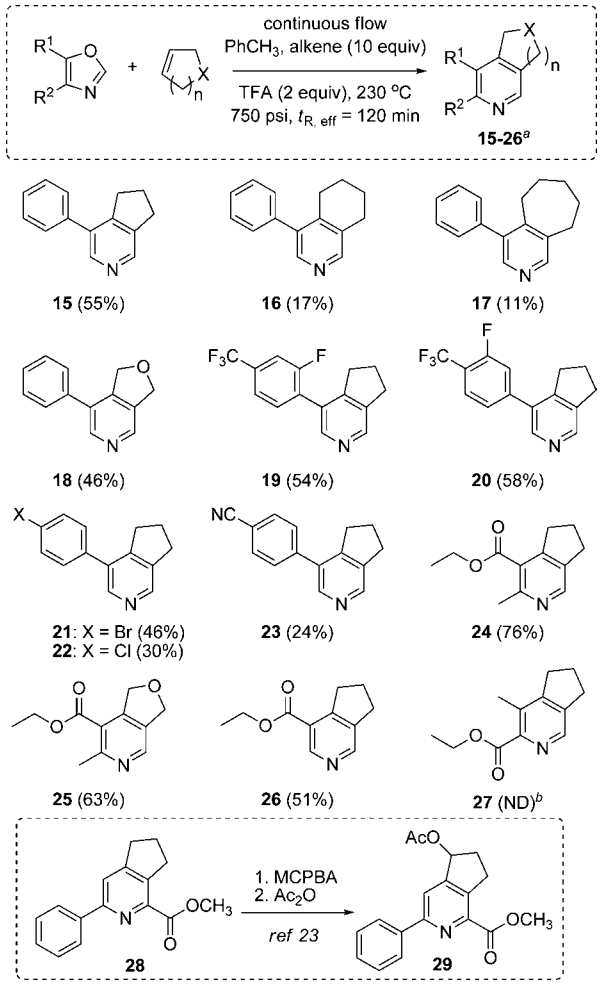

Figure 2. Continuous flow synthesis of annulated pyridines and the oxidation of **28**. [a] Isolated yield. [b] No product detected.

proceeded with much lower yields. However, each of these annulated pyridines is prepared in a single step from commercial materials, a significant improvement over traditional approaches (e.g., tethering of reactants) that limit their ready incorporation into medicinal chemistry programs. As indicated in Figure 2, the yield of the 2,5-dihydrofuran adduct **18** also increased considerably using the continuous flow protocol, and several additional aryl-substituted annulated pyridines **19**–**23** that possess functional and diversifiable groups (e.g., cyano, bromo, chloro, fluoro) were readily prepared following our standard protocol. Finally, the *ied*K reaction of ethyl 4-methyl-5-oxazolecarboxylate or ethyl 5-oxazolecarboxylate with cyclopentene or 2,5-dihydrofuran was examined, and each afforded the desired annulated pyridines (e.g., **24**–**26**) in good yield. To demonstrate the scalability of this process, the reaction between ethyl 4-methyl-5-oxazolecarboxylate and cyclopentene was also repeated on the 8.7 g scale and delivered 6.9 g (60% yield) of the annulated pyridine **24**.[13] Notably, the total processing time for this experiment was 6.75 h, during which no increase in pressure was detected, further indicating that there was no insoluble particle buildup. As depicted in Figure 2, reaction of the isomeric ethyl 5-methyl-4-oxazolecarboxylate with cyclopentene failed to provide any of the corresponding annulated pyridine **27**. Notwithstanding, the annulated pyridines **15**–**26** produced through this one-step process represent excellent scaffolds for medicinal chemistry.

In summary, a continuous flow *inverse-electron-demand* Kondrat'eva reaction has been developed that affords direct access to annulated pyridines and is superior to the corresponding batch reactions. Notably, the cycloadditions of both unactivated alkenes and deactivated oxazoles are promoted in continuous flow at elevated temperatures and pressures (230 °C, 750 psi). Considering this reaction provides a range of cycloalka[*c*]pyridines that can be diversified or further functionalized following standard procedures (e.g., oxidative conversion of **28** → **29**),[23] the continuous flow *ie*K reaction is well suited for medicinal chemistry purposes. The application of annulated pyridines made readily available by this one-step process to ongoing drug discovery programs will be reported in due course.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.