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TiF_4-Mediated Regioselective Cycloaddition of 2-(Trifluoromethyl)-*N*-tosylaziridine to Nitriles

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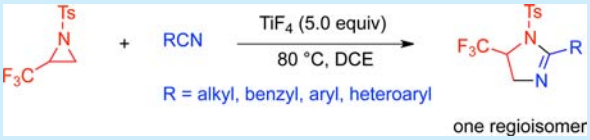
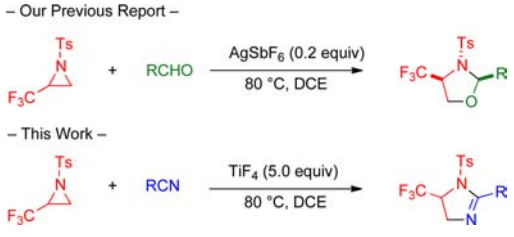
Supporting Information

ABSTRACT: We report the first [3 + 2] cycloaddition of 2-(trifluoromethyl)-*N*-tosylaziridine to nitriles using TiF_4 as an effective Lewis acid under mild reaction conditions. The reaction proceeded smoothly and afforded the corresponding 4-(trifluoromethyl)-1,3-imidazolines in good yields and with excellent regioselectivity.



The selective introduction of a trifluoromethyl group (CF_3) on the aromatic and heteroaromatic rings has received much attention in many chemical fields.[1] Therefore, many reports on this topic appear in recent chemistry journals.[2] The major strategy for the synthesis of such compounds may be classified in the following two categories. One is the transition-metal-catalyzed cross-coupling reactions and the other is the trifluoromethylation reactions of various nucleophiles with appropriate electrophilic trifluoromethylation reagents. Because of our interest in the building block strategy, we focused on the synthesis of diverse trifluoromethylated compounds. We recently reported the facile preparation of 2-(trifluoromethyl)-*N*-tosylaziridine and evaluated its reactivity with various reaction partners.[3] Among them, the cycloaddition of the aziridine to aldehydes afforded the corresponding trifluoromethylated 1,3-oxazolidines with excellent regio- and stereoselectivity.[3b] We envisaged that if nitriles could be used as the reaction partner instead of aldehydes in a similar cycloaddition reaction, then the corresponding trifluoromethylated 1,3-imidazolines would be synthesized for the first time (Scheme 1). Several [3 + 2] cycloaddition reactions of fluorine-free

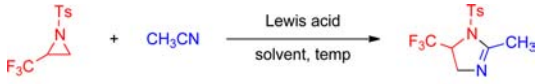
Scheme 1. [3 + 2] Cycloaddition Reactions of 2-(Trifluoromethyl)-*N*-tosylaziridine



aziridines with nitriles have been reported.[4] Herein, we report a TiF_4-mediated cycloaddition reaction of the above-mentioned trifluoromethylated aziridine with nitriles, affording the desired trifluoromethylated 1,3-imidazolines with excellent regioselectivity.

To perform this transformation, we first selected acetonitrile as the model substrate and 2-(trifluoromethyl)-*N*-Ts-aziridine as the other reactant. Then, various Lewis acids were screened, and various reaction conditions were examined (Table 1). To simplify the reaction, acetonitrile was used as the solvent (entries 1–5). No reaction occurred when $AgSbF_6$ was used as the Lewis acid (entries 1 and 2), even though it was the most

Table 1. Optimization of Reaction Conditions for the Preparation of 3a



1 2a 3a

entry	Lewis acid (equiv)	2a (equiv)	solvent	temp (°C)	time (h)	yield[a] (%)
1	$AgSbF_6$ (0.2)	excess	CH_3CN	80	168	NR
2	$AgSbF_6$ (1.0)	excess	CH_3CN	80	96	NR
3	$BF_3{\cdot}Et_2O$ (1.0)	excess	CH_3CN	80	168	trace
4	$BF_3{\cdot}Et_2O$ (2.0)	excess	CH_3CN	80	8	60
5	$BF_3{\cdot}Et_2O$ (3.0)	excess	CH3CN	80	6	84
6	$BF_3{\cdot}Et_2O$ (3.0)	5.0	DCE	80	120	68
7	$BF_3{\cdot}Et_2O$ (3.0)	5.0	CH_3NO_2	80	8	50
8	$BF_3{\cdot}Et_2O$ (3.0)	5.0	dioxane	80	24	NR
9	$BF_3{\cdot}Et_2O$ (3.0)	5.0	HFIP[b]	60	3	45[c]
10	$TiCl_4$ (3.0)	5.0	DCE	80	16	0[d]
11	TiF_4 (3.0)	5.0	HFIP[b]	60	3	63[c]
12	TiF_4 (3.5)	5.0	DCE	80	1	65

[a]Isolated yield. [b]1,1,1,3,3,3-Hexafluoro-2-propanol. [c]Including a small amount of unidentified product. [d]Only chlorinated byproduct.

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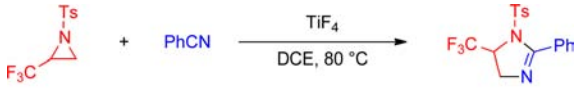
effective for the synthesis of 1,3-oxazolidines. However, in the presence of 2 equiv of $BF_3{\cdot}OEt_2$ the reaction proceeded at 80 °C and was complete after 24 h, yielding the desired imidazoline as a single regioisomer in 60% yield (entry 4). The increased Lewis acid loading (3.0 equiv) increased the yield to 84% (entry 5). However, to investigate other nitriles as the reactant, the reaction solvent was changed from acetonitrile to other solvents. Unfortunately, compared to acetonitrile, other solvents required very long reaction time (entry 6) or resulted in less product yields (entries 7–9). Therefore, we searched for a more effective Lewis acid for this reaction. After a long screening for better conditions, we found that TiF_4 is the most suitable Lewis acid for the reaction (entries 11 and 12).[5] Thus, the reaction of the aziridine (1.0 equiv) with acetonitrile (5.0 equiv) in the presence of an excess amount of TiF_4 (3.5 equiv) at 80 °C for 1 h proceeded smoothly, affording only one regioisomer in 65% yield (the best reaction conditions so far) (entry 12).

To improve the efficiency of this reaction, we next selected benzonitrile as the second nitrile substrate and optimized the amounts of benzonitrile and TiF_4. We considered that the reactivity of benzonitrile would be lower than that of acetonitrile. The results are shown in Table 2. The product

Table 2. Optimization of Reaction Conditions for the Preparation of 3f



1 2f 3f

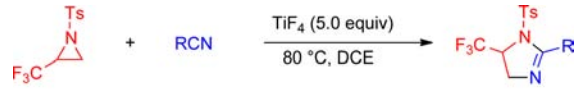
entry	2f (equiv)	TiF_4 (equiv)	time (h)	yield[a] (%)
1	1.0	1.0	2.5	29[b,c]
2	2.0	2.0	1.5	68[b,c]
3	3.0	3.0	1.5	84[c]
4	3.0	3.5	1	86
5	1.1	3.5	1	77[c]
6	1.5	3.5	1	85[c]
7	1.5	5.0	1	89

[a]Isolated yield. [b]GC–MS yield. [c]The remaining **1** was detected in the reaction mixture by GC–MS.

yield increased with the increase in the quantity of both benzonitrile and TiF_4. However, a slight amount of the aziridine remained in the reaction mixture as determined by GC–MS analyses (entries 1–3). For the complete consumption of the aziridine, an increased amount of TiF_4 (3.5 equiv) was effective, affording the product in 86% yield (entry 4). However, a lesser amount of benzonitrile (1.1 equiv) resulted in an incomplete reaction along with a slightly decreased yield (entry 5). Finally, the best result was obtained using more TiF_4 (5.0 equiv) and 1.5 equiv of benzonitrile (entry 7). At present, it is not clear why an excess amount of TiF_4 was necessary for the successful reaction. One reason may be the insolubility of TiF_4 in 1,2-dichloroethane (DCE).[5h]

With the optimized reaction conditions, the substrate scope of the reaction was investigated (Table 3).[6] The primary and secondary alkylnitriles without halogen afforded the desired products in good yields and with excellent regioselectivity (entries 1, 3, and 4). Unfortunately, the use of chloroacetonitrile and pivalonitrile afforded the desired products in low yields along with unidentified byproducts (entries 2 and 5). When aromatic nitriles were used in this cycloaddition reaction, the

Table 3. Synthesis of 4-(Trifluoromethyl)-1,3-Imidazolines (3a–m)[a]



1 2a~2m 3a~3m

entry	R	time (h)	product	yield[b] (%)
1	Me	1	**3a**	82
2	$ClCH_2$	2	**3b**	32[c]
3	$PhCH_2$	2	**3c**	80
4	^{i}Pr	2	**3d**	85
5	^{t}Bu	2	**3e**	35[c]
6	Ph	1	**3f**	85
7	2-MeC_6H_4	2	**3g**	85
8	3-MeC_6H_4	2	**3h**	81
9	4-MeC_6H_4	2	**3i**	91
10	4-ClC_6H_4	3	**3j**	69
11	2-naphthyl	2	**3k**	93
12	9-anthryl	2	**3l**	78
13	2-thienyl	8	**3m**	62

[a]The reaction was carried out using **1** (1.0 equiv) and RCN (1.5 equiv) in the presence of TiF_4 (5.0 equiv) in DCE at 80 °C. [b]Isolated yield. [c]The lower yields were attributed to unidentified byproducts.

desired products were obtained in 69–91% yields. For example, *o*-, *m*-, and *p*-methylbenzonitrile reacted with the aziridine to afford the corresponding products in high yields (entries 7–9). *p*-Chlorobenzonitrile bearing an electron-withdrawing group also participated in the reaction to provide the corresponding product in a slightly decreased yield of 69% yield. Thus, both the nature of the substituent and the substitution pattern on the benzene ring did not significantly affect the product yield. Besides, polyaromatic nitriles such as 2-naphthalenecarbonitrile and 9-anthracenecarbonitrile also participated in the reaction to furnish the corresponding products in good yields (entries 11 and 12). Interestingly, 2-thiophenecarbonitrile bearing a heteroaromatic moiety also participated, affording the corresponding trifluoromethylated product in a slightly decreased yield of 62% yield, albeit with a prolonged reaction time (8 h) (entry 13). Furthermore, we tried performing the reaction of **1** and phenylsulfonylacetonitrile as a substrate having an electron-withdrawing group. Although the reaction proceeded affording the desired product, the yield was low along with inseparable unidentified byproducts.

To our delight, the configuration of product **3l** was confirmed to be correct as shown in Table 3 by its X-ray diffraction (XRD) analysis (Figure 1).[7]

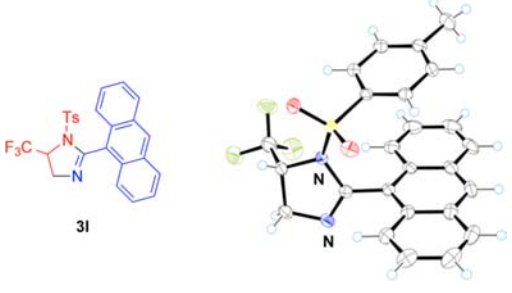


Figure 1. ORTEP drawing of the adduct **3l** with thermal ellipsoids shown at 50% probability level.

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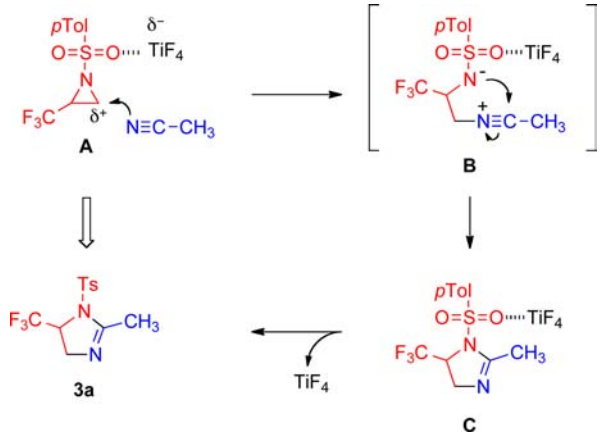
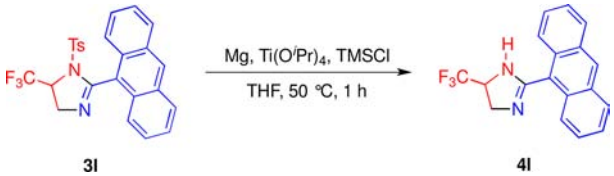
A plausible reaction mechanism for this [3 + 2] cycloaddition reaction is shown in Scheme 2. According to our previous report,[3b] first, the aziridine is activated by TiF_4 to form the polarized aziridine ring **A**, which is attacked by the nitrile to afford the betaine intermediate **B**, followed by the intramolecular ring closure to generate the 1,3-imidazoline **C**. However, we cannot rule out the concerted reaction pathway in the bond formation step. The regioselectivity of the product may be controlled by the CF_3 group because of its strong electron-withdrawing property during the ring-opening stage. Although we do not have good evidence to support the above reaction mechanism at present, based on the correct structure of **3l** by XRD analysis, the proposed mechanism appears reasonable.

Scheme 2. Plausible Reaction Mechanism for this Reaction



Finally, deprotection of the N-Ts group to free NH was preliminarily examined. According to the procedure reported by Okamoto et al., the adduct **3l** was exposed to the reductive cleavage conditions.[8] The reaction proceeded giving the corresponding free CF_3-imidazoline **4l** in 53% yield (Scheme 3).

Scheme 3. Deprotection of 3l To Furnish 4l



In summary, we developed a mild and efficient [3 + 2] cycloaddition reaction of 2-(trifluoromethyl)-*N*-tosylaziridine with diverse nitriles in the presence of relatively unfamiliar TiF_4 as the Lewis acid to afford the corresponding 4-(trifluoromethyl)-1,3-imidazolines with excellent regioselectivity. Considering the mild reaction conditions, simple operation, wide substrate scope, and high yields, this method is attractive to prepare 4-(trifluoromethyl)-1,3-imidazolines as promising building blocks for further synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(6) See the Supporting Information for details.

(7) CCDC-1014784 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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