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Mechanistic insights into the rearrangement of azetidine N-oxides to isoxazolidines

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ABSTRACT

Various functionalized azetidines were oxidized with *m*CPBA or hydrogen peroxide, to produce the corresponding N-oxide and study its fate in the [1,2] Meisenheimer rearrangement. This ring expansion leading to isoxazolidines occurs readily, without trapping of the transient N-oxide. Starting with azetidines bearing a nitrile or an ester group at C-2, the rearrangement is regioselective. However, a varying amount of epimerization on the migrating radical is observed, which can also be observed with the related [1,2] Stevens rearrangement.

The [1,2] Meisenheimer rearrangement of amine N-oxides is a reaction that has found some applications in the synthesis of alkaloids.[1] When carried out with cyclic amines, this thermally induced reaction produces the corresponding ring expanded product including an oxygen atom. Together with its vinyl homologue that is, the [2,3] Meisenheimer rearrangement, for which asymmetric versions have appeared,[2] its mechanism has been thoroughly examined both experimentally[3] and, more recently, in silico.[4] It is now well-established that this reaction goes through a diradical species, produced via the homolytic cleavage of the C–N bond, that further recombines to form the C–O bond (Fig. 1).

This rearrangement is quite similar to the Stevens rearrangement, for which it has been demonstrated that the migrating carbon radical recombines in the solvent cage mainly with retention of configuration[5] (Fig. 2).

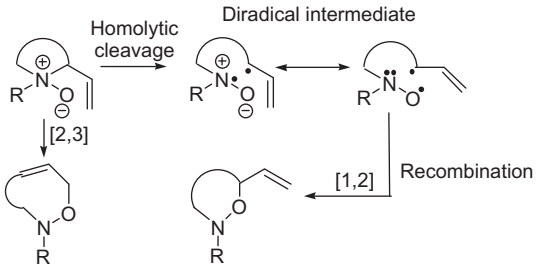

Figure 1. [1,2] and [2,3] Meisenheimer rearrangement of amine N-oxides.

However, this issue of stereoselectivity is different from the Meisenheimer rearrangement, for which Schöllkopf[3a] earlier demonstrated that, when starting with optically enriched α-deutero-*N*,*N*-dimethylbenzylamine oxide, the deuterated benzylic radical migrates with ca. 70% of racemization, and the 'cage effect' which accounts for the stereospecificity of the recombination was later on estimated to be 40%.[3c] This is indeed a major parameter for this reaction, but which has been very rarely studied. Isolated examples in cyclic systems allowing a quantitative measurement of the amount of retention of configuration for the recombination step are very scarce.[1]

Azetidines, that is, four-membered ring nitrogen heterocycles are ideal substrates for studies directed to this rearrangement because the ring strain present in these heterocycles facilitates the rate limiting step, that is, the homolytic bond cleavage. Furthermore, the produced isoxazolidines, usually prepared by cycloadditions,[6] are of high synthetic interest. The first report of the

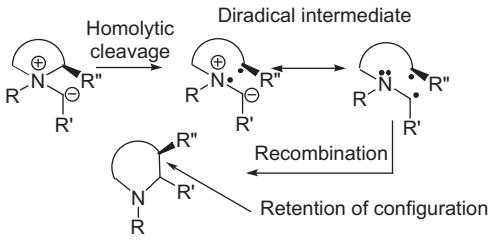

Figure 2. Stevens rearrangement occurs with retention of configuration.

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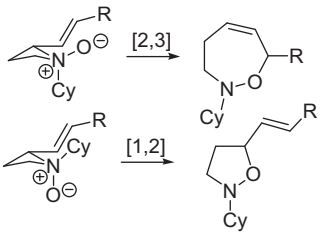


Figure 3. Importance of the configuration of the N-oxide, when [1,2] and [2,3] Meisenheimer rearrangements can compete.

Meisenheimer rearrangement in azetidine N-oxides came from Kurihara et al.,[7] who noticed their ease and applied this reaction to the synthesis of alkaloids. Later on, they engaged in a study[8] on the [2,3] Meisenheimer rearrangement of 2-alkenyl azetidine N-oxides and pointed out the importance of the configuration of the N-oxide on the outcome of the reaction. Thus, when the oxygen is *cis* to the adjacent alkenyl moiety, then [2,3] Meisenheimer rearrangement occurs, but when it is *trans*, then exclusive [1,2] rearrangement is observed (Fig. 3). We have noticed a similar behavior in the Stevens rearrangement of such systems, which afford unsaturated azocanes through [2,3] rearrangement.[9]

In this Letter, in continuation with our interest in the ring expansion and ring cleavage of azetidines,[10] we describe further studies on [1,2] Meisenheimer rearrangement of azetidines, addressing the issues of regioselectivity for the cleavage step, and stereoselectivity for the produced isoxazolidine.

For this study, we selected an array of diversely substituted azetidines **1**–**8** shown in Figure 4. These compounds were chosen to answer the following questions: (i) is this ring expansion feasible with unsubstituted azetidines (substrate **1**) and (ii) does it occur regioselectively when a nitrile or an ester is present at C-2 (substrate **2**[11] and **3**[12])? In the case of regioselective ring opening at C-2, substrates **4–5**,[13] **6**,[14] **7**,[15] and **8**[16] were selected to study the issues of diastereoselectivity.

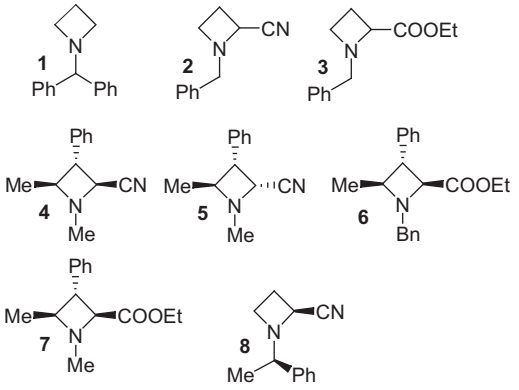
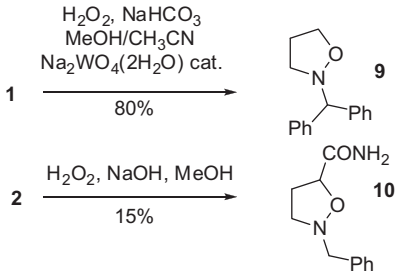
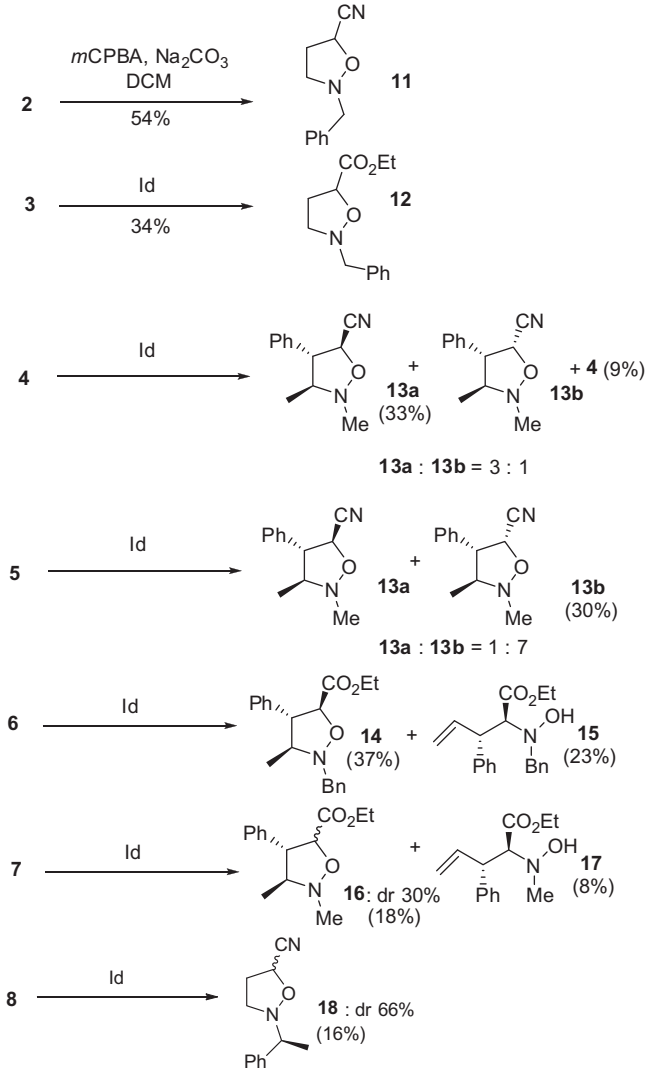


Figure 4. Structure of selected azetidines **1**–**8**.



Scheme 1. Reactions with hydrogen peroxide.

Screening of the conditions for the oxidation of the nitrogen included *m*CPBA with Na_2CO_3,[8] hydrogen peroxide with sodium hydroxide,[17] hydrogen peroxide with $NaHCO_3$ in the presence of Na_2WO_4, $2H_2O$ catalyst,[18] or TFAA, K_2CO_3, UHP.[19] It appeared that in no case, starting with these substrates and under these conditions, we have been able to isolate or characterize by NMR the intermediate azetidine N-oxide. As a matter of fact, azetidine N-oxides have been isolated in previous work in isolated cases[7c] and proved stable enough only if stabilization by intramolecular H-bonding[7a,20] is possible. Here, the produced N-oxide undergoes a rapid [1,2] Meisenheimer rearrangement to give the corresponding isoxazolidine, but isolated yields are usually low due to incomplete oxidation of the starting material and competing oxidation of the produced isoxazolidine leading to polar nitrones. The latter could be identified by a signal around 6.9 ppm in ^{1}H NMR of the crude reaction mixture.[8] For azetidine **1**, the best conditions were identified as hydrogen peroxide in the presence of Na_2WO_4, $2H_2O$ catalyst and gave N-benzhydryl isoxazolidine **9** in 80% isolated yield. We next realized that presence of a nitrile or an ester in the azetidine substrate precluded the use of hydrogen peroxide in the basic medium as the oxidant, since, for example, isoxazolidinyl amide **10**, in which the nitrile had been hydrolyzed, was



Scheme 2. Reactions of azetidines with *m*CPBA. Yields in brackets refer to pure isolated compounds. Ratios of isomers were determined by ^{1}H NMR on the crude reaction mixture.

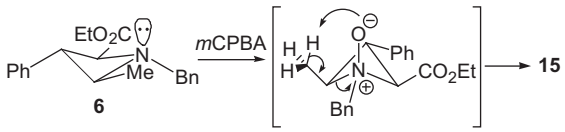


Figure 5. Competing Cope elimination in N-oxide derived from azetidine **6**.

produced in low 15% isolated yield starting from **2** (Scheme 1). Structure of **10** was ascertained by X-ray crystallography.[21]

With functionalized substrates **2**–**8** we therefore switched to *m*CPBA oxidations and results are shown in Scheme 2.

This set of experiments allows to answer all the questions initially programmed. First, this rearrangement takes place very rapidly and efficiently with an unsubstituted azetidine: even though the intermediate primary carbon radical should be less stabilized, we could not observe any transient N-oxide when the oxidation of **1** leading to **9** with *m*CPBA was carried out in a NMR tube. Then, the ring cleavage is highly regioselective when an ester or nitrile is present at C-2, which is in agreement with the stabilization of the intermediate α-cyano or α-ethoxycarbonyl intermediate radical. Finally, the configuration of the migrating carbon stereocenter is retained only in one case, starting from azetidine **6**. Starting from diastereoisomers **4** and **5**, up to 25% of epimerization is observed, but the ratio of epimers depends on the configuration in the starting material. This suggests a partial retention of configuration, though relative configuration in isoxazolidines **13a** and **13b** could not be clearly ascertained by NOE experiments. This degree of epimerization also depends on the nature of the substituent on the radical intermediate (nitrile or ester), since no epimerization is observed starting from azetidine ester **6**. Furthermore, the nature of the nitrogen substituent is also a crucial parameter, since extensive epimerization is observed starting from *N*-Me azetidine **7**, while no epimerization is observed starting with *N*-Bn analogue **6**. Note that in the former case, major epimer retains the stereochemistry of the starting azetidine based on the examination of the coupling constants (see Supplementary data). These experiments also allowed to put in light a possible competing process when the N-oxide is stereoselectively produced in a *cis* relationship to the 4-methyl substituent. In this case, a Cope elimination yielding hydroxylamine **15** and **17** can occur. This *syn* elimination is observed with esters **6** and **7**, but not with nitriles **4** and **5**, suggesting that the homolytic cleavage leading to isoxazolidine is easier in the latter case (Fig. 5).

In conclusion, we have demonstrated that [1,2] Meisenheimer rearrangement in azetidine N-oxides occurs very rapidly and regioselectively. The stereospecificity of the reaction is however low and depends on several parameters, such as the nature of the intermediate carbon radical, and the nature of the substituents on the azetidine ring.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterization data for compounds **9**–**18**. Crystallographic data for isoxazolidine **1**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06.092.

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