Switchable reactivity of 2-Azetines: Ionic *versus* radical pathway for accessing β-aminocarbonyls and 2,3-disubstituted azetidines

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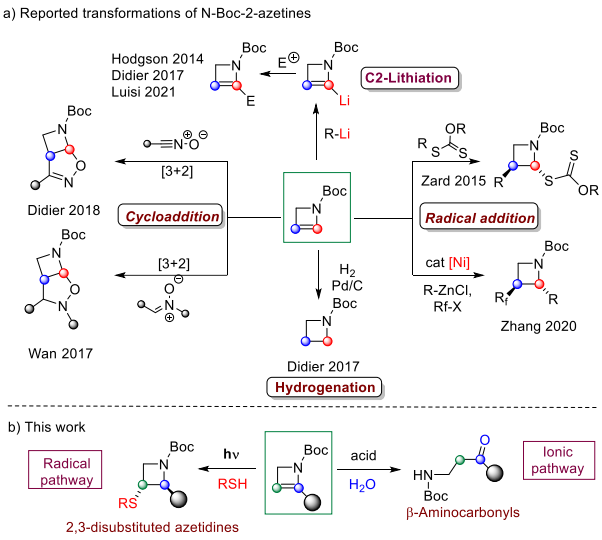
Abstract. Two unprecedented transformations of 2-azetines are reported. Varied C2-functionalized 2-azetines, prepared under continuous flow conditions, acted as linchpin for the preparation of either β-aminocarbonyls or C3-thiolated azetidines. Interestingly, the two transformations occurred following an ionic or radical pathway depending on the reaction conditions. The ionic pathway is triggered under acidic conditions in the presence of water, while the radical process is initiated using white light irradiation following a thiol-ene reactive scheme. These two methods have been applied to the synthesis of several products including bioactive fragments. Mechanistic evidence for the two pathways is provided.

Keywords: 2-Azetines; Azetidines; Thiolation; Flow Chemistry; Carbonyls

Introduction

2-Azetines are reported as highly strained four-membered azacycles and have been overlooked as useful building blocks in organic synthesis. Surprisingly, to the best of our knowledge, this structural motif has not yet been reported in any isolated natural product. Nevertheless, effective synthetic methods involving 2-azetines have been recently reported showcasing the versatility as synthons for the synthesis of structurally diversified azetidines.[1] The chemistry of 2-azetines generally involves a selective elaboration of the carbon-carbon double bond.[2] The explored reactivity of 2-azetines focused on their use as dienophiles for Diels-Alder reactions[3] or 1,3-dipolar cycloaddition reactions (Scheme 1a, cycloaddition). Another possibility to exploit the reactivity of 2-azetine relies on the C2-lithiation by using strong bases, followed by trapping with electrophiles. (Scheme 1a, C2-lithiation).[4,5] The reactivity of 2-azetines also includes rare examples of radical additions, as in the case of xanthates[6] or nickel-catalyzed tandem processes (Scheme 1a, radical addition).[7] Further, 2-azetines could undergo chemo and stereoselective hydrogenation reactions, in the presence of Pd and molecular hydrogen to provide the corresponding azetidines (Scheme 1a, hydrogenation).[5a]



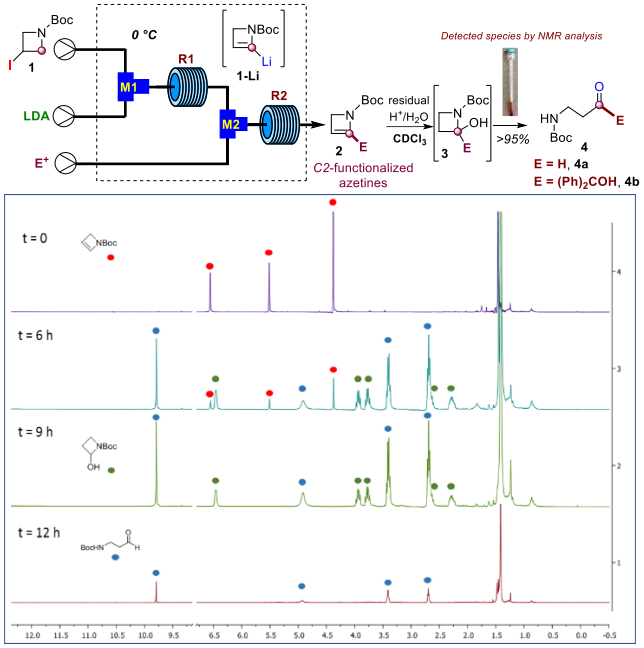
Scheme 1. Common synthetic transformations of 2-azetines.

In continuation of our research interest in the field of four-membered nitrogenated heterocycles,[8] we report herein an unprecedented switchable reactivity disclosed by C2-functionalized 2-azetines leading to β-aminocarbonyls or 2,3-disubstituted azetidines depending on the reaction conditions – i.e. ionic or photochemical conditions - (Scheme 1b).

Results and Discussion

Relying on our experience in the field of flow technology,[9] we have recently developed a sustainable continuous flow protocol to access either C3-functionalized azetidines or C2-functionalized 2-azetines by using 3-iodo N-Boc-2-azetidine **1** as common starting material.[10] This synthetic protocol was found highly efficient and robust for the preparation of several C2-functionalized 2-azetines. It is worth pointing out that N-Boc-2-azetines are strained endocyclic ene-carbamates. Hence, we envisioned that these compounds could be hydrolysed *en route* to β-aminocarbonyls, that are useful synthons and represent a class of pharmaceutically relevant motifs. In this context, Baumann and co-workers reported the preparation of γ-aminoketones from N-Boc pyrrolidines via water addition to an N-acyliminium intermediate.[11] Surprisingly, while ring-opening transformation of azetidine leading to α-aminoketones and diversely β-functionalized amines have been recently reported, the acid-promoted hydrolysis of 2-azetines to the putative β-aminocarbonyls remains unexplored.[12,13]

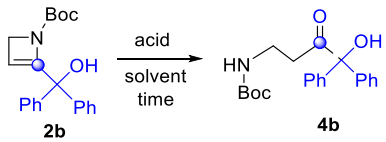
To fill this gap and gather some unambiguous mechanistic information, we first monitored by NMR the mild transformation of compound **2a** with the residual water content and traces of HCl in commercial $CDCl_3$ (Scheme 2). With our delight, we observed the quantitative formation of β-aminoaldehyde **4a** after 12h. In detail, the NMR monitoring revealed the formation of reaction intermediate after 6 hours, and complete disappearance of the signals of **2a** after 9 hours (Scheme 2). This intermediate was thoroughly analyzed (see Supporting Information) and ascribed to 2-hydroxy azetidine **3**. This transient hemiaminal **3** completely disappeared in the next 3-6 hours leading to exclusive formation of β-aminoaldehyde **4a** (Scheme 2). Similarly, the dissolution of azetine **2b** in commercial $CDCl_3$ resulted in a quantitative ring opening with formation of β-aminoketone **4b**, suggesting that the reaction could proceed smoothly also employing 2-substituted-2-azetines.



Scheme 2. NMR evidence of the acid-promoted ring opening of 2-azetines in $CDCl_3$.

With this evidence in hand, we decided to optimize the reaction to develop a general and robust synthetic protocol for the easy formation of β-aminocarbonyl derivatives (Table 1).

Table 1. Optimization of the acidic ring opening for **2b**.

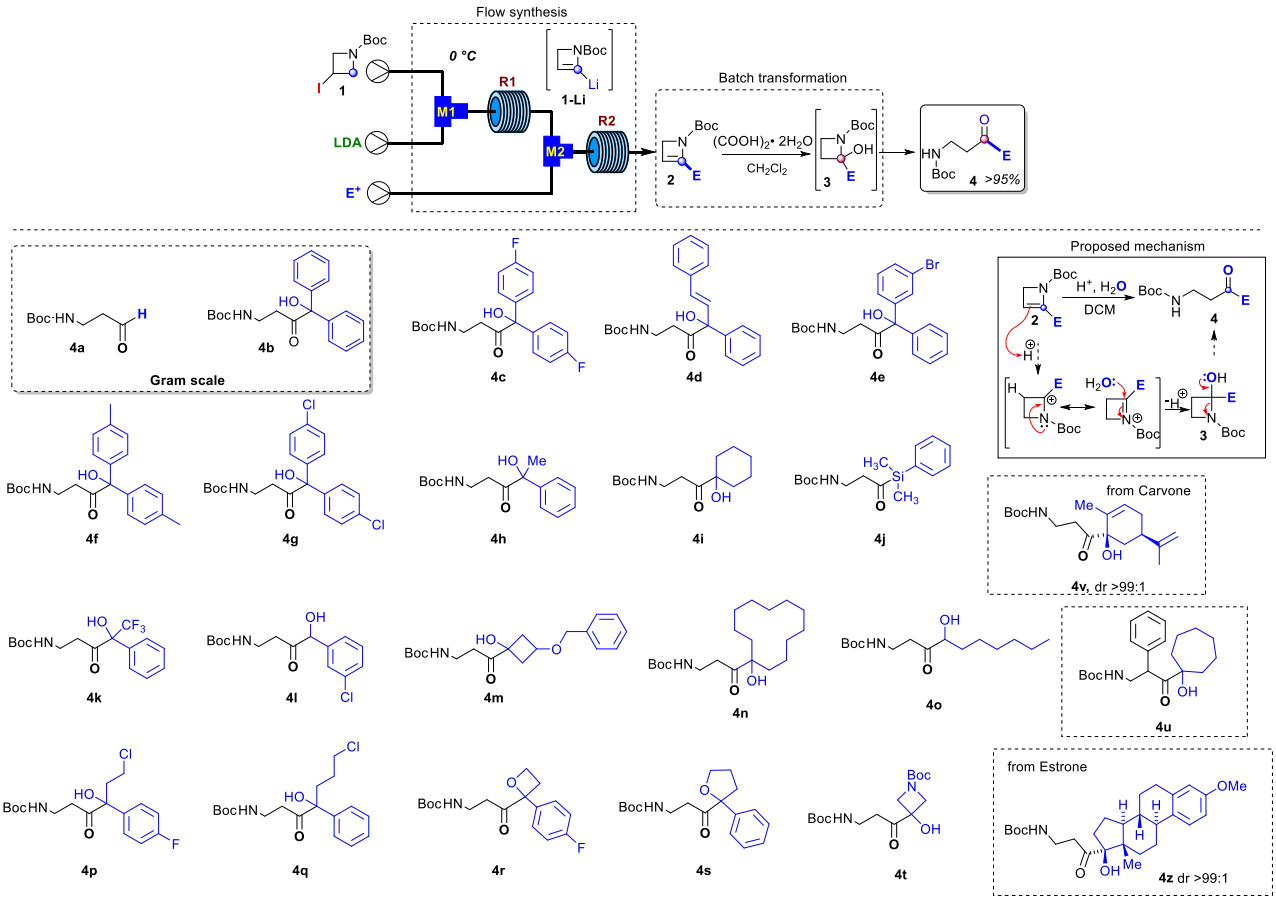


entry	Acid	equiv.	Solvent[b]	Time	**4b** Yield (%)[a]
1	-		DCM	16h	-
2	Oxalic acid·$2H_2O$	0.5	DCM	1h	80
3	Oxalic acid·$2H_2O$	0.5	DCM	1.5h	98
4	Oxalic acid·$2H_2O$	0.5	DCM/H_2O	1.5h	98
5	Acetic acid	1.0	DCM	1.5h	70[c]
6	TsOH	0.1	$CDCl_3$	0.5h	50
7	TsOH	1.0	$CDCl_3$	2h	90

[a)]Calculated by ^{1}HNMR on the crude reaction mixture. [b)]Treated with Na_2SO_4 or distilled over CaH_2.[c)] Unidentified side-products detected.

Azetine **2b** was selected as model substrate and tested under different reaction conditions reported in Table 1 (see also Supporting Information). First, the role of water was assessed and as expected, the reaction did not occur in absence of water even for prolonged reaction times (entry 1). As a result, oxalic acid

dihydrate (0.5 equiv) was selected as the best promoter for the reaction providing complete conversion after 1.5 hours (entries 3,4). The use of not-anhydrous acetic acid resulted in 70% yield of the desired product **4b** (entry 5), and several unidentified side products that made difficult the purification step. The use of TsOH in sub-stoichiometric (0.1 equiv) or stoichiometric (1 equiv) amount was additionally tested in an NMR tube (see Supporting Information) providing evidence on the role of water and enabling the preparation of **4a** in 50% and 90% of yield after 0.5 and 2h respectively (entries 6−7). The results from optimization experiments and NMR monitoring allow to propose the mechanism reported in Scheme 3. In detail, azetine **2** is first protonated at C3 to provide a stabilized azetidinium ion that undergo nucleophilic addition of water leading to hemiaminal **3**. Spontaneous ring-opening of **3** provide the β-aminocarbonyl derivative **4**. Next, by using the optimal conditions reported in Table 1, entry 3, we decided to explore the scope of the reaction for several C2-functionalized azetines **2** prepared using the efficient continuous flow protocol previously developed.[10] As reported in Scheme 3, the process proceeds under mild conditions using oxalic acid in CH_2Cl_2 at 25°C allowing for the preparation of β-aminocarbonyls **4a-z** in almost quantitative yields. The protocol was found highly efficient regardless of the nature of the substituent installed at the C2 position of the N-Boc-2-azetines (**2a-z**) and occurred with high chemoselectivity and functional group tolerance. For example, in the case of **4d** no potentially competitive hydration of the double bond was observed. The reaction proved effective in the presence of haloalkyl moieties (**4p**,**q**) as well as with aliphatic, aromatic and cyclic alcohols (**4b-i**, **4k-o**). Heterosubstituted ketones **4r-t** could also be obtained in very high yields (>95%) leaving untouched the heterocyclic core. Interestingly, an unusual and difficult to make acylsilane **4j** could be easily prepared in good yield using this strategy. To further test the usefulness of this methodology, the β-aminopropanoyl group was installed on natural or biorelevant chiral scaffolds such as (-)-carvone and *O*-methyl-estrone. The corresponding products **4v** and **4z** formed quantitatively and with high chemoselectivity and preserving the stereochemistry. Remarkably, the method was successfully applied also to a 2,3 disubstituted azetine (**2u**) obtaining the corresponding β-aminoketone **4u**.



Scheme 3. Scope of the reaction and proposed mechanism for acid promoted conversion of 2-azetines to b-aminocarbonyls.

Next, we evaluated the possibility to use 2-substituted-2-azetines as synthetic platform for a radical addition process such as a thiol-ene type reaction en route to poly-functionalized azetidines.

We identified the hydrothiolation reaction as a highly atom efficient click-type reaction that could be run under photochemical conditions. In fact, the homolytic rupture of the S-H bond could be easily achieved under light irradiation, without using metals or photocatalysts, in order to generate the putative thiyl radical.[15-17] Although this reaction has been widely studied, the hydrothiolation of 2-azetines, to the best of our knowledge, has not been reported to date. In fact, this transformation has been documented only for a selected bicyclic 2-azetine in the early 80s, and detailed information about the stereo- and chemoselectivity of the S-H radical addition to these strained compounds is lacking. [18] To support our hypothesis, 2-azetines **2a** and **2b**, used as model substrates, were reacted under white light irradiation with thiophenol in DCM at 50 °C (see Supporting Information for optimization study). To our delight, the expected adduct **5a** and **5d** were isolated in 95% and 85% yield respectively (Scheme 4). Remarkably, good trans/cis stereoselectivity (dr 84/16) was observed in **5d**. Additionally, the regiochemistry of the reaction resulted opposite (i.e. C3 *vs* C2) to the radical addition of xantates reported by Zard (see Scheme 1), thus making our protocol a valid complementary strategy.[6] The optimization study demonstrated that light irradiation was essential, and that a 1:2 azetine:thiol molar ratio was required. The optimization study also allowed to demonstrate the involvement in this process of radical species and to confirm the mechanism reported in Scheme 4. [16] In detail, the process starts with the generation, from the corresponding thiol and under light irradiation, of thiyl radical **A**.[19] Radical **A** reacts with azetine **2** to provide azetidnyl radical **B** that undergoes thiol-mediated hydrogen radical transfer to furnish the final product **5**. Remarkably, the azetidinyl radical **B** was trapped using TEMPO as radical scavenger leading to product **6** (see Supporting Information). With optimal conditions in hand, the scope of the reaction was explored (Scheme 4) using several 2-azetines **2** and varied aromatic and aliphatic thiols. The reaction occurred with good to excellent yields furnishing azetidines **5a-q**. The stereoselectivity of the reaction was affected by the steric requirement brought by the C2-substituent of the azetine, and the steric hindrance of the thiol. High level of trans stereoselectivity were observed when bulky substituents were installed at the C2 (i.e **5d-g**, **5m**). In striking contrast, reducing the steric requirement at C2 resulted in lower stereoselectivity (i.e. **5h**, **5l**). However, the steric requirement of the thiol seemed to be important, as observed for **5j**. Moreover, a complete cis-stereoselectivtiy was observed in **5i** likely as the result of reduced steric requirement at C2 and at the thiol. The radical protocol was found highly chemoselective as in the case of the reaction involving chiral azetine **2v** deriving from (-)-carvone. In fact, under radical conditions, only the azetine p-system was involved in the reaction leaving untouched the remaining double bonds in **5o**. The use of cysteine as thiyl radical precursor was also evaluated on azetines **2a** and **2b**. Interestingly, the reaction occurred smoothly furnishing the corresponding azetidines **5q** and **5p** in 86% and 78% yields respectively. In conclusion, we have demonstrated a switchable reactivity for C2-functionalized 2-azetines

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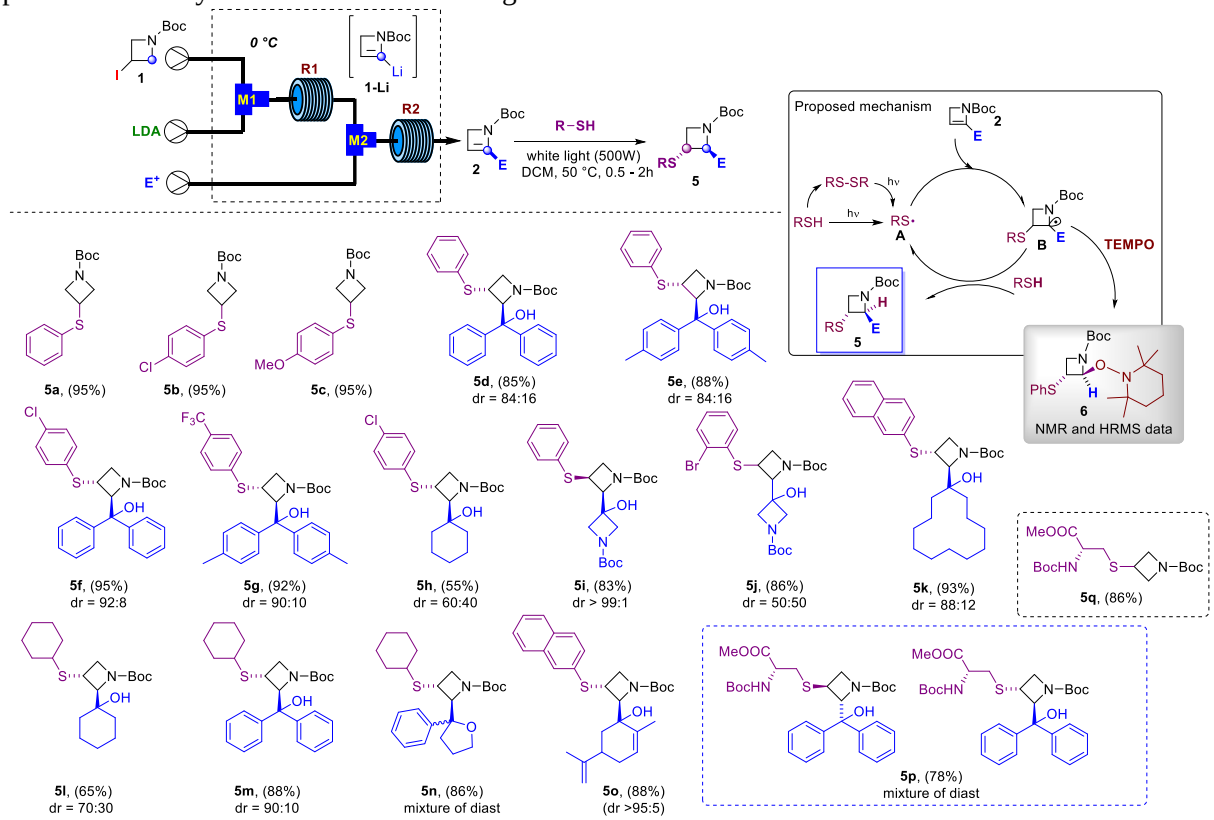

Scheme 4. Scope of the radical hydrothiolation of 2-azetines and proposed mechanism.

Conclusion

In conclusion, two unprecedented reactive pathways have been identified. An ionic pathway, operated under acidic conditions and in the presence of water, leading to a quantitative transformation of 2-azetines into valuables β-aminocarbonyls. The resulting products could be easily isolated without requiring a purification step. This protocol has been engaged also on bio-relevant scaffolds and heterosubstituted systems allowing for an easy installation of the β-aminocarbonyl unit in more complex structures. A radical pathway consisting in a highly atom efficient photochemical hydrothiolation reaction. The use of white light irradiation allowed to generate thiyl radicals that add to the π-system of the azetine ring to provide an azetidinyl radical intermediate that terminate the radical cascade by hydrogen insertion. The process was found highly regio- chemo- and stereoselective complementing the rather rare methods for the thiolation of azetines. Both strategies (i.e. ionic and radical) have been proved to be compatible with sensitive and highly functionalized substrates. Remarkably the use of flow technology allowed for easy access to a broad array of C2-substituted 2-azetines employed in this study. Further applications of this protocol are currently under investigation.

Experimental Section

General procedure for the acid-promoted ring opening of 2-azetines. Preparation of products 4a-4z.

To a stirred solution of azetine **2** (0.25 mmol, 1 equiv) in dichloromethane (2.5 mL), oxalic acid dihydrate (0.125 mmol, 0.5 equiv) was added. After 1.5 hours, the reaction mixture was filtered, and the solvent was removed under reduced pressure obtaining the desired products **4** without further purification unless otherwise specified.

General procedure for the thiol-ene reaction. Preparation of products 5a-5z

To a stirred solution of azetine **2** (0.25 mmol, 1 equiv) in dichloromethane (2.5 mL), thiol (0.5 mmol, 2 equiv) was added. The reaction mixture was irradiated by using a household tungsten lamp (white light, 500W). The light source was placed 3 cm from the reaction mixture. Under these conditions, the reaction mixture reached a temperature of around 50 °C. Consequently, a reflux apparatus was adopted. The transformation progression was monitored by TLC and/or GC analyses. After 0.5 - 2 hours, the solvent was removed under reduced pressure. The desired product **5** was obtained by washing the reaction crude with hexane/diethyl ether 9:1 (v/v) or after flash column chromatography.

Acknowledgements

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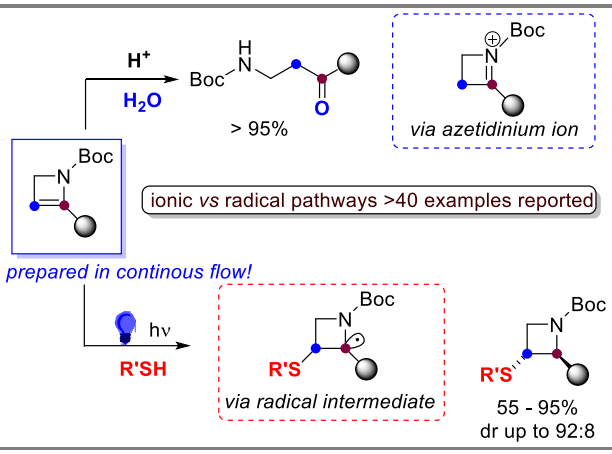
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