A Mechanistic Study for Aziridination of Nitroalkenes Mediated by N-Chlorosuccinimide

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Abstract: Direct aziridination of a nitrostyrene is achieved upon treatment with an alkylamine and N-chlorosuccinimide. The reaction is initiated by the Michael addition of amine to nitroalkene. Subsequent N-chlorination and nucleophilic substitution at the nitrogen atom afford 1-alkyl-2-nitroaziridine diastereoselectively. This reaction mechanism was clarified by NMR studies.

**Key words:** nitroaziridine, nitroalkene, chloramine, intramolecular nucleophilic substitution

1 Introduction

Aziridines are an important class of aza heterocycles¹–². Owing to the inherent ring strain and high electrophilicity, they undergo the ring-opening with various nucleophiles to afford various nitrogen-containing compounds such as amino acids, amino sugars, and alkaloids³–⁵. In contrast to epoxides, aziridines can be readily metalated and can react with electrophiles⁶, producing a broad range of functional derivatives that can serve as versatile building blocks in organic synthesis¹,²,⁷–¹². Indeed, a large number of functionalized aziridines have been transformed into useful compounds such as an HIV protease inhibitor¹³, communesin¹⁴, ceramide¹⁵, and oseltamivir¹⁶ via rearrangement, cycloaddition, and ring-expansion reactions⁷–¹². Among the functional groups, the nitro group is highly attractive in synthetic chemistry because of its strong electron-withdrawing ability and diverse reactivity¹⁷,¹⁸. Hence, the direct aziridination of nitroalkene will allow the rapid construction of a library of nitroaziridines that will be useful for identifying new biologically active compounds.

In our previous work, we demonstrated a direct aziridination of 3-nitro-2-quinolone 1 (Scheme 1a)¹⁹ and a nitrostyrene 3 (Scheme 1b)²⁰ which are mediated by N-chlorosuccinimide (NCS). Although several direct aziridination methods of a nitroalkene were reported²¹, the N-substituent is limited to an aromatic group or an electron-withdrawing group. Thus, N-alkyl nitroaziridines are synthesized via β-bromination of β-nitrostyrene²²,²³. It is noteworthy that N-alkylated nitroaziridine is directly synthesized by this method.

Initially, we considered that aziridine 4 was formed by conjugate addition of an amine 2 to a nitrostyrene 3, chlorination by NCS, and intramolecular nucleophilic substitution of the intermediately formed aminochlorinated product 6. However, depending on the reaction conditions (solvent and base), cleavage of the carbon–carbon bond occurs, giving a significant amount of imine 5. As reported by Mpourmpakis and Lykakis²⁴, protic solvent, methanol, promoted the retro-aza-Henry reaction to form imine 5.

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Accepted March 5, 2022 (received for review December 3, 2021)
Journal of Oleo Science ISSN 1345-8957 print / ISSN 1347-3352 online
http://www.jstage.jst.go.jp/browse/jos/ http://mc.manuscriptcentral.com/jjocs

Scheme 1 NCS-mediated aziridination of nitroalkenes.
predominantly, and aprotic polar solvents such as THF, acetonitrile, and dichloromethane were found to be suitable for this aziridination. Furthermore, using bulky bases such as DBU and tert-ButOK accelerated formation of imine 5 while Cs₂CO₃ increased the yield of 4a (R = Pr) up to 85%. On the other hand, the role of NCS in the reaction mechanism of Scheme 1 has not been fully understood. Therefore, in this paper, we discussed the reaction mode of the aziridination with focusing on the role of NCS.

2 Experimental

2.1 General

The melting points were determined on SRS-Optimelt Automated Melting Point System and were uncorrected. All the reagents and solvents were commercially available and used as received. The ¹H NMR spectra were measured on a Bruker Ascend-400 and JEOL JMN-ECZ40085 at 400 MHz with tetramethylsilane as an internal standard. The ¹³C NMR spectra were measured on a Bruker Ascend-400 and JEOL JMN-ECZ40085 at 100 MHz, and assignments of ¹³C NMR spectra were performed by DEPT experiments. To a solution of nitrostyrene and propylamine, while Cs₂CO₃ increased the yield of 8b could not be separated.

2.3 Chlorination of octylamine 2b

N-chloro-N-octylamine (8b): To a solution of octylamine (2b) (129 mg, 1 mmol) in THF (4 mL), NCS (133 mg, 1 mmol) was added, and the resultant mixture was stirred at room temperature for 0.5 h. Hexane (10 mL) was added, and precipitates were filtered off. The filtrate was concentrated to afford a mixture of chloramine 8b and dichlorinated product (85/15) as a colorless oil, in which 78% of 8b was contained. Despite various attempts, these products could not be separated. The ¹H NMR (400 MHz, CDCl₃) δ 8.96 (t, J = 6.8 Hz, 3H), 1.17–1.37 (m, 10H), 1.58 (t, J = 7.2 Hz, 2H), 3.05 (t, J = 6.8 Hz, 2H), 3.95–4.70 (br s, 1H), ¹³C NMR (100 MHz, CDCl₃) δ 14.2 (CH₃), 22.7 (CH₂), 26.7 (CH₃), 28.7 (CH₃), 29.3 (CH₉), 29.5 (CH₉), 31.9 (CH₂), 57.1 (CH₃); IR (KBr/cm⁻¹) 3400–3100 (br), 2955, 2926, 2855; HRMS (ESI/TOF) calcd. for C₃₉H₃₅ClN [(M + H)⁺]: 572.2520, found: 572.2520.
Aziridination of Nitroalkenes Caused by N-Chlorosuccinimide

N-Chloramines have been used in organic syntheses as N1 units possessing both nucleophilicity and electrophilicity. This helps them to bind to polar functional groups such as C=O and C=N, thus facilitating the construction of di-aziridine\(^\text{28-30}\) and oxaziridine\(^\text{31}\) frameworks, respectively. For addition to a C=C bond, anionic forms of N-chloramine that are stabilized by electron-withdrawing groups such as carbonyl\(^\text{22}\) and sulfonyl\(^\text{32-33}\) are often used. On the other hand, except for some examples of intramolecular addition\(^\text{36-37}\), the addition of N-alkylated chloramine to a C=C bond has not been reported in the literature. This prompted us to study the reaction of 3 with nitrostyrene 3.

N-Chloro (propyl) amine 8a\(^\text{25}\) derived from propylamine 2a cannot be isolated because of its low boiling point; accordingly, octylamine 2b was employed as the substrate. After stirring a solution of 2b and NCS in THF at room temperature for 0.5 h, hexane was added to it, and succinimide precipitate formed was filtered. The filtrate contained chloro (octyl) amine 8b (78% yield) and N,N-dichlorinated amine 9b (14% yield) at a ratio of 85:15 (Scheme 2a). After the solution was allowed to stand at room temperature for 2.5 h, the oily mixture solidified, and the ratio changed to 76:24. This indicated that chloro (octyl) amine 8b underwent gradual disproportionation at room temperature. When the mixture containing 8b was allowed to react with nitrostyrene 3 in the presence of Cs\(_2\)CO\(_3\), aziridine 4b was obtained in only 5% yield. This indicated that 8b was not an actual active species for aziridination. Instead, Michael adducts 7b and 10b, derived from 3 and 8b, respectively, were mainly produced, suggesting that chloramine 10b was the precursor for the formation of aziridine.

3 Results and Discussion

The role of NCS in this reaction was studied by \(^1\)H NMR spectroscopy using CDCl\(_3\) as the solvent. When NCS was added to a solution of nitrostyrene 3, no change in signals for either compound was observed; thus, the possibility of activation of 3 by NCS was quite less. On the other hand, a noticeable change in the signals was observed when propylamine 2a (Fig. 1b) was added to a solution of NCS (Fig. 1a)—signals corresponding to 2a were shifted to the lower field, and a new singlet signal appeared at higher field, in addition to the signal of NCS (Fig. 1c). This indicated the \textit{in situ} formation of N-chloramine 8a and succinimide\(^\text{25-27}\). Indeed, comparison of the NMR data with those in the literature\(^\text{27}\) indicated the formation of N-chloramine.

![Fig. 1](image-url)

\(^1\)H NMR spectra of NCS (a), and propylamine 2a (b), and N-chloramine 8a generated by mixing NCS and 2a in CDCl\(_3\) solution (*signals from N, N-dichloropropylamine*).

J. Oleo Sci. 71, (6) 897-903 (2022)
To confirm our hypothesis, the reaction was monitored by \( ^1 \)H NMR spectroscopy. When propylamine \( \text{2a} \) was added to a solution of nitrostyrene \( \text{3} \) in CDCl\(_3\), signals corresponding to olefinic protons disappeared, and signals from three protons appeared at a higher field, indicating the efficient formation of Michael adduct \( \text{7a} \) (Scheme 2b). The signals from \( \text{7a} \) shifted to the lower field upon the addition of NCS, indicating the formation of chloro(propyl)amine \( \text{10a} \) via N-chlorination (Fig. 2a). During the reaction, the signals from nitrostyrene \( \text{3} \) increased, presumably because of the increased leaving ability of propylamine as a result of N-chlorination. Using 3.0 equiv. of propylamine \( \text{2a} \) and 2.0 equiv. of NCS in THF effectively afforded \( \text{7a} \) and \( \text{10a} \) in 95% (from \( \text{3} \)) and 73% (from \( \text{7a} \)) yields, respectively. Compound \( \text{10a} \) was obtained in 72% yield from \( \text{3} \) via a one pot reaction (Scheme 3a). Compound \( \text{10a} \) was converted to aziridine \( \text{4a} \) in 62% yield upon treatment with Cs\(_2\)CO\(_3\) (Scheme 3b).

In contrast, using \( N \)-bromo- and \( N \)-iodosuccinimides (NBS and NIS) instead of NCS did not furnish aziridine \( \text{4a} \). To study the differences in the reactivities, the above-mentioned NMR experiments were conducted using NBS. When NBS was added to a solution of propylamine \( \text{2a} \) in CDCl\(_3\), the signals corresponding to \( \text{2a} \) were shifted to the lower field in the \( ^1 \)H NMR spectrum, confirming the formation of \( N \)-bromamine. However, when NBS was added to a solution of Michael adduct \( \text{7a} \) in CDCl\(_3\), quantitative formation of \( N \)-propylimine \( \text{5a} \) was observed instead of \( N \)-bromination, confirming that aziridination did not occur under these conditions.

\( \text{cis} \)-Nitrostyrene \( \text{3} \) was subjected to this reaction under the same conditions. The reactivity was similar to that of \( \text{trans} \) isomer \( \text{3} \), and \( \text{trans} \)-aziridine \( \text{4a} \) was formed, indicating that this reaction proceeded in a stepwise manner via a common intermediate (Schemes 4a and 4b).
Aziridination of Nitroalkenes Caused by N-Chlorosuccinimide

A plausible reaction mechanism is shown in Scheme 5. This reaction is initiated by the Michael addition of amine 2a to the double bond of 3 to furnish 7a. Subsequent N-chlorination of 7a by NCS affords chloramine 10a (path a). However, competitive C–C bond cleavage also occurs at this stage, furnishing imine 5a (path b). Deprotonation of 10a by a base generates nitronate ion 11a, thereby eliminating the steric hindrance from the adjacent aryl group. Intramolecular substitution of nitronate ion 11a on the nitrogen atom afforded aziridine 4a (path c). Elimination of chloramine 8a from 11a regenerates nitrostyrene 3 (path d).

Since bulkier base or NBS cannot approach 7a, N-halo- genation does not occur. In this case, competitive C–C bond cleavage occurs predominantly to give imine 5a (Scheme 5, path b). Another possibility is the α-bromination of the nitro group, which facilitates the elimination of bromo(nitro)methane, to give 5a.
4 Conclusion

A mechanistic study for diastereoselective aziridination of nitrostyrene 3 was performed. Amine 2 undergoes Michael addition to nitrostyrene 3. The amino group of the produced adduct 7 is chlorinated by NCS to afford 10, and trans-substituted aziridine 4 is formed by intramolecular nucleophilic substitution at the nitrogen atom by nitrate. The insights obtained here will be useful for researchers treating heterocyclic compounds, amines and halogenated compounds.

Conflicts of Interest

The authors declare that they have no competing interests.

Supporting Information (J-STAGE DATA)

This material is available free of charge via the internet (J-STAGE DATA) at doi: 10.57342/data.jos.19752910

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