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Direct Aziridination of Nitroalkenes Affording *N*-Alkyl-*C*-nitroaziridines and the Subsequent Lewis Acid Mediated Isomerization to β-Nitroenamines

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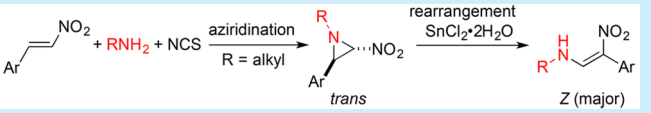
Supporting Information

ABSTRACT: A mild and highly diastereoselective one-pot synthesis of *trans*-*N*-alkyl-*C*-nitroaziridines was achieved by treatment of nitroalkenes with aliphatic amines and *N*-chlorosuccinimide. Treatment of the obtained aziridines with a Lewis acid resulted in a facile ring opening reaction, accompanied by rearrangement and isomerization into functionalized (*Z*)-β-nitroenamines.



The aziridines are an important class of nitrogen-containing heterocycles and can be found in a number of biologically active compounds, such as mitomycin, porfiromycin, and azinomycin.[1] Besides, functionalized aziridines also serve as versatile building blocks in organic synthesis.[1,2] The ring opening reaction of aziridines with nucleophiles affords various 1,2-difunctionalized compounds.[1,2] A substantial number of functionalized aziridines can also be transformed into useful products such as HIV protease inhibitor,[3] communesin,[4] ceramide,[5] oseltamivir,[6] and isochroman[7] through rearrangement, cycloaddition, and ring expansion reactions.[2] Among the functionalized aziridines, C-nitroaziridines play an important role in chemical transformations because of the strong electron-withdrawing ability of the nitro group.[8] Hence, the development of efficient methods for the preparation of C-nitroaziridines has attracted much attention among organic chemists.

Among preparative methods for C-nitroaziridines, the direct aziridination of nitroalkenes is the most efficient approach from a practical viewpoint, as it requires only simple experimental manipulations. *N*-Imidoaziridines are obtained by treatment of *N*-aminoimides with nitroalkenes in the presence of an oxidant (Scheme 1, eq 1).[9] $NsONHCO_2Et$ and $TsONHCO_2Et$ serve as an N1 unit that can undergo direct aziridination of nitroalkenes under basic conditions to afford *N*-alkoxycarbonylaziridines (Scheme 1, eq 2).[10] Additionally, *N*-arylaziridines are also available through the reaction of electron-deficient nitroalkenes with aromatic amines followed by ring closure (Scheme 1, eq 3).[11] Unexpectedly, there are no reports on the synthesis of *N*-alkyl-C-nitroaziridines from nitroalkenes through direct aziridination, except for the multistep synthesis via α-bromonitroalkenes; however, the substrate scope is not investigated further (Scheme 1, eq 4).[12] Thus, a facile and efficient aziridination of nitroalkenes for the synthesis of *N*-alkylated nitroaziridines is of great interest.

As part of our continuing interest in methods for the direct functionalization of the 2-quinolone framework, we achieved the direct aziridination by sequential treatment of 3-nitro-2-quinolones with an amine and *N*-chlorosuccinimide (NCS) (Scheme 1, eq 5).[13] Inspired by this protocol, we envisaged that direct aziridination of nitroalkenes might proceed to afford *N*-alkyl-C-nitroaziridines by sequential treatment with aliphatic amine and NCS (Scheme 1, eq 6).

When β-nitrostyrene **1a** was reacted with propylamine **2a** and NCS at room temperature in THF in the presence of Et_3N, *N*-propyl-C-nitroaziridine **3a** was successfully obtained (Supporting Information (SI), Table S-1, entry 1). In the ^1H NMR, signals for the ring protons H2 and H3 were observed at 3.85 and 4.90 ppm, respectively, with a coupling constant of 1.6 Hz, located in the range (≤2 Hz) for the *trans* configuration.[14] Moreover, a correlation between protons H3 and Ho of the benzene ring in the NOESY spectrum revealed the resultant aziridine is a *trans* isomer. We also confirmed that the product was not formed *via cis*-isomer (SI). Screening of the reaction conditions, such as solvents, bases, temperature, and molar ratio of reagents, increased the yield to 85%; THF was used as the solvent and Cs_2CO_3 (1.1 equiv) as the base, together with a slightly excess amount of propylamine **2a** (1.1 equiv) and NCS (1.1 equiv) at room temperature (SI, Table S-1).

The conjugate addition of amine to **1a** affords intermediate **5**, in which the conformation is fixed by an intramolecular hydrogen bond (Scheme 2). Thus, NCS approaches to **5** from the *anti*-direction of the aromatic group to avoid the steric hindrance, affording the adduct **6**. The subsequent backside attack of the amino group affords aziridine **3a** with the *trans* configuration (Path a).[12,14a] Meanwhile, the competitive proton transfer followed by elimination of anionic nitromethane leads to imine **4a** (Path b).[15] Indeed, **4a** was quantitatively obtained when the reaction was conducted in the absence of NCS.

Although the yield of the conversion of β-nitrostyrene **1a** into aziridine **3a** reached up to 85%, the isolated yield

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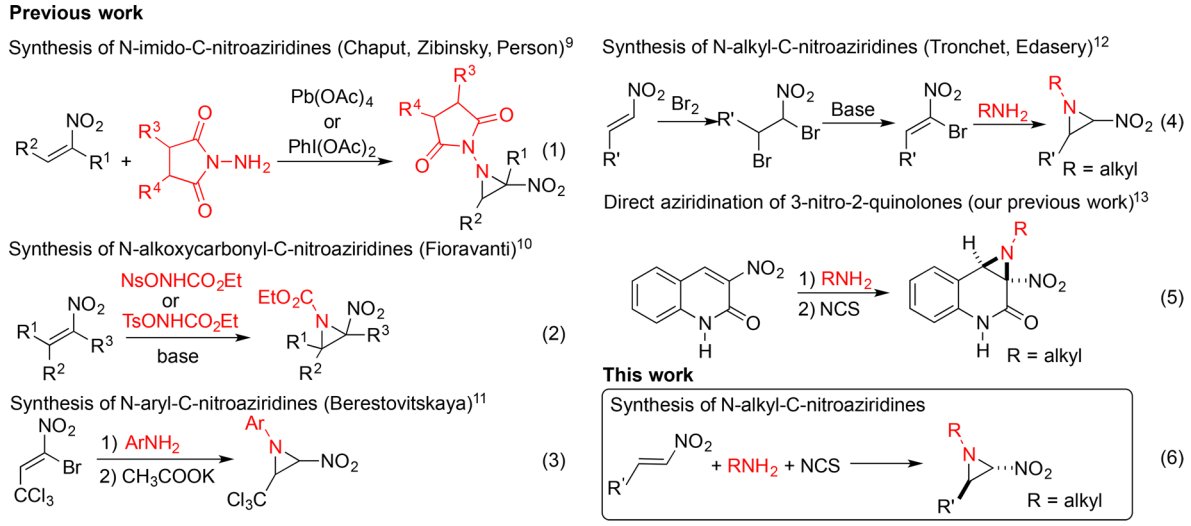
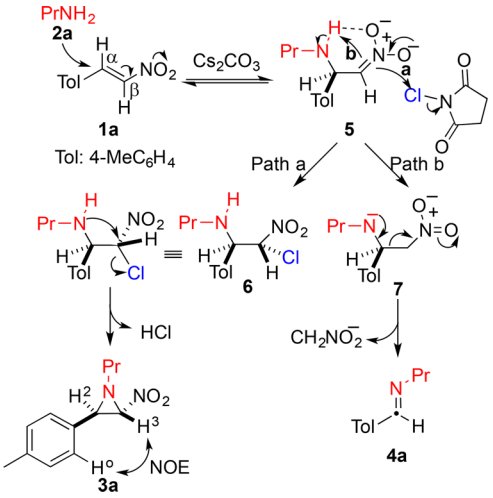
Scheme 1. Previous Work and This Work



Scheme 2. A Plausible Mechanism for Aziridination

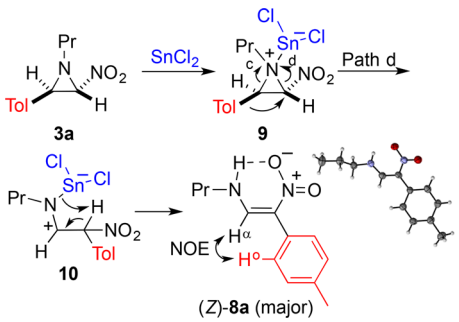


decreased to 31% after workup using water and purification by column chromatography. Control experiments revealed that aziridine **3a** was unstable, easily decomposing into *p*-tolualdehyde under ambient conditions and on silica gel (SI). Therefore, we studied the conversion of the unstable **3a** into a useful and easily treatable reagent.

N-Propyl-*C*-nitroaziridine **3a** was found to isomerize into *β*-aryl-*β*-nitroenamine **8a** in the presence of a Lewis acid (SI, Table S-2). Notably, the aryl group rearranged to the adjacent carbon. Due to their "push−pull" property, *β*-nitroenamines serve as key synthetic intermediates for functional materials such as bioactive compounds and optical materials.[16] However, very few reports are focused on *β*-aryl-*β*-nitroenamines because of their poor availability.[17] Therefore, our method potentially yields a novel class of *β*-nitroenamines with structural diversity. Among the several Lewis acids tested in MeCN, the isomerization of **3a** occurred most efficiently in the presence of $SnCl_2{\cdot}2H_2O$, giving **8a** with a 76% yield, as a mixture of *Z*/*E*-isomers with a 93/7 ratio (SI, Table S-2). The correlation between protons H^{α} and the *ortho* proton (Ho) of the benzene ring in the NOESY spectrum revealed the major isomer has a *Z*-configuration, which was finally confirmed by X-ray crystallography (SI, Figure S-2).

Lewis acid catalyzed conversion of aziridines into enamines is hitherto unknown to the best of our knowledge. Sugihara et al. reported a BF_3-catalyzed aza-pinacol rearrangement of *N*-tosylaziridines into *N*-tosylimines, tautomers of enamines, in which the hydrogen migration is preferable to the alkyl migration.[18] On the basis of our preliminary results and Sugihara's study, a plausible mechanism for this isomerization is illustrated in Scheme 3. Coordination of the Lewis acid to the

Scheme 3. Lewis Acid Mediated Ring Opening and Rearrangement of Aziridine



ring nitrogen facilitates the ring opening. Although a stable benzyl cation should be predominantly formed (Path c),[19] the ring closure occurs to regenerate aziridine ring instead of the migration of the electron-deficient nitro group. Thus, the ring opening is considered to proceed in Path d, in which the migration of the electron-rich tolyl group is preferable to the hydrogen migration due to the formation of lower-energy bridged phenonium ion; the subsequent deprotonation affords **8a**. This mechanism is consistent with the fact that nitroenamines possessing an electron-rich aromatic group were efficiently obtained. In this step, the (*Z*)-isomer was mainly formed due to the stabilization by an intramolecular hydrogen bond.[10a,17]

With the optimized reaction conditions in hand, the scope of these successive reactions was explored. We first screened a wide array of nitroalkenes (Table 1). After reactions of nitroalkenes **1** with amine **2a** and NCS, the mixtures were treated by a sequential workup: evaporation of the solvent, aqueous wash, extraction with CH_2Cl_2, and evaporation, which

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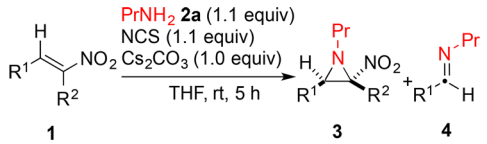
Table 1. Scanning of Nitroalkenes



1 3 4

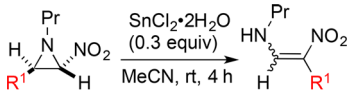
entry	R^1	R^2		yield[a] (%) 3	4	3/4
1	4-MeC_6H_4	H	**a**	72	5	93:7
2	4-$MeOC_6H_4$	H	**b**	53[c]	8	87:13
3	2-$MeOC_6H_4$	H	**c**	54[c]	4	93:7
4	3,5-$(MeO)_2C_6H_3$	H	**d**	63	8	89:11
5	C_6H_5	H	**e**	63	9	88:12
6	4-BrC_6H_4	H	**f**	56	16	78:22
7	4-ClC_6H_4	H	**g**	51	20	72:28
8	4-NCC_6H_4	H	**h**	30	24	56:44
9	4-$O_2NC_6H_4$	H	**i**	6[c]	29	17:83
10	2-naphthyl	H	**j**	63	10	86:14
11	4-MeC_6H_4	Me	**k**	0	19	0:100
12	4-MeC_6H_4	COOEt	**l**	0	100	0:100
13	2-thienyl	H	**m**	34[c]	27	56:44
14	2-furyl	H	**n**	40[c]	11	78:22
15	3-pyridyl	H	**o**	46	13	78:22
16[b]	C_6H_5	H	**e′**	55	11	83:17

[a]The yield was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b](*Z*)-*β*-Nitrostyrene was used. [c]These compounds were characterized by ^{1}H NMR because they were unstable and rearranged to enamines **8** on silica gel.

affords the crude aziridines **3** as an oil. Under the optimized reaction conditions, *β*-nitrostyrenes **1a**−**g** bearing electron-donating Me and MeO groups or weakly electron-withdrawing halo groups successfully gave the corresponding aziridines **3a**−**g** in moderate to good yields, respectively (Table 1, entries 1−7). However, introduction of the strong electron-withdrawing groups such as CN and NO_2 markedly decreased the formation of aziridines **3h** and **3i** (Table 1, entries 8 and 9). In these cases, the low electron density at the benzylic position increases the acidity and decreases the nucleophilicity of the adjacent amino group in the intermediate **5** (Scheme 2). Consequently, the imidization is promoted. While *α*-naphthylalkene **1j** afforded aziridine **3j** efficiently, neither electron-rich *β*-methylalkene **1k** nor electron-poor *α*-nitroacrylate **1l** underwent aziridination owing to the steric hindrance of the *β*-substituents, which suppressed the chlorination of the carboanion (Table 1, entries 10−12). Furthermore, the hetaryl-substituted nitroalkenes were also usable as the substrates to afford the corresponding aziridines **3m**−**o**, respectively (entries 13−15). Even though (*Z*)-nitroalkene **1e′** was reacted instead of (*E*)-isomer **1e**, *trans*-aziridine **3e** was obtained with similar reactivity and selectivity, indicating that both substrates **1e** and **1e′** afforded common intermediate **5** (Table 1, entries 5 and 16). This protocol was also compatible with the aliphatic nitroalkene **1p**, affording *N*-alkyl-C-nitroaziridine **3p** in a moderate yield (Table 1, entry 17).

The $SnCl_2$-mediated conversions of crude aziridines **3a**−**p** to *β*-nitroenamines **8a**−**p** were studied (Table 2). While electron-rich aromatic groups efficiently migrated (Table 2, entries 1−3, 9−11), the efficiency of rearrangement of the slightly electron-poor aromatic group decreased (Table 2, entries 4−7). Furthermore, strongly electron-poor 4-cyanophenyl and 2-pyridyl groups did not migrate at all, which is due to the low

Table 2. Isomerization of Aziridines into *β*-Nitroenamines



3 8

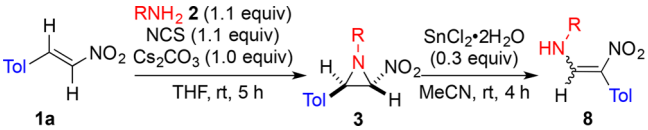
entry	R^1		8,[c] yield (%)/(*Z*/*E*)[d]
1	4-MeC_6H_4	**a**	76 (93:7)
2	4-$MeOC_6H_4$	**b**	87 (93:7)
3[a]	2-$MeOC_6H_4$	**c**	89 (89:11)
4[b]	3,5-$(MeO)_2C_6H_3$	**d**	45 (93:7)
5[a]	C_6H_5	**e**	40 (94:6)
6[b]	4-BrC_6H_4	**f**	49 (96:4)
7[b]	4-ClC_6H_4	**g**	45 (96:4)
8[b]	4-NCC_6H_4	**h**	n.d.[e]
9[a]	2-naphthyl	**j**	83 (94:6)
10[a]	2-thienyl	**m**	quant (94:6)
11[a]	2-furyl	**n**	80 (92:8)
12[b]	3-pyridyl	**o**	n.r.[f]
13[a]	$PhCH_2CH_2$	**p**	n.r.[f]

[a]1.0 equiv of $SnCl_2{\cdot}2H_2O$ was used. [b]1.5 equiv of $SnCl_2{\cdot}2H_2O$ was used. [c]Isolated yield based on **3**. [d]The ratio of *Z* and *E* isomers was determined by the integral of ^{1}H NMR. [e]No desired product. [f]No reaction.

migratory ability (Table 2, entries 8 and 12). *N*-Alkylaziridine **3p** did not undergo the isomerization because of a similar reason (Table 2, entry 13). In all these successful cases, *β*-nitroenamines **8** were diastereoselectively obtained in (*Z*)-configuration.

Next, the scope of this protocol was expanded to other aliphatic amines such as isobutylamine and *sec*-butylamine, which afforded the corresponding aziridines **3q** and **3r** in moderate to good yields; however, bulkier *tert*-butylamine did not furnish product **3s** while benzylamine afforded product **3t** (Table 3, entries 1−5). In the case of an aromatic amine, no aziridination proceeded (Table 3, entry 6). Pleasingly, an allyl group was well tolerated, facilitating further functionalizations (Table 3, entry 7). Additionally, it was possible to introduce a hydroxy group on the alkyl group; however, decomposition of

Table 3. Study on Amine Scope



1a 3 8

entry	R	3[a], yield	8[b], yield (*Z*/*E*)[d]
1	Pr	**3a**, 72%	**8a**, 76% (93:7)
2	*i*-Bu	**3q**, 54%	**8q**, 73% (93:7)
3[c]	*sec*-Bu	**3r**, 31%	**8r**, 80% (93:7)
4	*t*-Bu	**3s**, 0%	–
5[c]	benzyl	**3t**, 41%	**8t**, 86% (92:8)
6	4-$MeOC_6H_4$	**3u**, 0%	–
7	allyl	**3v**, 67%	**8v**, 82% (92:8)
8	$HOCH_2CH_2$	**3w**, 30%	**8w**, 64% (93:7)
9	$HOCH_2CH_2CH_2$	**3x**, 35%	**8x**, 74% (92:8)
10	$H_2NCH_2CH_2$	**3y**, cm[e]	–

[a]The yield was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as internal standard. [b]Isolated yield based on **3**. [c]1.0 equiv of $SnCl_2{\cdot}2H_2O$ was used. [d]The ratio of *Z*- and *E*-isomers was determined by the integral of ^{1}H NMR. [e]Complex mixture.

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aziridines **3w** and **3x** to *p*-tolualdehyde was considerably accelerated (Table 3, entries 8−9). On the other hand, when ethylenediamine was employed to undergo the ring expansion, a complex mixture was obtained (Table 3, entry 10). The produced crude aziridines were subjected to the next isomerization step without further purification, by which the corresponding *β*-nitroenamines **8q−x** were furnished in satisfactory yields (Table 1). Regardless of different N-substituents in **3**, *β*-nitroenamines **8** were formed with high *Z*-selectivity.

In conclusion, we have developed an efficient and highly diastereoselective one-pot synthesis of *trans*-*N*-alkyl-*C*-nitroaziridines **3** upon treatment of nitroalkenes **1** with aliphatic amines **2** and NCS under mild conditions. The resultant aziridines **3** were isomerized into functionalized (*Z*)-*β*-nitroenamines **8** with high diastereoselectivity through Lewis acid mediated ring opening and rearrangement. Further efforts in the application of these protocols for synthesizing versatile functionalized compounds is under investigation in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02724.

Detailed optimization, experimental procedures, characterization data including copies of ^{1}H and ^{13}C NMR spectra (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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