



Facile construction of trifluoromethyl-azirines via one-pot metal-free Neber reaction

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ABSTRACT

A Et₃N-mediated Neber reaction of aryl/alkyl-2,2,2-trifluoroethylketoximes has been developed. This one-pot metal-free protocol enables the facile construction of an array of trifluoromethyl-substituted azirines in moderate to high yields under mild reaction conditions. Further transformations of azirines to CF₃-containing pyrrole and amino-alcohol derivatives are also demonstrated.

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1. Introduction

Azirines represent a highly valuable class of compounds found in many naturally occurring products and bioactive molecules (Fig. 1).¹ Owing to the high ring strain of these smallest unsaturated heterocycles, azirines hold great potential for versatile use in organic synthesis such as ring expansion reactions,² cycloaddition reactions,³ ring-opening reactions⁴ and reduction reactions.⁵ As a type of powerful building blocks, azirines have been extensively utilized for the synthesis of functionalized amines and N-containing heterocycles. Notably, the applicability of azirines in various transformations is strongly determined by the nature of the substituents equipped on the small ring. In this context, previous studies have been focused on azirines substituted by functional groups such as carbonyl group,⁶ nitrile,⁷ phosphate,⁸ and halogens.⁹ On the other hand, trifluoromethyl group (CF₃) has attracted considerable attention in past decades due to its unique properties in pharmaceuticals and agricultural chemicals.¹⁰ Therefore, we

envisioned that the introduction of a CF₃ group into azirines would further enrich the existing azirine chemistry, especially would open new access for the rapid construction of trifluoromethylated N-containing heterocycles.¹¹ It should be noted that an elegant copper-catalyzed transformation of alkyne with azide to trifluoromethyl-azirines was reported by Liu and Liang groups independently in 2015 (Scheme 1a).¹² In these procedures, Togni's reagent was employed to introduce the CF₃ moiety into target skeletons. Alternatively, direct use of readily available CF₃-containing building blocks is another complementary and interesting access to trifluoromethyl-substituted azirines. In this regard, aryl-2,2,2-trifluoroethylketoximes, which can be potentially converted to corresponding CF₃-azirines via Neber reaction, became our choice for this study. Generally, Neber reaction has been recognized as one of the most reliable and flexible approaches for the construction of azirines.¹³ Nevertheless, to the best of our knowledge, no reports have disclosed the preparation of trifluoromethyl-azirines via Neber reaction, possibly due to difficult generation of unstable α -trifluoromethylated carbanion species.¹⁴ Herein, we report our efforts in the synthesis of trifluoromethyl-azirines by the means of Neber reaction (Scheme 1b). The features of this method include mild reaction conditions, one-pot procedure, simple operation and good substrate scope. The utility of CF₃-azirines in synthetic chemistry was also demonstrated by further transformations to CF₃-containing pyrrole and amino-alcohol derivatives.

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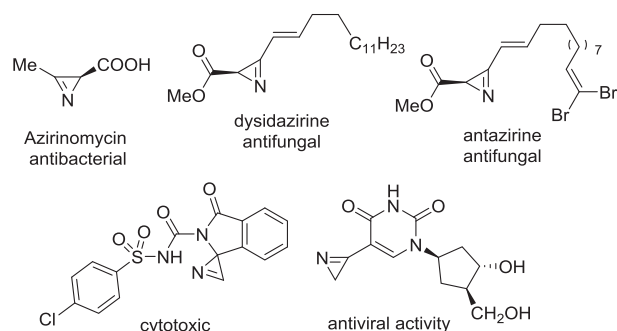
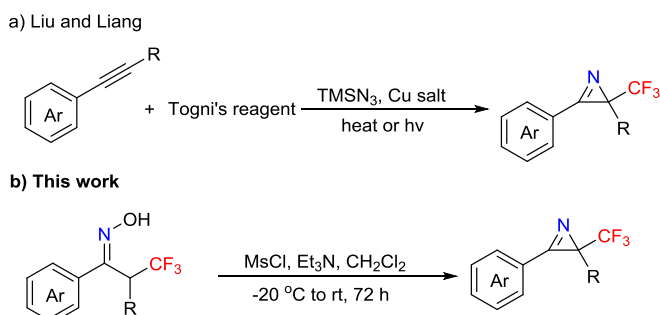


Fig. 1. Representative biologically active compounds containing azirine moieties.



Scheme 1. Synthesis of 3-aryl-2-trifluoromethyl-azirines.

2. Results and discussion

We commenced our investigation with **1a** as model substrate which is easily prepared from corresponding ketone.¹⁵ In the presence of methylsulfonyl chloride, Et₃N was chosen as the organic base in protecting step, meanwhile DBU was selected to be responsible for cyclization step (Table 1, entry 1). To our great

Table 1
Optimization studies for the Neber reaction of **1a** to 2H-azirine **2a**.^a

Entry	PG-Cl	Base (equiv.)	Solvent	T (°C)	Yield (%) ^b
1	MsCl	Et ₃ N (1.5) + DBU (1.5)	CH ₂ Cl ₂	rt	39
2	TsCl	Et ₃ N (1.5) + DBU (1.5)	CH ₂ Cl ₂	rt	32
3	MsCl	Et ₃ N (1.5) + DBU (1.5)	CH ₂ Cl ₂	0	50
4	MsCl	Et ₃ N (3.0) + DBU (1.5)	CH ₂ Cl ₂	0	66
5	MsCl	Et ₃ N (3.0) + DBU (1.5)	CH ₂ Cl ₂	−10	73
6	MsCl	Et ₃ N (3.0) + DBU (1.5)	CH ₂ Cl ₂	−20	77
7	MsCl	Et ₃ N (3.0)	CH ₂ Cl ₂	−20	70
8	MsCl	Et ₃ N (4.0)	CH ₂ Cl ₂	−20	92
9	MsCl	Et ₃ N (5.0)	CH ₂ Cl ₂	−20	77
10	MsCl	Et ₃ N (4.0)	DCE	−20	75
11	MsCl	Et ₃ N (4.0)	toluene	−20	52
12	MsCl	Et ₃ N (4.0)	THF	−20	30
13	MsCl	Et ₃ N (4.0)	Et ₂ O	−20	trace
14	MsCl	Et ₃ N (4.0)	EtOH	−20	trace

^a Reaction conditions: **1a** (0.5 mmol, 1.0 equiv.), PG-Cl (0.75 mmol, 1.5 equiv.), and Et₃N dissolved in specific solvent (5 mL) were stayed at indicated temperature for 2 h, then another base was added and the system was kept at rt for 70 h.

^b Yield of isolated product.

delight, the desired product **2a** was obtained in 39% yield when the reaction was conducted in CH₂Cl₂ at rt. A slightly lower yield was observed when tosyl chloride was employed in this reaction (entry 2). The yield of 2H-azirine **2a** could be remarkably increased to 77% when lowering the reaction temperature and raising the amount of Et₃N (entries 3–6). With these promising results in hand, we envisioned that the same base probably could facilitate this reaction in one-pot manner. Indeed, in the presence of only Et₃N as the base, the desired product **2a** was still afforded in 70% yield (entry 7). Pleasingly, the result was subsequently improved to 92% when 4 equiv. of Et₃N was employed (entry 8). Further increasing the amount of Et₃N came out with inferior yield (entry 9). Then, several other solvents were screened under identical reaction conditions (entries 10–14), while no better results were observed.

With optimized conditions in hand, the substrates scope of this Neber rearrangement to trifluoromethyl-azirines was further explored. These results are summarized in Table 2. In general, a broad range of CF₃-containing azirines were obtained from corresponding ketoximes with moderate to high yields under mild conditions. A series of aryl-2,2,2-trifluoroethylketoximes with halogen-substituted at different positions on the phenyl ring, including *ortho*-, *meta*-, and *para*-, all underwent this transformation smoothly, thus generating desired products **2b–i** in high yields (80–92%). The 3,4-dichloro di-substituted ketoxime underwent this reaction as well to give 2H-azirine **2j**, albeit in 51% yield. Subsequently, trifluoromethyl-, methyl- and phenyl-substituted aromatic ketoximes were also probed in this reaction and resulted in the generation of **2k–o** in 65–90% yields. Noteworthy is that 3,4-dimethyl-substituted phenyl ketoxime is well compatible with current conditions and provided **2n** in 82% yield. Then three ketoximes with alkyl substituents on the phenyl ring were also found to be viable substrates in this reaction, providing **2p–i** in 79–97% yields. In addition, it was found that phenylthio-substituent phenyl ketoxime and 2-thiophenyl ketoxime were also tolerant in this transformation (products **2s** and **2t**). Moreover, the scope is not only limited to 2H-azirines, as CF₃-containing tri-substituted azirine **2u** could still be produced, albeit in decreasing yield (47%). It should be mentioned that for compound **2u**, a stronger base DBU was employed to promote the cyclization step (see experimental section for details). Finally, an alkyl-substituted ketoxime was also probed in this transformation, thus leading to the formation of 2H-azirine **2v** in decent yield.

Having successfully developed a facile one-pot metal-free Neber reaction, we directed our efforts to demonstrate the synthetic utility of afforded trifluoromethyl-azirines. Firstly, 2H-azirine **2l** was prepared smoothly on a gram-scale under standard conditions, thus demonstrating the robustness of this protocol (Scheme 2a). Subsequently, treatment of **2l** with hydrochloric acid provided ring-opening product **3a** in 97% yield (Scheme 2b). This α -CF₃-amino-ketone could be further readily reduced with NaBH₄ to generate norpseudoephedrine derivative **3b**. Furthermore, 2-CF₃-substituted pyrrole **3c** could also be provided in high yield by the cyclization of **2a** with phenylacetaldehyde in the presence of NiCl₂ (Scheme 2c).¹⁶ It is worth noting that CF₃-containing tri-substituted pyrroles are usually difficult to access within a few steps by other methods.¹⁷

In conclusion, a Et₃N-mediated Neber reaction of readily available aryl/alkyl-2,2,2-trifluoroethylketoximes has been successfully established. This one-pot metal-free protocol enables the facile construction of a wide range of trifluoromethyl-substituted azirines in moderate to high yields under mild conditions. Further transformations of afforded azirines to CF₃-containing amino-ketone, amino-alcohol and pyrrole were also demonstrated. Substrate scope expanding, asymmetric version and mechanistic investigations are currently underway in our laboratory.

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