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Synthesis of 1-Pyrroline by Denitrogenative Ring Expansion of Cyclobutyl Azides under Thermal Conditions

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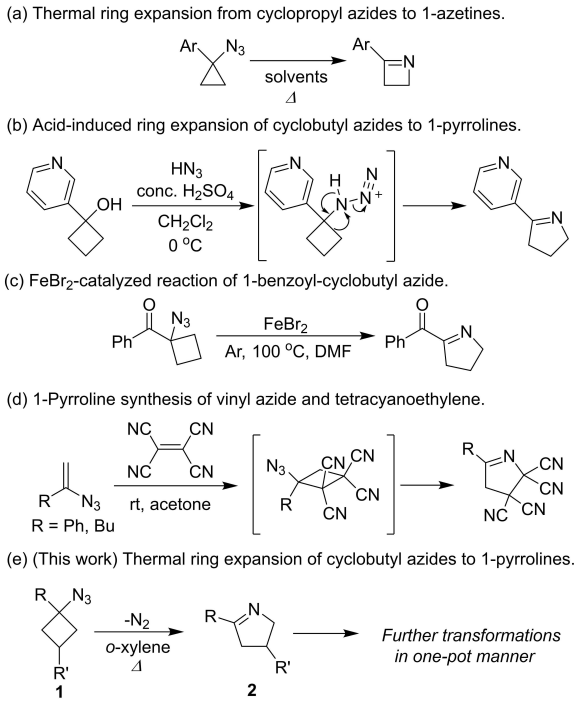
Abstract: We herein report an efficient and systematic synthesis of 1-pyrrolines from cyclobutyl azides under thermal and neutral conditions. The reaction proceeded without any additional reagents, and nitrogen was generated as the sole by-product. Furthermore, the generated 1-pyrrolines could be continuously transformed into pyrroles, *N*-Boc-amines, and oxaziridines in an one-pot manner.

Keywords: ring expansion; thermal conditions; cyclopropyl azide; one-pot reaction; heterocycles

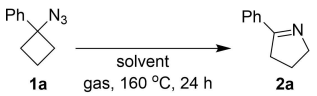
Pyrrolines have a stable five-membered cyclic imine skeleton and are frequently found in natural products and bioactive compounds.[1] They are also used as precursors[2] for the synthesis of pyrroles by oxidation[2a] and pyrrolidines via reduction.[2d] Although some synthetic methods have been reported,[3] the applicable substrates are limited, and there seems to be no systematic method for the synthesis of 1-pyrrolines. The reaction of 4-chlorobutyronitrile with Grignard reagents gave imine intermediates, which underwent intramolecular nucleophilic substitution to the chlorine substituent to produce 1-pyrrolines.[3a] Although *N*-vinylpyrrolidone derivatives could be converted to 1-pyrrolines via aminoketone intermediates under the conditions using alkyl lithium[3b] or ester derivatives,[3c] a strong acid or base was required for steps such as the devinylation and intramolecular annulation of aminoketone intermediates. 1-Pyrrolines could also be synthesized by the Hofmann rearrangement and subsequent ring expansion of cyclobutane carboxylamides with more than 2 equiv. of phenyliodine(III) bis(trifluoroacetate).[3d] On the other hand, cyclopropyl azides underwent denitrogenative ring expansion under thermal conditions to produce 1-azetines, while the reactivity of cyclobutyl azides was relatively lower (Scheme 1a).[4] However, only a few examples of the synthesis of 1-pyrroline from cyclobutyl azides possessing specific structures have been reported.[5–7] (3-Pyridyl)-cyclobutyl azide generated in situ from cyclobutanol using the highly toxic hydrogen azide was transformed into a 1-pyrroline derivative by the strong acid-induced Schmidt rearrangement-type ring expansion (Scheme 1b),[5] while 1-benzoyl-cyclobutyl azide was transformed to 1-pyrroline in the presence of catalytic $FeBr_2$ under thermal conditions[6] (Scheme 1c). Additionally, [2+2]-cycloaddition of vinyl azide with tetracyanoethylene and subsequent ring expansion gave the corresponding 1-pyrrolines at room temperature (the role of cyano group is unclear; Scheme 1d).[7] We herein demonstrate an efficient and systematic synthesis of 1-pyrrolines (**2**) from cyclobutyl azides (**1**) in *o*-xylene under thermal and neutral conditions. Nitrogen was generated as the sole by-product. Furthermore, the generated 1-pyrrolines could continuously undergo further transformations in an one-pot manner (Scheme 1e).

First, several solvents (0.4 mL) were screened using 1-phenyl cyclobutyl azide (**1a**; 0.1 mmol) as a substrate at 160 °C (temperature of the external heating device) under argon for 24 h (Table 1). The reaction performed in *N*,*N*-dimethylformamide (DMF) gave the desired 2-phenyl-1-pyrroline (**2a**) in 58% yield (entry 1). *N*,*N*-Dimethylacetamide (DMA) and dimethyl sulfoxide (DMSO) were inefficient, and lower yields



Scheme 1. Denitrogenative ring expansion of cycloalkyl azides.

Table 1. Solvent Screening.[a]



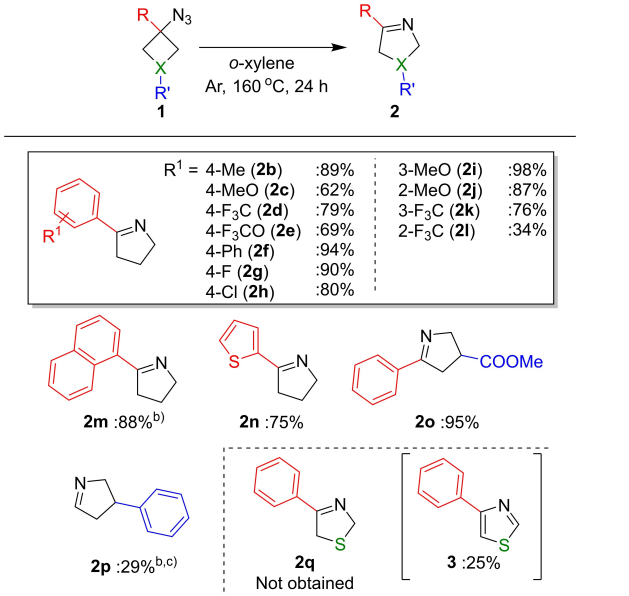
entry	solvent	gas	yield of **2a** (%)
1	DMF	Ar	58
2	DMA	Ar	31
3	DMSO	Ar	0
4	*o*-xylene	Ar	82
5	mesitylene	Ar	70
6	*o*-xylene	air	73
7	*o*-xylene	H_2	82
8	*o*-xylene	O_2	81
9[b]	*o*-xylene	Ar	99

[a] **1a** (0.1 mmol) and solvent (0.4 mL) were used.
[b] **1a** (2.0 mmol) and *o*-xylene (1.0 mL) were used.

were obtained in these solvents (entries 2 and 3). Compound **2a** was obtained in 82% and 70% yields in *o*-xylene and mesitylene, respectively (entries 4 and 5). The reaction under air, hydrogen, or oxygen atmosphere also afforded **2a** without any decrease in the reaction efficiency, suggesting that a strict control of the inner gas was not required for this denitrogenative ring expansion of cyclobutyl azide (entries 6–8). Since nitrene intermediates usually react with oxygen to form the corresponding nitro compound,[8] a concerted mechanism via the denitrogenation of azido and subsequent ring expansion of cyclobutane was proposed. However, a rapid stepwise formation of the nitrene intermediate by denitrogenation of azido could not be completely ruled out. The scale-up reaction using a highly concentrated *o*-xylene (1 mL) solution of **1a** (2.0 mmol) smoothly proceeded to give **2a** in quantitative yield (entry 9).[9,10]

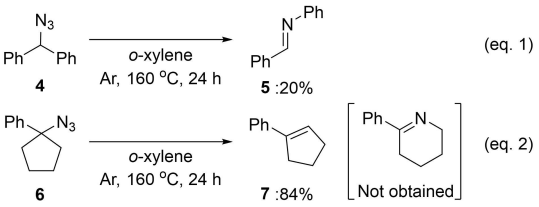
The substrate scope was next investigated (Table 2). 1-Aryl-cyclobutyl azides (**1b**–**1e**) bearing electron-donating or electron-withdrawing group at the *para* position on the aromatic nucleus were efficiently transformed into the desired 2-aryl-1-pyrrolines (**2b**–**2e**) in moderate to good yields. Phenyl-, fluoro-, or chloro-substituted substrates (**1f**–**1h**) could also be transformed to the corresponding 1-pyrrolines (**2f**–**2h**) in high yields. *Ortho*- or *meta*-methoxy-substituted products (**2i** and **2j**) and *meta*-trifluoromethyl-substituted product (**2k**) were obtained in high yields; only 2-(2-(trifluoromethyl)phenyl)-1-pyrroline (**2l**) was obtained in a low yield. The naphthyl- or thienyl-substituted cyclobutyl azide derivatives (**1m** and **1n**) could also be transformed into the corresponding 1-pyrrolines (**2m** and **2n**). Furthermore, the reaction of the 3-methyl ester-substituted cyclobutyl azide (**1o**) gave the corresponding 1-pyrroline (**2o**) in an excellent yield. A secondary-azido substrate (**1p**) was also converted to an aldimine-type product (**2p**). Meanwhile, 3-azido-3-phenyl-thietan (**1q**) was not transformed to **2q**. Instead, a further oxidized product, 4-phenyl-thiazole (**3**), was obtained presumably due to air oxidation of **2q** during post-treatment.[11]

Table 2. Substrate scope.[a]

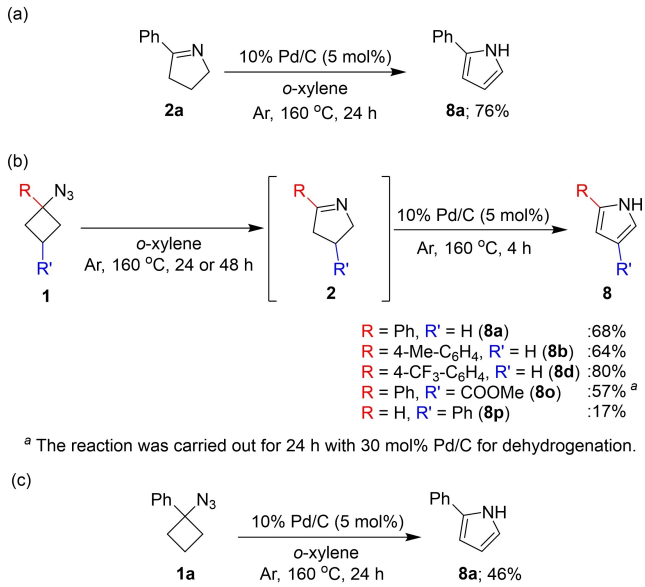


[a] **1** (0.1 mmol) and *o*-xylene (0.4. mL) were used.
[b] The reaction was carried out for 48 h.
[c] The yield was determined by ^{1}H NMR with CH_2Br_2 as an internal standard.

The reaction of diphenylmethyl azide (**4**) having no cyclobutane ring afforded *N*-benzylideneaniline (**5**) via the rearrangement of the phenyl group (eq. 1). Meanwhile, the product resulted from the rearrangement of the phenyl moiety was never obtained in the reaction of 1-phenyl-cyclobutyl azide (**1a**), as shown in Table 1. Meanwhile, 1-phenyl-cyclopentyl azide (**6**) was converted to 1-phenyl-cyclopentene (**7**), and no ring-expanded product was obtained (eq. 2). During this process, the azido group behaved as the leaving group. Therefore, the strain in the cyclobutane ring is an important factor for promoting the desired denitrogenative ring expansion.



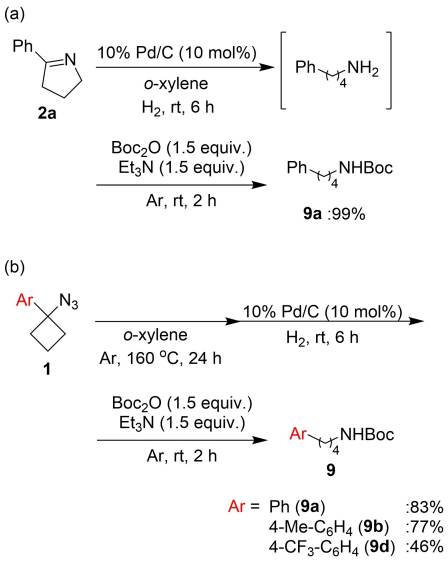
Nitrogen was produced as the sole by-product in the transformation of cyclobutyl azide to 1-pyrroline. Additionally, the Pd/C-catalyzed dehydrogenative aromatization of 1-phenyl-1-pyrroline (**2a**) to 1-phenylpyrrole (**8a**) efficiently proceeded in *o*-xylene under thermal conditions (Scheme 2a).[2a] Therefore, the one-pot transformation of 1-pyrrolines (**2**) to pyrroles (**8**) was next investigated (Scheme 2b). After the denitrogenative ring expansion of cyclobutyl azide (**1**), Pd/C was added, and the reaction mixture was heated again. Consequently, various functionalized pyrroles (**8a**, **8b**, **8d**, **8o**, and **8p**) were successfully synthesized from **1** in an one-pot manner. However, if Pd/C is added at the beginning of the reaction, rather than being added after the denitrogenative ring expansion, the reaction did not proceed smoothly, and the yield of **8a** was reduced significantly (46%, Scheme 2c).



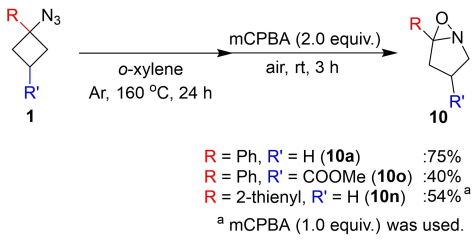
Scheme 2. Synthesis of pyrroles (**8**) by Pd/C-catalyzed dehydrogenation of 1-pyrrolines.

Furthermore, the Pd/C-catalyzed hydrogenation of **2a** could be performed at room temperature to afford a primary amine, which was isolated as the *tert*-butoxycarbonyl (Boc)-protected form (**9a**) in an excellent yield by the treatment with Boc_2O and Et_3N (Scheme 3a). Additionally, the one-pot synthesis of Boc-protected primary amines (**9**) from cyclobutyl azides (**1**) was successfully achieved (Scheme 3b). These one-pot transformations provide a novel method for the synthesis of primary amines, which are important compounds in various chemistry-related fields.

Oxaziridines (**10a**, **10o**, and **10n**), which are useful synthetic precursors,[2c,12] were prepared through the denitrogenative ring expansion of cyclobutyl azide (**1**) and the subsequent *in situ* oxidation of 1-pyrroline intermediates (**2**) by mCPBA (Scheme 4). The



Scheme 3. One-pot synthesis of *N*-Boc-amines (**9**) via Pd/C-catalyzed hydrogenation.



Scheme 4. One-pot synthesis of oxaziridines (**10**).

thiophene skeleton of **10n** was tolerant during the oxidation.

In conclusion, we have developed an efficient method for the transformation of cyclobutyl azides to the corresponding 1-pyrroline derivatives by simply heating the starting compound in *o*-xylene. The reaction proceeded under neutral conditions, and nitrogen was generated as the sole by-product. The one-pot synthesis of various compounds (pyrroles, *N*-Boc-amines, and oxaziridines) was accomplished after the thermal denitrogenative ring expansion of cyclobutyl azides and their subsequent reactions.

Experimental Section

General procedure of 1-pyrroline synthesis (2); A solution of azide compound (0.10 mmol) in *o*-xylene (0.4 mL) was stirred at 160 °C (reflux) under Ar for 24 or 48 h. Then, the residue was cooled to room temperature and directly purified by silica-gel column chromatography to give the corresponding 1-pyrroline.

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[9] When **1a** (0.2 mmol) and *o*-xylene (0.05 mL) were used (small scale reaction using same concentration as Table 1, entry 9), the yield of **2a** decreased to 39%. The details are unclear.

[10] The following paper indicated, 'For organic azides to be manipulable or non-explosive, the rule is that ($Nc + No$)/$N_N \geq 3$ (N = number of atoms)'. See: S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem. Int. Ed.* **2005**, *44*, 5188. (Nc + No)/N_N of 1-phenyl-cyclobutyl azide (**1a**) as the simple substrate is 3.3, and the metallic reagents and reaction apparatus were not used in the present reaction.

[11] Although 1-nonyl cyclobutyl azide as a primary-alkyl-substituted substrate could be prepared in low yield, 2-nonyl 1-pyrroline was not obtained after the heating at 160 °C in *o*-xylene as the optimized reaction conditions. Meanwhile, the benzyl, cyclohexyl, and *tert*-butyl-substituted cyclobutyl azide substrates could not be prepared. The results are shown in Supporting Information.

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