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Generation and Ring Opening of Aziridines in Telescoped Continuous Flow Processes

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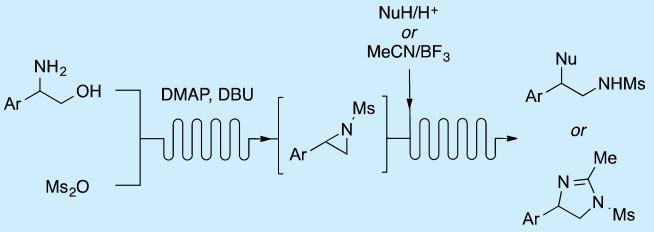
Supporting Information

ABSTRACT: A simple method for the preparation of a variety of *N*-sulfonyl aziridines (10 examples) from 1,2-amino alcohols under continuous flow conditions is described. Using flow based methods, the aziridines can be further ring opened with oxygen, carbon, and halide nucleophiles or ring expanded to imidazolines by Lewis acid promoted reaction with nitriles. Telescoping the aziridine generation and ring opening steps together in a microfluidic reactor allows the chemistry to be undertaken with limited exposure to the potentially hazardous aziridine intermediates.

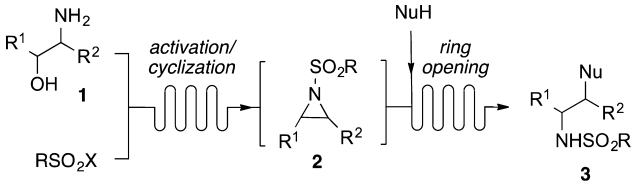


Aziridines are important building blocks in organic synthesis, widely used in academic and industrial laboratories to produce a variety of nitrogen containing molecules.[1,2] In particular, they serve as 'spring-loaded' electrophiles for C−C and C−heteroatom bond formation by way of nucleophilic ring opening. The excellent scope, efficiency, selectivity, and atom economy displayed by these processes has led them to be included in the small group of highly valued "click" reactions.[3] However, the high reactivity of aziridines does make them potentially rather hazardous reagents to handle. For example, aziridine (ethylenimine) is a powerful alkylating agent that has been classified as being possibly carcinogenic to humans with strong mutagenic and genotoxic activity.[4] While data on other aziridines are more limited, it is known that a number of aziridine containing natural products[5] such as the mitomycins[6] and azinomycins[7] act as cytotoxic agents due to their propensity to alkylate and cross-linking DNA. Consequently, it is important to limit exposure to aziridines as a compound class during their preparation and handling.

Recently, continuous flow methodology has emerged as a powerful new technique in chemical synthesis.[8,9] One of its many advantages over batch processes is that it can be used to generate and handle hazardous and reactive reagents in a safe way.[10] For this reason, we felt that flow methodology might provide a simple and attractive way to produce and handle aziridines more safely. Surprisingly, the preparation and utilization of these electrophilic species in laboratory-scale flow chemistry has received only scant attention.[11−14] As far as we are aware, the only report describing the generation of aziridines in flow is that by Booker-Milburn, who used intramolecular photorearrangements of substituted pyrroles to produce complex tricyclic scaffolds containing the aziridine ring.[11] In other work, Yoshida has lithiated and *C*-alkylated *N*-Bus aziridines in flow[12] and, with Luisi, reported their lateral lithiation and ring opening to 1,2,3,4-tetrahydroisoquinolines.[13] Finally, aziridines have been used as precursors to azomethine ylids in flow as a way to functionalize carbon nanotubes.[14]

Here, we report a simple, general method for the synthesis of *N*-sulfonyl aziridines **2** from 1,2-amino alcohols **1** and explore their further ring opening to amines **3** (Scheme 1), and ring expansion to imidazolines, under continuous flow conditions. Importantly, by telescoping the processes together, we show that efficient sequences can be realized without exposure to the potentially hazardous aziridine intermediates.

Scheme 1. Proposed Approach for the Generation and *in Situ* Ring Opening of Aziridines under Continuous Flow Conditions



One of the most common and efficient routes to aziridines involving activation/ring closure of 1,2-amino alcohol was used for our studies.[2] Importantly, the precursors are widely available, the reaction tolerates good variability in aziridine structure and it can be used to access these heterocycles as single enantiomers. The flow system we used was constructed from simple, readily available components. Computer-controlled syringe pumps were used to independently deliver the reagents to a commercial microreactor made from borosilicate glass via a premixing unit (total reactor volume ca. 2 mL). Residence times (R_t) were conveniently controlled through

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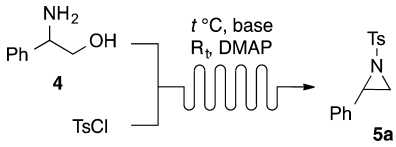
addition rates and substrate concentrations. Most of the chemistry was conducted using a simple two-input microreactor, although the telescoped processes employed a three-channel system. Full details of the experimental setup are provided in the Supporting Information.

Our studies began with an investigation into the cyclization of 2-phenyl-2-aminoethanol (**4**) to *N*-tosyl aziridine **5a**. The established batch process is performed using TsCl (2.5 equiv), triethylamine (3 equiv), and *cat.* DMAP in CH_2Cl_2 at rt.[15] However, this transformation is very slow, taking up to 24 h, and leads to the formation of $Et_3N{\cdot}HCl$ as a solid precipitate. To ensure the corresponding flow reaction is homogeneous, thus preventing potential reactor blockages, we switched to the use of chloroform as solvent. To reduce the reaction time, the use of elevated temperatures and larger quantities of reagents was examined. Details of the optimization process are provided in Table 1. Variation in the nature of the base was also investigated but hampered by the fact that precipitates occurred using many bases in the aziridine formation such as pyridine, 2,4,6-collidine, 2,6-lutidine, or piperidine. Hence they proved unsuitable for use in this flow method and are not detailed in Table 1. Through these optimization studies, a practical continuous flow procedure was identified (Table 1, entry 5). This involved premixing the amino alcohol in $CHCl_3$ with DMAP (0.5 equiv) and Et_3N (4.5 equiv) and combining it in the microreactor at 30 °C with TsCl (2.5 equiv). In this way, high yields of **5a** could be obtained using a 40 min residence time. These new conditions are also useful for accelerating batch processes; for example, they can be used to produce **5a** in 72% yield.

Table 1. Optimization of Conditions for Ring Closure of 2-Phenyl-2-aminoethanol (4) to Aziridine 5a in a Continuous Flow Reactor

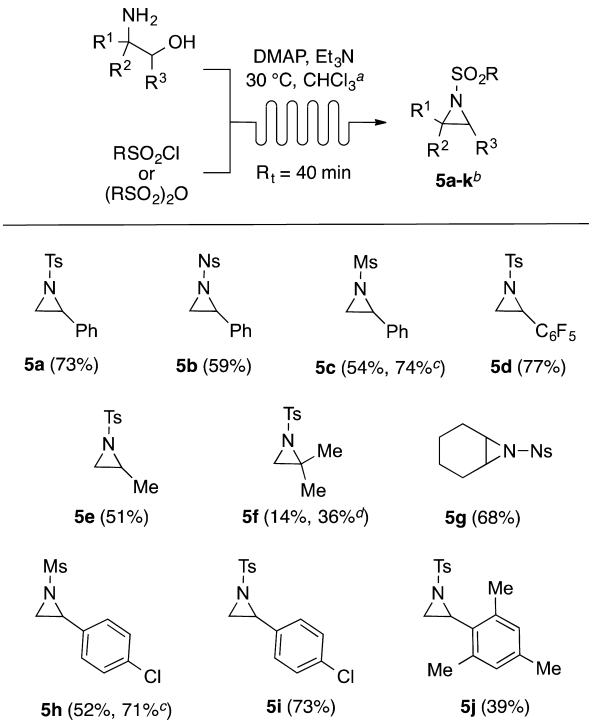


entry	t (°C)	DMAP[a] (equiv)	base (equiv)	TsCl (equiv)	R_t[b] (min)	yield[c] (%)
1	21	0.5	Et_3N (4.5)	2.0	8	30
2	21	0.5	Et_3N (4.5)	2.5	8	51
3	21	0.5	Et_3N (4.5)	2.5	13	53
4	21	0.5	Et_3N (4.5)	2.5	40	67
5	**30**	**0.5**	**Et_3N (4.5)**	**2.5**	**40**	**73**
6	35	0.5	Et_3N (4.5)	2.5	40	70
7	30	0	Et_3N (4.5)	2.5	40	trace
8	30	0.5	Et_3N (3.8)	2.5	40	53
9	30	0.5	Et_3N (5.3)	2.5	40	74
10	30	0.5	DBU (4.5)	2.5	40	trace
11	30	0.3	Et_3N (4.5)	2.3	40	61
12	30	1.0	Et_3N (4.5)	2.5	40	70
13	30	1.0	Et_3N (4.5)	3.0	40	77

[a]All reactions performed in $CHCl_3$. [b]Residence time in microreactor. [c]Isolated yield after chromatography.

Next, the synthesis of a variety of mono- and disubstituted aziridines from 1,2-amino alcohols under the optimized continuous flow conditions were explored (Scheme 2). Moderate to good yields are seen across a range of substitution patterns. Tosyl (Ts), methanesulfonyl (Ms), and 4-nitrobenzenesulfonyl (Ns) groups can be introduced at nitrogen through variation in the sulfonyl chloride used. For *N*-Ms derivatives **5c** and **5h**, better yields were achieved using methanesulfonyl anhydride in combination with DBU. In these examples, a mixed solvent system ($CHCl_3/CH_2Cl_2$) was required to keep the anhydride in solution. Using *S*-2-phenyl-2-aminoethanol (**4**), the preparation of **5a** could be achieved without detectable racemization. For the synthesis of 2,2-dimethylaziridine **5f**, improved yields were obtained using a three-input microreactor. After initial reaction of 2-amino-2-methylpropan-1-ol with TsCl/Et_3N to give the intermediate ditosylate, DBU was then added to induce ring closure.

Scheme 2. Synthesis of Mono- And Disubstituted Aziridines 5a–j under Continuous Flow



[a]Reaction conditions: RSO_2Cl (2.5 equiv), DMAP (0.5 equiv), Et_3N (4.5 equiv), $CHCl_3$. [b]Isolated yield after chromatography. [c]Ms_2O (2.5 equiv), DBU (4.5 equiv), DMAP (0.5 equiv), $CHCl_3/CH_2Cl_2$ (1:1), R_t = 16 min, 30 °C. [d]DMAP (2.1 equiv), TsCl, $CHCl_3$, R_t = 15 min then DBU (4.5 equiv), $CHCl_3$, R_t = 15 min.

Next, we explored the nucleophilic ring opening of representative aziridines under continuous flow conditions. The use of a variety of oxygen, carbon, and halide nucleophiles was examined (Scheme 3). Good to excellent yields were obtained in most cases by simply combining the aziridine with a premixed solution of the nucleophile and acid catalyst at elevated temperatures. Many of these ring openings were undertaken using Brønsted acids bearing non-nucleophilic counterions (H_2SO_4 or $MeSO_3H$) as activators. The reactions were efficient with 40 min residence times. For the addition of chloride and fluoride respectively, HCl and $BF_3{\cdot}Et_2O/i$PrOH[16] were used as the source of both the nucleophile and activator. Using unsymmetrical 2-phenyl aziridines **5a** and **5c**, only a single regioisomer was observed with attack at the more substituted carbon. For **6f**, produced by Friedel–Crafts alkylation of 1,3,5-trimethoxybenzene,[17] this regiochemical outcome was unambiguously confirmed by X-ray crystallography. With 1,2-disubstituted aziridines, *trans*-**6g–j** were

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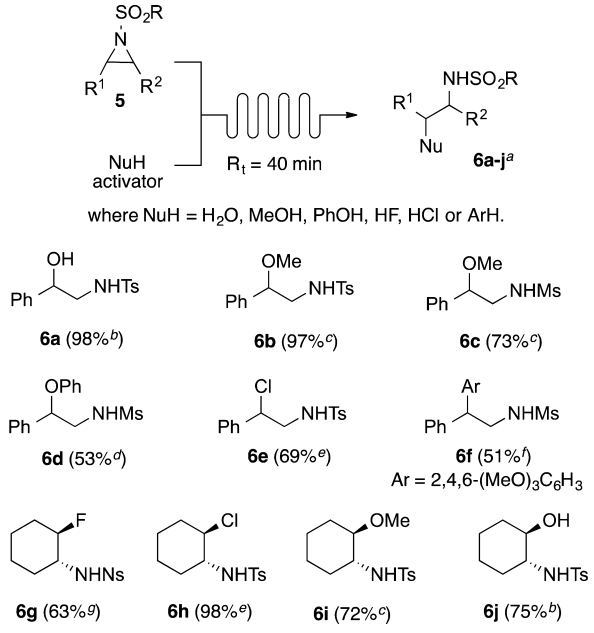
Scheme 3. Nucleophilic Ring Opening of Aziridines under Continuous Flow Conditions



[a]Isolated yield after chromatography. [b]H_2SO_4, H_2O/acetone, 70 °C. [c]H_2SO_4, MeOH/$CHCl_3$, 70 °C. [d]PhOH, MsOH, $CHCl_3$, rt. [e]HCl, Et_2O/$CHCl_3$, 70 °C. [f]1,3,5-Trimethoxybenzene, MsOH, $CHCl_3$, rt. [g]BF_3·Et_2O, *i*PrOH, $CHCl_3$, rt.

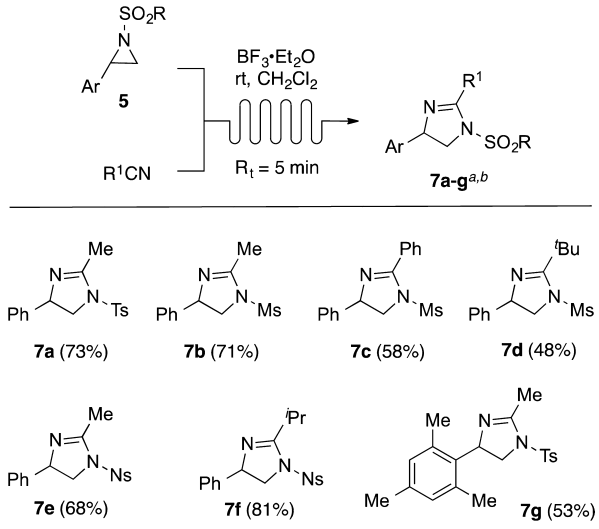
formed as the only stereoisomer by way of S_N2-type opening. In the case of **6g**, produced by fluoride opening of aziridine **5g**, this stereochemical assignment was confirmed by X-ray crystallography.

Additionally, the synthesis of imidazolines by the Lewis acid mediated ring expansion of 2-aryl aziridines with nitriles under continuous flow conditions has been examined.[18,19] Using boron(III) fluoride as a Lewis acid in combination with various nitriles, imidazolines **7a**−**g** were produced in moderate to good yields from 2-aryl aziridines (Scheme 4). The yields are broadly comparable with those obtained in conventional batch processes.[18] A single regioisomer was seen in all cases by way of initial nucleophilic ring opening at the more substituted carbon by the nitrile, prior to ring closure. This regiochemical outcome was confirmed for **7b** and **7c** by single crystal X-ray diffraction.

With practical conditions for the synthesis, ring opening, and ring expansion of aziridines under continuous flow conditions, we set about ascertaining if telescoped reactions could be undertaken in which the aziridine is generated and further reacted without recourse to handling or isolation. Our preliminary findings are very encouraging as illustrated in Scheme 5. For this chemistry, a three-input microreactor was used (see Supporting Information). The use of anhydrides for aziridine formation gave the best results in these telescoped sequences.[20] The total residence time for these reactions was 28 min (aziridine generation = 16 min; ring opening = 12 min).

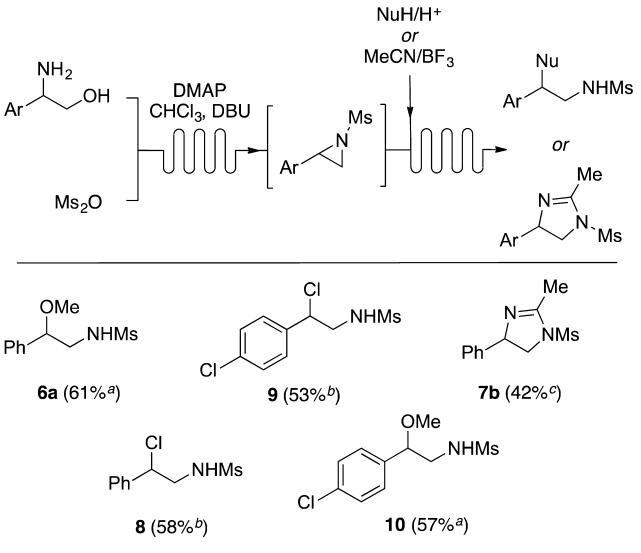
In conclusion, we have devised a simple, general route to aziridines through ring closure of the corresponding 1,2-amino alcohols under continuous flow conditions. A variety of substitution patterns are accessible using this method. Further reactions of the aziridines in flow provides access to a variety of useful nitrogen containing products by way of regio- and stereocontrolled opening with nucleophiles, or by ring

Scheme 4. Imidazoline Synthesis by Formal (3 + 2) Cycloaddition of Aziridines 5 with Nitriles under Continuous Flow Conditions



[a]Reaction conditions: R^1CN (5 equiv), BF_3·Et_2O (5 equiv), CH_2Cl_2, R_t = 5 min. [b]Isolated yield after chromatography.

Scheme 5. Telescoped Sequences for Generation and Opening of Aziridines under Continuous Flow Conditions



[a]NuH/H^+ = MeOH/MsOH. [b]NuH/H^+ = HCl. [c]MeCN/BF_3·Et_2O.

expansion. The flow-based processes described generally give similar yields/selectivities to conventional batch reactions. However, by telescoping the flow processes together, it is possible to limit exposure to this potentially hazardous class of electrophilic reagents and exploit other benefits of this new technology.[9] Work to explore other routes to aziridines in microreactors is ongoing in our laboratory and will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

Details of continuous flow apparatus, experimental procedures, characterization data for all compounds, chiral HPLC analysis for **5a**, and X-ray data for **6f**, **6g**, **7b**, and **7c**. The Supporting

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Notes

The authors declare no competing financial interest.

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