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$AgSbF_6$-Promoted Cycloaddition Reaction of 2-Trifluoromethyl-*N*-tosylaziridine with Aldehydes

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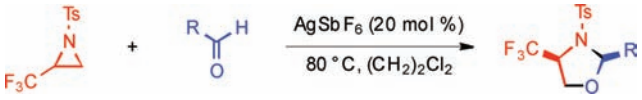
ABSTRACT



2-Trifluoromethyl-*N*-tosylaziridine reacted with various aldehydes in the presence of a catalytic amount of $AgSbF_6$ to provide the corresponding *cis*-4-trifluoromethyl-2-substituted-*N*-tosyl-1,3-oxazolidines with excellent regio- and stereoselectivity.

Aziridines, which are saturated three-membered azaheterocycles, have high reactivity due to their molecular strain, which has received much attention. In addition to their high reactivity, their structural scaffolds often have been encountered in pharmaceutical products such as antitumor agents and antibiotics. From a synthetic viewpoint, both factors make them very attractive and valuable.[1] Regarding the reactivity, a representative example is the regio- and stereoselective ring-opening reaction of aziridines with a wide range of nucleophiles.[2] Moreover, aziridines function as a masked 1,3-dipole, giving a variety of cycloadducts.[3] Although the latter reaction pattern frequently emerged in current reports, the most often used reagents are 2-aryl- or 2-alkyl-substituted aziridines. For example, they reacted with carbonyl compounds or nitriles to give the corresponding 1,3-oxazolines or 1,3-imidazolines[4] and with alkynes to give the corresponding 2-pyrrolines[5] in the presence of several Lewis acids.

On the other hand, it has been reported that many pharmaceuticals, agrochemicals, and functional materials contain fluorine.[6] Incorporation of fluorine into organic molecules often offers new products of high value due to enhanced bioactivity, stability, lipophilicity, and physical

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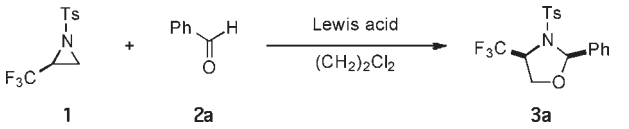
properties. Among them, the trifluoromethyl group ($-CF_3$) plays an important role due to its unique stereoelectronic property. Consequently, a facile preparation of versatile trifluoromethylated compounds has still attracted intense interest.[7] Despite the high potential utility of aziridines as briefly mentioned above, the few reports available are on the use of trifluoromethylated aziridines as building blocks for trifluoromethylated compounds.[8] The lack of an appropriate synthetic protocol can be mainly attributed to a related study on the reaction of trifluoromethylated aziridines. We have very recently reported the convenient synthesis of 2-trifluoromethyl-*N*-tosylaziridine **1** from (β-trifluoromethyl)vinyl sulfonium salt in high yield in one step.[9] As a part of our continuous study on **1**, we herein report the first $AgSbF_6$-promoted 1,3-dipolar cycloaddition reaction of **1** with aldehydes to give the corresponding *cis*-4-trifluoromethyl-2-substituted-*N*-tosyl-1,3-oxazolidines with excellent regio- and stereoselectivity.

Our investigation started by using aziridine **1** and benzaldehyde **2a** as a model compound in the presence of several Lewis acids in order to explore the viability in a 1,3-dipolar cycloaddition reaction. Some results for optimization of reaction conditions are shown in Table 1. The most efficient Lewis acid examined was proven to be $AgSbF_6$ (entry 12).[5b]

Table 1. Optimization of Reaction Conditions



1 2a 3a

entry	Lewis acid (equiv)	**2a** (equiv)	temp (°C)	time (h)	yield (%)[a]
1	$Cu(OTf)_2$(1.0)	1.1	25	24	0
2	$Cu(OTf)_2$(1.0)	1.1	80	24	0
3	$Cu(OTf)_2$ (0.2)	3.0	80	240	0
4	$Sc(OTf)_3$ (0.2)	1.1	25	240	0
5	$Sc(OTf)_3$ (0.2)	1.1	80	240	19
6	$Sc(OTf)_3$(1.0)	1.1	80	240	22[b]
7	$Sc(OTf)_3$ (0.2)	3.0	80	240	23[b]
8	$Zn(OTf)_2$ (0.2)	3.0	80	24	49[b]
9	BF_3•Et_2O (0.2)	3.0	80	24	13
10	$AgPF_6$(0.2)	3.0	80	24	0
11	$AgSbF_6$ (0.2)	1.5	80	24	16
12	$AgSbF_6$(0.2)	3.0	80	2.5	74
13	$AgSbF_6$(0.1)	3.0	80	3.5	67
14	$AgSbF_6$(0.05)	3.0	80	3.5	56

[a] Isolated yield. [b] GC-MS yield.

Initial attempts with $Cu(OTf)_2$ (entries 1−3) completely failed to give any desired cycloadducts. The starting material aziridine **1** was recovered intact. This could be due to the low Lewis acidity of $Cu(OTf)_2$. The second choice of a Lewis acid was $Sc(OTf)_3$. Although no reaction occurred at 25 °C (entry 4), the cycloaddition reaction proceeded at 80 °C for 10 days giving the cycloadduct **3a** albeit in low yields regardless of catalyst loadings (entries 5−7). For the complete consumption of the unreacted **1**, the longer reaction times caused **3a** to decompose and decrease the yield by contrast. The yield was not satisfying; however it is noteworthy that a single isomer was observed by GC−MS analysis from four possible producible isomers (stereo- and regioisomers). To improve the yield, we continued to examine other Lewis acids. The reaction in the presence of $Zn(OTf)_2$ for 24 h gave better results; however the longer reaction times caused **3a** as in the case of $Sc(OTf)_3$ (entry 8). BF_3•OEt_2 showed low catalytic efficiency, and $AgPF_6$ gave no adduct (entries 9 and 10). The optimal conditions were eventually obtained in entry 12. The reaction proceeded well giving the desired product **3a** in 74% yield. Thus, $AgSbF_6$ offered the best results among the several Lewis acids attempted to promote the reaction; however its intrinsic role is unclear. Unfortunately, lower catalyst loadings and a small excess of **2a** resulted in lower yields (entries 11, 13, and 14).

As mentioned above briefly, it is worthy of attention that the cycloaddition reaction gave the single isomer **3a**. The

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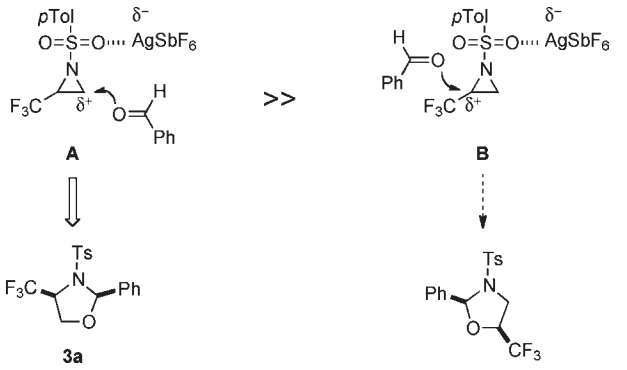
(10) **Typical procedure:** A 25 mL two-neck flask equipped with a magnetic stir bar, a stopcock, and a three-way stopcock was charged with 2-(trifluoromethyl)-*N*-tosylaziridine **1** (99.5 mg, 0.38 mmol) in 0.2 mL of DCE (1,2-dichloroethane) under argon. To this solution was added benzaldehyde (114 μL, 1.13 mmol) and a catalytic amount of $AgSbF_6$ (0.05 M in DCE, 1.5 mL, 20 mol%). The reaction mixture was heated at 80 °C for 2.5 h. After cooling to 0 °C, the excess of benzaldehyde was reduced by the addition of ethanol (3 mL) and $NaBH_4$ (42.5 mg, 1.13 mmol). (This operation facilitates the separation of the desired product **3a** using column chromatography.) After the mixture was quenched with water, the organic layer was extracted with CH_2Cl_2. Additional extraction with CH_2Cl_2 was repeated twice. The combined solution was dried over sodium sulfate. The solution was concentrated in vacuo, and the residual oil was purified by silica gel chromatography (hexane/ether/triethylamine = 200/200/1) to give the desired product **3a** as a white solid (102.2 mg, 74%): Mp 106.8−107.5 °C. Elemental analysis: calcd for $C_{17}H_{16}F_3NO_3S$: C, 54.98; H, 4.34; N, 3.77. Found: C, 55.06; H, 3.80; N, 3.80. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.37 (3H, s), 4.06 (1H, dd, J = 8.9, 7.6 Hz), 4.34 (1H, dd, J = 9.9, 1.8 Hz), 4.69 (1H, ddq, J = 7.2, 2.2, 7.2 Hz), 6.10 (1H, s), 7.14 (2H, d, J = 8.3 Hz), 7.29−7.43 (7H, m) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 58.9 (q, J = 33.0 Hz), 66.8 (q, J = 1.9 Hz), 94.0, 124.1 (q, J = 281.5 Hz), 127.7, 127.8, 128.3, 129.47, 129.54, 135.4, 135.5, 144.4 ppm; ^{19}F NMR ($CDCl_3$, 283 MHz) δ −75.5 (d, J = 7.1 Hz) ppm; IR (NaCl) 2958, 1598, 1460, 1366, 1289, 1165, 981, 698 cm^{-1}; GC−MS m/z 216 [M^+ −155 (Ts), 40], 155 (19), 139 (3), 119 (4), 105 (20), 91 (100), 77 (26), 65 (25), 51 (8).

structure of **3a** was tentatively assigned 4-trifluoromethyl-2-phenyl-*N*-tosyl-1,3-oxazolidine on the basis of a similar reaction mechanism reported in the previous reports.[4,5] The partially positive charge is born not only by the nitrogen but also by two carbons of the aziridine after the coordination of the Lewis acid. Most of the positive charge on carbon should reside at the originally more electron-rich position. The reason for the excellent regioselectivity should be attributed to the large contribution of the plausable intermediate **A** in terms of both the steric and electronic effect prior to benzaldehyde addition. Another possible intermediate **B** should be unfavorable due to the attached electron-withdrawing group (CF_3) (Scheme 1). At this point, however, it was difficult to make clear the stereochemistry of the cycloadduct **3a** as another subject.

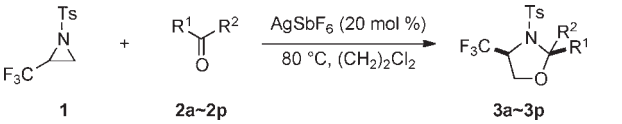
Scheme 1. Proposed Regiochemistry of **3a**



The scope of aldehydes examined in the reaction is summarized in Table 2.[10] Electron-deficient benzaldehydes generally provided the corresponding products in better yields compared to an electron-rich benzaldehyde (entries 2–4). A nitro group on the aromatic ring completely retarded the cycloaddition reaction, recovering the starting materials intact (entry 5).[11] Sterically demanding bezaldehydes also participated in the cycloaddition reaction albeit with a longer reaction time (entries 7 and 8). Naphthaldehydes also underwent a cycloaddition reaction (entries 9 and 10). Although a linear aliphatic aldehyde gave a moderate yield, a branched alipatic aldehyde gave a high yield (entries 11 and 12). An α,β-unsaturated aldehyde was also applicable to this reaction. The reaction of heteroaromatic aldehyde furnished the product in a low yield maybe due to coordination of the sulfur atom to the Lewis acid (entry 14). In contrast to aldehydes, no reactions of **1** and ketones occurred under same reaction conditions, giving the starting materials intact. It is again noteworthy that all reactions provided the corresponding single isomers. This should be attributed to a powerful electronic and steric effect of the CF_3 group at the 2-position of aziridine **1** compared to that of 2-aryl or 2-alkyl groups.

(11) In the case of the cycloaddition of 2-phenyl-*N*-tosylaziridine to 4-nitrobenzaldehyde in the presence of $Zn(OTf)_2$, a similar observation was reported in ref 4a.

Table 2. Synthesis of *syn*-4-Trifluoromethyl-2-substituted-*N*-tosyl-1,3-oxazolines



entry	R^1	R^2	time (h)	product	yield (%)[a]
1	Ph	H	2.5	**3a**	74
2	4-Ph-C_6H_4	H	2.5	**3b**	71
3	4-MeO-C_6H_4	H	3.5	**3c**	60
4	4-CF_3-C_6H_4	H	2.5	**3d**	76
5	4-NO_2-C_6H_4	H	48	**3e**	0
6	3-CF_3-C_6H_4	H	20	**3f**	83
7	2−Cl-C_6H_4	H	23	**3g**	80
8	2-Cl-6-F-C_6H_3	H	44	**3h**	66
9	1-Naphthyl	H	4	**3i**	62
10	2-Naphthyl	H	2	**3j**	78
11	$PhCH_2CH_2$	H	5	**3k**	37
12	$(CH_3CH_2)_2CH$	H	4	**3l**	91
13	PhCH=CH	H	52	**3m**	63
14	2-Thienyl	H	20	**3n**	19
15	Ph	Me	8	**3o**	0
16	$PhCH_2CH_2$	Me	24	**3p**	0

[a] Isolated yield.

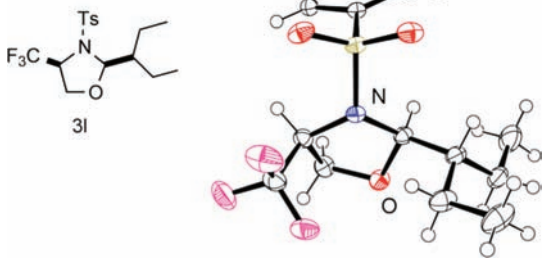


Figure 1. X-ray structure of compound **3l**.

The problem remaining unsolved in the cycloaddition reaction was confirming the regio- and stereochemistry of the adducts. To our delight, X-ray crystallographic analysis of the product **3l** revealed unambiguous proof of the regio- and stereochemistry. A crystal drawing of **3l** is shown in Figure 1. As expected, the carbonyl oxygen of aldehyde attached to the methylene carbon of **1** to afford 4-trifluoromethyl-2-(3-pentyl)-*N*-tosyl-1,3-oxazolidine. The stereochemistry between the CF_3 group at the 4-position and the alkyl group at the 2-position on the five-membered ring was a

cis-relationship. The reason for this *cis*-stereochemistry is that it avoids the severe steric repulsion between the bulky tosyl group at the nitrogen and two substituents at the carbon on both sides. The other products (**3a**−**3n**) would also have the same regio- and stereochemistry like **3l**.

In summary, we have developed an efficient method for the synthesis of *cis*-4-trifluoromethyl-2-substituted-*N*-tosyl-1,3-oxazolidine with excellent regio- and stereoselectivity. Further studies on synthetics are underway in our laboratory.

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Supporting Information Available. Spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.