Continuous Flow Synthesis of 2*H*-Azirines and their Diastereoselective Transformation to Aziridines

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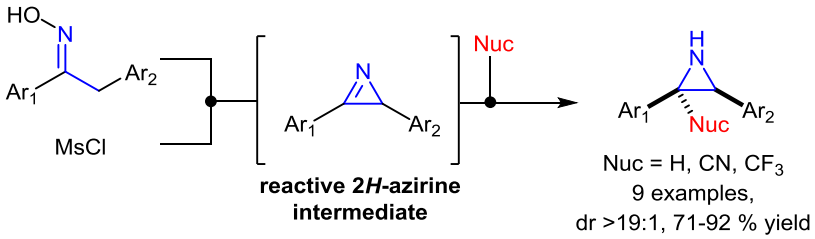
We dedicate the star of this paper to Prof. Steven V. Ley on the occasion of his 70th birthday. A guiding light for many researchers in Organic Chemistry; Matthew 2:1–2.



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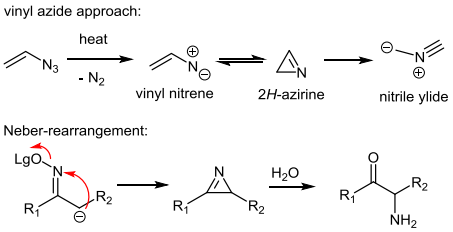
Abstract Using continuous flow techniques a small selection of 2*H*-azirines was prepared from oxime precursors via mesylation and base promoted cyclisation. The 2*H*-azirines were either isolated after in-line purification or derivatised into a selection of 2-substituted aziridines through a telescoped reaction sequences involving nitrile, trifluoromethyl or hydride nucleophile addition. Importantly, these 2-substituted aziridines were produced with high *cis*-diastereoselectivity providing access to small chiral heterocyclic entities which hold promise for medicinal chemistry programs because of their drug-like features.

Key words flow synthesis, heterocycles, azirine, aziridine, microreactor, monolith, in-line purification

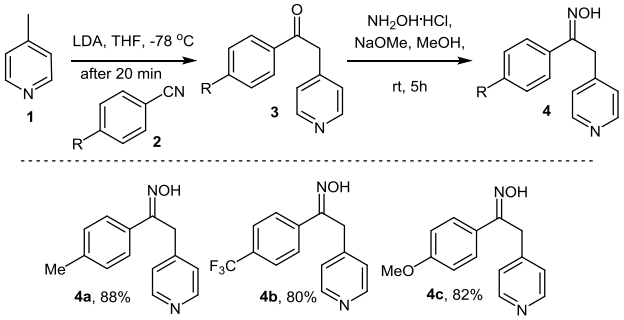
Introduction: 2*H*-Azirines and their saturated aziridine counterparts represent intriguing small heterocyclic components.[1] Synthesis of 2*H*-azirines commonly involves the photolysis of vinyl azides[3] or the Neber-rearrangement of activated oximes[4]. Due to the inherently high ring strain of the 2*H*-azirine structures their conversion into aziridines through nucleophilic attack at the imine carbon is a very thermodynamically favourable process accompanied by release of ~20 kcal/mol.[2] In addition 2*H*-azirines readily undergo ring opening into synthetically valuable nitrile ylide dipoles[5] (Scheme 1).



Scheme 1: Synthetic approaches towards 2*H*-azirines.

Current synthetic protocols towards 2*H*-azirines involve time and labour intensive batch manipulations were product instability results in decreased yield and the requirement for extensive purification. In the past we have successfully demonstrated several efficient flow processes yielding selections of chiral [6] and achiral [7] heterocyclic architectures displaying various versatile functionalization sites. We therefore aimed to harness the processing power of flow chemistry to deliver a stream of *2H*-azirine based on an interrupted Neber-rearrangement process. The intermediate *2H*-azirine would be subsequently telescoped through a second step involving addition of various nucleophiles to furnish di- and tri-substituted aziridines [8].

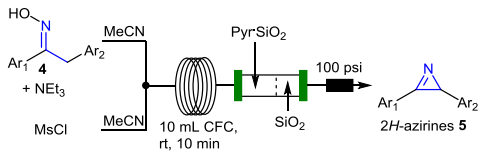
Results and Discussion: We commenced our studies with the efficient synthesis of different substrates bearing a 4-pyridyl moiety adjacent to the methylene carbon of the oxime motif, which itself would be derived from the corresponding ketone precursor.[Nik paper] It was quickly established that these ketone structures (**3**) could be readily accessed through the addition of lithiated picolines (**1**) into nitriles (**2**, Scheme 2, see SI for full details). The desired oximes **4** where subsequently prepared by condensation of the ketones **3** with hydroxylamine hydrochloride under basic conditions.



Scheme 2: Synthesis of oxime precusors **4**.

Flow Synthesis of 2*H*-Azirines: Having gained rapid entry to quantities of the oxime precusors we next turned our attention

towards developing a flow process for their conversion into 2*H*-azirines and related aziridines. To this end we configured a Vapourtec E-series flow system so that a stream (stream A, Scheme 3) containing the oxime substrate (**4**, 0.1 M MeCN) and triethylamine (1.2 equiv.) were mixed at a T-piece with a second stream containing mesyl chloride (0.12 M, MeCN; stream B, Scheme 3) before entering a tubular convection flow coil (CFC, 10 mL volume) maintained at 40 °C. The resultant mesylated oxime would then enter a packed glass column filled with silica-supported pyridine (2.5 g, 1.39 mmol/g functional loading, [9]) as a base to promote displacement of the mesylate and thus formation of the desired *2H*-azirines via a *3-exo-trig* cyclisation.



Scheme 3: Flow set-up generating 2*H*-azirines **5**.

It was proven that this simple set-up was indeed suitable for delivering the desired 2*H*-azirine products (**5**) in a mild and efficient flow sequence within an overall residence time of 20 minutes (16 minutes mesylation in CFC and 4 minutes cyclisation in the glass column). ^{1}H-NMR analysis of the crude output indicated >85% conversion of the oxime substrates to the 2*H*-azirine products. We therefore slightly modified the set-up to incorporate a small plug of silica gel (1 g) following the immobilised pyridine base in order to trap the triethylamine hydrochloride salt formed in the process. This not only resulted in a simple yet effective in-line purification, but also removed coloured impurities from the product stream. The set-up was used to rapidly delivering a small selection of 2*H*-azirine products depicted in Figure 1.

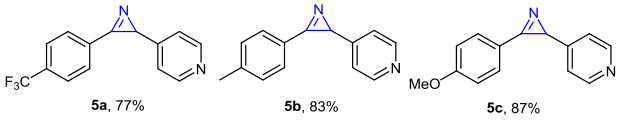
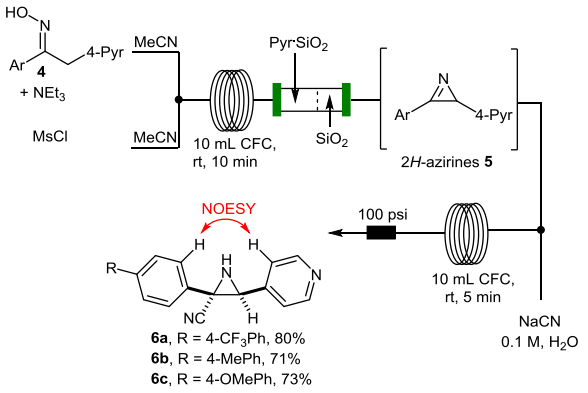


Figure 1: 2*H*-azirines **5a-c** prepared in flow (isolated yields).

Additional experiments also revealed that other solvents like EtOAc or THF were also suitable for this transformation however; the diminished solubility of the triethylamine hydrochloride generated presented a potential risk towards clogging of the narrow bore tubing connectors. It was found that although complete exclusion of triethylamine still yielded the desired 2*H*-azirines they existed as hydrochloride salts due to the embedded basic pyridyl moiety. As these required later free-basing this approach was not followed up further.

Telescoped Synthesis of 2-Substituted Aziridines: Next we explored the addition of various nucleophiles, such as nitrile, trifluoromethyl and hydride into the *2H*-azirines **5**. To this end we designed an extended process that would merge the initial reaction stream containing the *2H*-azirine product (~0.05 M, MeCN) with an aqueous solution of sodium cyanide (0.1 M, H_2O) in order to generate the corresponding nitrile derivatives (Scheme 4). After passing through a second tubular reactor coil (10 mL) maintained at ambient temperature the desired nitrile product was isolated after evaporation and aqueous extraction. Pleasingly it was quickly established that the desired adducts formed not only in good yield but moreover in excellent diastereoselectivity (d.r. >19:1).



Scheme 4: Continuous synthesis of aziridine-2-carbonitriles **6**.

Using NOESY-NMR techniques it was shown that a *cis*-relationship between the two aryl rings exists as a result of the nitrile approaching the azirine electrophile from the sterically least hindered face. In addition, single crystal X-ray diffraction was used to confirm the stereochemical assignment (Figure 2).

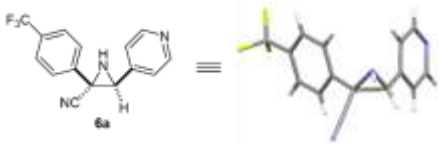
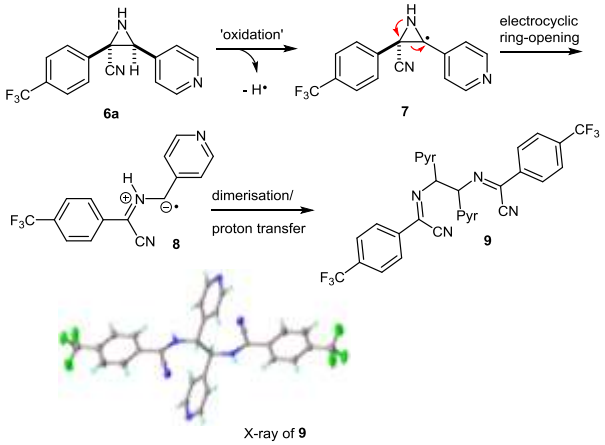


Figure 2: Relative stereochemistry of **6a** as established by X-ray crystallography.

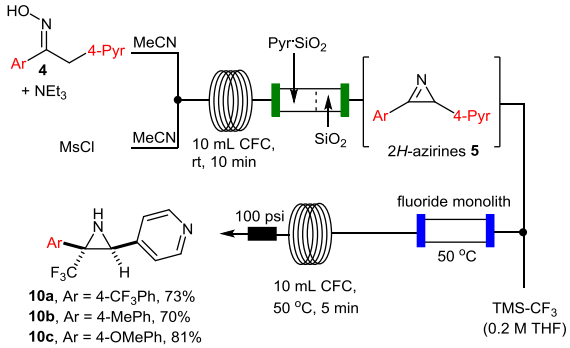
One interesting feature of these aziridines bearing a nitrile substituent is their distinct red colour when in solid form, whereas solutions appear to have a yellow-orange colour. This is possibly indicative of a 'push-pull' interaction between the electron-withdrawing nitrile group and the electron-rich aziridine nitrogen atom. It was furthermore found that these structures can slowly undergo decomposition via a process likely to comprise of a sequence of C-H oxidation, followed by electrocyclic ring opening of the resulting radical **7** which undergoes dimerisation to generate a *bis*-cyanoimine species **9**, whose structure was confirmed by X-ray crystallography (Scheme 5).



Scheme 5: Proposed mechanism for the decomposition of **6a**.

Next, we decided to evaluate the viability of introducing a trifluoromethyl group by reacting the azirine flow stream with Ruppert's reagent (TMS-CF_3) to yield the alternative

trifluoromethyl-aziridines. Due to their drug-likeness such fluorinated heterocyclic structures are predisposed for potential applications in medicinal chemistry programs [10]. In order to achieve the synthesis of these entities we decided to draw from our previous studies that had shown how flow chemical processing offers a robust solution for safely and efficiently performing fluorination reactions with various reagents such as DAST [11], Ruppert's reagent and Selectfluor [12]. Of particular benefit in these studies was the successful development of a fluoride containing ion exchange monolith which previously had allowed us to activate TMS-CF_3 towards addition into aldehydes without requiring TBAF as a solution phase reagent that is often difficult to remove by chromatography. We therefore prepared a monolithic reactor cartridge and loaded it with fluoride as previously reported [12a]. The crude 2*H*-azirine flow stream was therefore mixed via a T-piece with a stream containing the Ruppert's reagent (0.1 M, 2.0 equiv., THF) before passing through the fluoride monolith maintained at 50 °C. A CFC reactor (10 mL volume, 50 °C) was placed after the monolithic reactor to increase residence time for the trifluoromethylation reaction. Finally, a 100 psi back-pressure regulator was placed at the exit of the reactor to maintain the system pressure and product isolated by direct evaporation of the output (Scheme 6).



Scheme 6: Telescoped flow approach towards trifluoromethylated aziridines (**10a-c**).

Pleasingly, this new set-up proved successful for the telescoped synthesis of a small selection of trifluoromethylated aziridines starting from the corresponding oxime precursors. Importantly, all final products where isolated as single diastereomers in good yield and high purity after column chromatography. In order to evaluate the relative stereochemistry of our products we firstly turned to using 2D-NMR techniques, specifically ^{1}H-^{19}F-HOESY experiments, confirming the expected *cis*-relationship between the CF_3-group and the adjacent proton. As such it was quickly established that there was indeed a *cis*-correlation between these groups through the observation of a through space coupling at an estimated spatial distance of ~2.7 Å (established via ChemDraw 3D; compared to ~ 4.1 Å for the trans-diastereomer). Finally, as a single crystal X-ray structure of compound **10a** was secured and confirmed the assignment unambiguously (Figure 3).

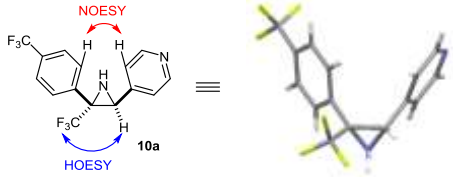


Figure 3: Relative stereochemistry of **10a** established by 2D-NMR (^{1}H-^{19}F-HOESY, left) and X-ray crystallography (right).

Finally, we elected to study the conversion of *in situ* prepared 2*H*-azirines into their corresponding aziridine derivatives. In order to achieve this reduction a number of options were evaluated including flow-based hydrogenations with the H-Cube system [13]. In view of operational simplicity it was however established that collecting the 2*H*-azirine stream into a flask containing $NaBH_4$ (1.5 equiv, 0.1 M THF) would lead to the clean formation of the desired aziridine products (**11a-c**), which again were isolated as single diastereomers. After aqueous work-up and column chromatography the relative stereochemistry of these entities was established using NOESY-NMR confirming the expected *cis*-relationship (Figure 4).

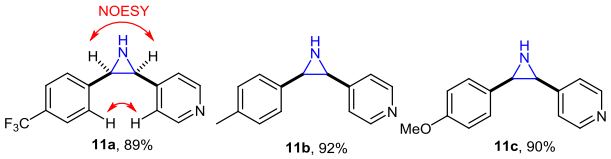


Figure 4: Disubstituted aziridines **11a-c** prepared in flow.

In summary, we have developed a simple, yet robust flow process generating a selection of 2*H*-azirines from readily accessible oxime precursors. The value of these species was furthermore demonstrated through a selection of telescoped reaction sequences showcasing the rapid formation of a number of aziridine derivatives accomplished by reaction with hydride, trifluoromethyl and nitrile nucleophiles. Importantly, these structures were obtained in high yield and with exclusive *cis*-diastereoselectivity presenting opportunities towards further exploitation of this versatile methodology.

Acknowledgment

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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Also, see reference 6 (a).

(14) **Typical flow procedure for the synthesis of 2*H*-azirines:** Using a Vapourtec E-Series flow system two streams containing the oxime substrate (**4**, 0.1 M MeCN, 1.0 equiv.; stream A) and triethylamine (1.2 equiv.; 0.3 mL/min; stream A) and mesyl chloride (0.12 M MeCN, 1.2 equiv.; 0.3 mL/min; stream B) are mixed in a T-piece prior to entering a tubular flow coil (10 mL volume, 40 °C) in which the mesylation occurs. The exiting flow stream is then directed into an Omnifit glass column (10 mm i.d., 150 mm length) filled with silica supported pyridine[9] (2.5 g, 1.39 mmol/g loading) and silica gel (1 g) which is maintained at ambient temperature. After exiting this column the crude reaction mixture passes a backpressure regulator (100 psi) before being collected. Final purification can be achieved via silica column chromatography (20-50% EtOAc/ hexanes) yielding the desired 2*H*-aziridines typically in high yield as yellow oils.
4-(3-(4-(Trifluoromethyl)phenyl)-2*H*-azirin-2-yl)pyridine 5a: Yield: 201 mg (0.77 mmol, 77%). Appearance: yellow oil. **^{1}H-NMR ($CDCl_3$, 400 MHz): δ/ppm** 8.47 (2H, d, J = 8.0 Hz), 7.97 (2H, d, J = 8.0 Hz), 7.79 (2H, d, J = 8.0 Hz), 7.02 (2H, d, J = 8.0 Hz), 3.29 (1H, s). **^{13}C-NMR ($CDCl_3$, 101 MHz): δ/ppm** 161.9 (C), 149.5 (2CH), 149.4 (C), 135.1 (C, q, J = 23 Hz), 130.3 (2CH), 126.4 (2CH, q, J = 4 Hz), 126.3 (C), 123.3 (CF3, q, J = 271 Hz), 120.9 (2CH), 33.6 (CH). **^{19}F-NMR ($CDCl_3$, 376 MHz): δ/ppm** -63.3 (s). **IR (neat): ν/cm^{-1}** 1602 (w), 1413 (w), 1322 (s), 1168 (m), 1126 (s), 1065 (s), 1017 (m), 851 (m). **LC-MS (ESI-TOF):** 263.1 (M+H). **HR-MS (ESI-TOF):** calculated for $C_{14}H_{10}N_2F_3$ 263.0796, found: 263.0792 (Δ 0.4 mDa).

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