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A Sustainable Strategy for the Straightforward Preparation of 2H-azirines and Highly Functionalized NH-aziridines from Vinyl Azides Using a Single Solvent Flow-Batch Approach

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Abstract

The reported flow-batch approach enables the easy preparation of 2H-azirines and their stereoselective transformation into highly functionalized NH-aziridines, starting from vinyl azides and organolithiums. The protocol has been developed using cyclopentylmethylether (CPME) as an environmentally responsible solvent, resulting into a sustainable, safe and potentially automatable method for the synthesis of interesting strained compounds.

Keywords

2H-Azirines; Aziridines; Flow Chemistry; Green Chemistry; Organolithiums.
Introduction

Since their conception in early 1990s, Green Chemistry Principles (GCP) have been applied with increasing effort towards the design of efficient production processes.[1-3]. As a result, a number of sustainable synthetic strategies have been recently developed, lowering the environmental impact and reducing the chemical hazards associated to the preparation of highly valuable compounds.[4] Among the elements that impact the sustainability of a synthetic method, the choice of the solvent is crucial.[5] In fact, chemical solvents represent most of the total amount of chemical species used in manufacturing processes, and therefore strongly affect waste disposal requirements and process related risks.[6] Recently, a variety of sustainable solvents have been therefore identified, and their use have been combined with those of enabling technologies. In this landscape, the development of continuous flow synthetic methodologies has found its fortune in the past two decades.[7-9] A number of chemical hazards can be effectively controlled through the use of microfluidic systems, because of the utilization of a reduced confined space and the exquisite control over heat and mass transfer.[10] As a consequence, efforts have been devoted to the development of synthetic processes combining GCP and enabling technologies[11].

Within the synthetic chemistry context, the preparation of aziridines still generates interest, mostly because of their importance as source for drug prototypes and drug discovery leads.[12] Interestingly, important advances have been recently addressed in the synthesis of NH-aziridines directly from olefins.[13,14] Aziridines are otherwise accessible from a variety of acyclic precursors,[15-17] even stereoselectively,[18-20] and through derivatization of 2H-azirines. The reactions using 2H-azirines as electrophiles proceed with several nitrogen, oxygen and sulfur nucleophiles, enabling to access aziridines with great structural variability.[21] The reaction of azirines with
Grignard and organolithium reagents has been poorly investigated, and without using green and renewable solvents. [22,23] In turn, 2H-azirines can be smoothly obtained through intramolecular cyclisation of vinyl azides, or by other strategies involving oximes, imines and oxazoles.[24] One appealing strategy for the preparation of 2H-azirines involves the use of readily available vinyl azides. [25-30] However, the batch cyclisation of vinyl azides into the corresponding 2H-azirines could generate some risks, due to the explosive nature of organic azides, and possible overpressure issues caused by nitrogen generation at high temperatures. Consequently, scalability and control of this processes represents a real challenge. The exploitation of microfluidic technologies has therefore resulted into safer procedures for the preparation of 2H-azirines, offering valuable alternatives for production purposes. In 2013, Kirschning harnessed the photoinduced electrocyclisation of vinyl azides in a microfluidic photoreactor yielding 2H-azirines as precursors of 1,3-dipolarophiles (Scheme 1, a).[27] Similarly, Maurya developed a microfluidic photoreactor for the synthesis of a fused β-carboline from an α-keto vinyl azide and a 1,2,3,4-tetrahydro-β-carboline (Scheme 1, b).[30] More recently, Kappe reported the generation of 2H-azirines under continuous flow conditions, and their transformation into functionalized oxazoles using acetone as the solvent (Scheme 1, c).[28] Inspired by these recent reports, we became interested in the development of an eco-friendly strategy for the safe preparation of highly functionalized NH-aziridines from acyclic precursors. We report herein a sustainable mixed flow-batch approach, that enables the direct preparation of functionalized NH-aziridines from vinyl azides.

**Scheme 1:** Flow generation and transformation of 2H-azirines
Results and Discussion

At the earliest stage of our research, we focused on the choice of the most suitable solvent for azides cyclisation and organolithium addition reactions. Most of the previously reported flow procedures involved acetonitrile, dichloromethane and acetone as solvents, however incompatibles with the utilization of reactive alkali
organometals. An exception is made for toluene, used by Kirschning for the photo-induced azirines formation.[27] Therefore, we investigated the thermally induced cyclisation of 1−(1−azidovinyl)−4−methylbenzene 1a in refluxing 2-MeTHF and cyclopentylmethylether (CPME) as green solvents, and compared the results with the reaction conducted in toluene (Table 1).

**Table 1:** Thermally induced cyclisation of 1−(1−azidovinyl)−4−methylbenzene 1a under batch conditions.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temperature</th>
<th>Time(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene</td>
<td>110°C</td>
<td>1.5 h</td>
</tr>
<tr>
<td>2-MeTHF</td>
<td>80°C</td>
<td>4.0 h</td>
</tr>
<tr>
<td>CPME</td>
<td>106°C</td>
<td>45 min</td>
</tr>
</tbody>
</table>

\(^a\) Time needed for complete consumption of 1a

The reaction proceeded rapidly in CPME, while the use of 2-MeTHF resulted in longer reaction times if compared with toluene. We therefore selected CPME as the most suitable solvent for our purposes. Interestingly, besides being characterized by low toxicity, CPME has a very low affinity to water, making it suitable for moisture sensitive reactions, without previous distillation.[31-33] Subsequently, the process was examined under continuous flow conditions employing special integrated coil reactor with two different operating temperatures (see Supporting Information). A solution of 1−(1−azidovinyl)−4−methylbenzene 1a (0.25M in CPME) was introduced, via a high pressure syringe pump, into the coil reactor maintained at the temperature of 130°C, and the residence time varied by adjusting the flow rate (Table 2). The reaction yield was calculated by \(^1\)H NMR analysis of the crude. In details, conversion of 1a in 2a
increased from 33% to >99% by adjusting the residence time from 4 min to 16 min respectively. From a technical point of view, the pressure generated during the course of the reaction, due to nitrogen evolution, could be managed by using high pressure pump, a stainless-steel reactor and a back-pressure of 8 bar.

**Table 2: Flow cyclisation of 1–(1–azidovinyl)–4–methylbenzene 1a**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Flow rate (F_r)</th>
<th>Residence Time (R_t)</th>
<th>Yield of 2a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.00 mL/min</td>
<td>4 min</td>
<td>33%</td>
</tr>
<tr>
<td>2</td>
<td>0.50 mL/min</td>
<td>8 min</td>
<td>65%</td>
</tr>
<tr>
<td>3</td>
<td>0.25 mL/min</td>
<td>16 min</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>

Under the optimized conditions, the scope of the reaction was explored on vinyl azides 1a–l that were transformed into the corresponding 2H–azirines 2a–l (Scheme 2). The methodology was found to be efficient with vinlyazides carrying aryls substituted with chlorine (2b), fluorine (2c), and bromide (2e–g). In details, ortho–, meta–, and para–bromo phenyl derivatives were quantitively transformed into the corresponding 2H–azirines 2e–g without substantial differences. Similarly, 3–(o–tolyl)–2H–azirine (2d) and 2,3–diphenyl–2H–azirine (2l) were also obtained in excellent yields. When 1–(1–azidovinyl)–2,3,4,5,6–pentafluorobenzene 1k was reacted under optimal flow conditions, a mixture of 1k and 2H–azirine 2k (20:80 ratio respectively) was recovered.
Unfortunately, it was not possible to isolate 3-(perfluorophenyl)-2H-azirine 2k due to its rapid polymerization in the crude mixture.

**Scheme 2**: Flow synthesis of 2H-azirines from vinyl azides.

Interestingly, aliphatic vinyl azides 1h–j were found less reactive, and the corresponding azirines 2h–j were obtained in just 74–77% of yield, in mixture with unreacted starting materials. However, when the reaction crudes were re-introduced into the flow reactor under the same conditions, azirines 2h-j were obtained quantitively (2h, 98%; 2i, 97%; 2j, 97%).
Pursuing in our aim to develop a green approach to prepare substituted NH-aziridines from vinyl azides in a single procedure, the solution of 2a from the microfluidic system was collected in a round bottom flask cooled at -78°C, and reacted with 1.2 equivalents of phenyllithium (PhLi). The mixture was stirred at the same temperature for 5 minutes, before quenching with water. With our delight, product 3a was isolated in 49% yield. 

Next, the reaction of several commercially available organolithiums was examined. As shown in Scheme 3, the reaction of 2a, generated in flow from 1a, proceeded smoothly also with hexyllithium (HexLi), n–butyllithium (n-BuLi) and iso–butyllithium (i-BuLi) affording the corresponding NH-aziridines 3a-c in good yields. Subsequently, other vinyl azides were tested for this flow-batch two-step procedure (Scheme 3).

**Scheme 3:** Mixed flow-batch approach for the preparation of functionalized NH-aziridines from vinyl azides.
Starting from vinyl azide 1d, the corresponding 3–(o-tolyl)–2H–azirine 2d was generated under flow conditions, and reacted with PhLi, HexLi and BuLi, furnishing NH-aziridines 3e–3g. Aliphatic vinyl azides 1j and 1k were also subjected to this mixed flow-batch protocol, generating NH-aziridines 3h,i in good yields (Scheme 3). The reaction was found to be efficient when PhLi was added to the collected solution of 2,3–diphenyl–2H–azirine 2m, affording 2,2,3-triphenylaziridine 3j in 62% yield. Moreover, the reaction was found highly stereoselective when HexLi or i-BuLi were added to 2m. In fact, only products deriving from the attack of the organolithium on the
less hindered face (i.e. *anti* with respect to the phenyl substituent at C3), leading to 3k (52%), and 3l (55%), were observed. The relative stereochemistry was assigned by NOESY experiments (see Supporting Information). Unfortunately, when the protocol was applied to 1-(1-azidovinyl)-2,3,4,5,6-pentafluorobenzene 1l, only a complex mixture was recovered likely because of the instability of the corresponding 2H-azirine 2k (*vide infra*).

**Conclusion**

In summary, we have developed a sustainable mixed flow-batch approach for the synthesis of functionalized NH-aziridines starting from vinyl azides using a single green solvent for two reaction steps. Several vinyl azides have been quantitively transformed into the corresponding 2H-azirines in a microfluidic reactor, overcoming the hazards associated with this transformation under batch conditions. A small library of functionalized aryl and alkyl substituted NH-aziridines has been created under operationally simple conditions. Notably, the addition reaction was found to proceed stereoselectively when organolithiums were added to 2,3-diphenyl-2H-azirine. This is a fast, safe, green and convenient method to access this interesting structural motif without requiring protection/deprotection steps or long synthetic pathways.

**Supporting Information**

Supporting Information File 1: Description of general methods, general procedures, characterization data for all compounds and copies of $^1$H, $^{13}$C, $^{19}$F, NOESY spectra.

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