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Copper(II) triflate promoted cycloaddition of α-alkyl or aryl substituted *N*-tosylaziridines with nitriles: a highly efficient synthesis of substituted imidazolines

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Abstract—$Cu(OTf)_2$ or $Zn(OTf)_2$ mediated [3+2] cycloaddition reactions of various α-alkyl or aryl substituted *N*-tosylaziridines with nitriles is described for the syntheses of substituted imidazolines. A mechanism for the cycloaddition is proposed to rationalize the formation of a nonracemic imidazoline from optically pure aziridine.

In recent years, aziridines have been used extensively in organic synthesis as building blocks and synthetic intermediates.[1] Their importance originates from their ability to undergo ring-opening reactions with various nucleophiles.[2] Aziridines, being a masked 1,3-dipole, can readily undergo a formal [3+2] cycloaddition with a range of dipolarophiles[3,4] to construct five-membered nitrogen-containing heterocycles which are part of various natural products.[5] $BF_3{\cdot}OEt_2$ promoted cycloaddition of acetonitrile or benzonitrile with *N*-alkoxycarbonylaziridines was reported by Hiyama et al. for the synthesis of the corresponding imidazolines.[3a] Some of these compounds are useful intermediates for designing molecules with pharmacological activities such as antiinflammatory,[6] antidiabetic[7] and anticancer.[8] In addition, they have been used as synthetic intermediates[9] and auxiliaries[10] or catalysts[11] for asymmetric synthesis. To date, only a few methods are established where nitriles have been used as the dipolarophile in [3+2] cycloaddition reactions with aziridines using boron complexes[3] or the recently reported $Sc(OTf)_2$ as catalysts[12] for the synthesis of imidazolines.[3,12] Although these methods are successful for aryl or silylmethyl substituted aziridines, for simple alkyl substituted aziridines including cycloalkyl aziridines, either the cycloaddition reaction was not studied or cycloadducts could not be isolated.[3a,f,12] Moreover, in most of these cases the reaction suffered from several disadvantages such as the use of a highly moisture sensitive catalyst, poor to moderate yields, etc. Thus, it is desirable to develop an easy and economically viable general method for the [3+2] cycloaddition of aziridines with nitriles. Recently, we reported the $ZnBr_2$ assisted [3+2] cycloaddition reaction of 2-phenyl-*N*-tosylaziridine with nitriles.[13] In continuation of our research in this area to establish a general method applicable for aryl, alkyl and cycloalkyl substituted *N*-tosylaziridines we found that $Cu(OTf)_2$ is an excellent catalyst for the [3+2] cycloaddition reaction of these substrates with nitriles. In the present communication, we report our preliminary study on the $Cu(OTf)_2$-mediated [3+2] cycloaddition of a variety of *N*-tosylaziridines with nitriles for the synthesis of substituted imidazolines. $Cu(OTf)_2$ has been used as an efficient catalyst in organic synthesis, promoting several transformations such as oxidative coupling,[14] aziridination,[15] asymmetric Friedel–Crafts reactions,[16] [4+2] cycloaddition reactions,[17] oxidation of alkyl radicals,[18] asymmetric conjugate additions[19] and catalytic asymmetric Mannich-type reactions.[20] To the best of our knowledge, $Cu(OTf)_2$ mediated cycloaddition of aziridines with nitriles is not known thus far.

To test the viability of our approach, we initially carried out the [3+2] cycloaddition of 2-phenyl *N*-tosylaziridine **1a** in acetonitrile as solvent at 65 °C in the presence of $Cu(OTf)_2$. A series of Lewis acids including $Zn(OTf)_2$,

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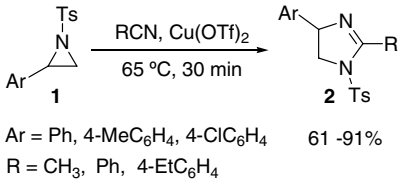
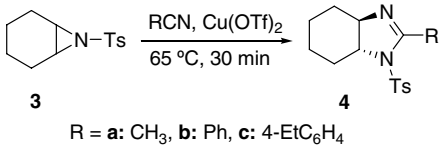


Scheme 1. [3+2] Cycloaddition reaction of 2-aryl-*N*-tosylaziridines with different nitriles.

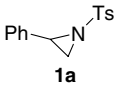
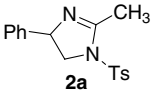
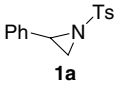
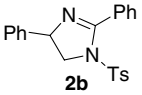
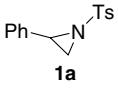
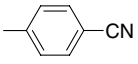
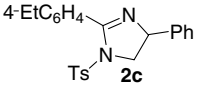
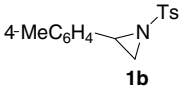
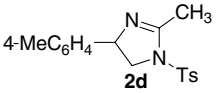
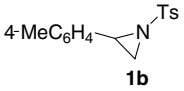
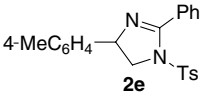
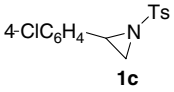
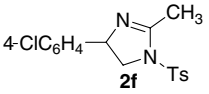
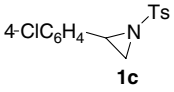
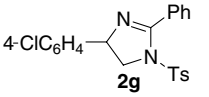
ZnX_2 (X = Cl, Br) were studied and $Cu(OTf)_2$ was found to be the most suitable catalyst in terms of a clean reaction, good yield and short reaction time. When **1a** was reacted in acetonitrile using 1 equiv of the catalyst, the reaction was complete within 30 min and the corresponding imidazoline **2a** was obtained in excellent yield (Scheme 1). Although the reaction proceeded in a similar fashion with $Zn(OTf)_2$, it was found to be slower. To determine the optimal reaction conditions employing $Cu(OTf)_2$ as the catalyst, we attempted the reaction with different equivalents of catalyst under different reaction conditions. When the reaction was performed in DCM with 1 equiv of nitrile or using 0.3–0.5 equiv of catalyst, it took longer to complete and a reduced yield of **2a** was obtained. It was concluded that the use of one equivalent of catalyst and nitrile as solvent were necessary to achieve the best results.[21a] To generalize this approach, the reactions of various 2-aryl-*N*-tosylaziridines (**1a**–**c**) with different nitriles were studied and the results are summarized in Table 1.

We next extended our study to cycloalkyl, benzyl and *n*-octyl substituted aziridines. Reported methods[3a,12] are not successful for these types of substrates. Under the optimum reaction conditions, *N*-tosylcyclohexeneaziridine **3** was treated with $Cu(OTf)_2$ in acetonitrile at 65 °C to yield bicyclic imidazoline **4a**[21b] in very high yield (Scheme 2). Generalization of the cycloaddition reaction of **3** with other nitriles is shown in Table 2. It was intriguing that *N*-tosyl-2-alkylaziridine **5** underwent [3+2] cycloaddition with nitriles in a regioselective fashion and produced **6** as the major cycloadduct along with another cycloadduct **7** as the minor regioisomer. In the case of *N*-tosyl-2-benzylaziridine **5a**, the corresponding cycloadducts **6b** (44%) and **7b** (11%) were isolated when benzonitrile was used as the dipolarophile. However, with acetonitrile, **6a** and **7a** were formed as an insepara-



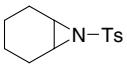
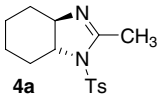
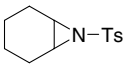
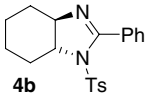
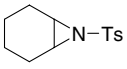
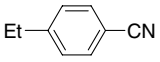
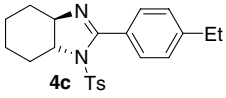
Scheme 2. [3+2] Cycloaddition reaction of *N*-tosylcyclohexylaziridine with nitriles.

Table 1. $Cu(OTf)_2$ promoted [3+2] cycloaddition of 2-aryl-*N*-tosylaziridines with nitriles[a]

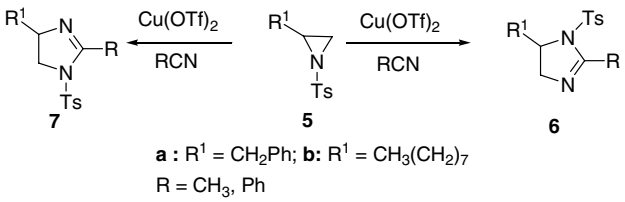
Entry	Aziridine **1**	Nitrile	Product **2**	Time (min)	Yield[b,d] (%)
1	 **1a**	CH_3CN	 **2a**	30	82 (91)[c]
2	 **1a**	PhCN	 **2b**	30	67
3	 **1a**		 **2c**	30	62
4	 **1b**	CH_3CN	 **2d**	30	77
5	 **1b**	PhCN	 **2e**	30	62
6	 **1c**	CH_3CN	 **2f**	30	72
7	 **1c**	PhCN	 **2g**	30	61

[a] In all cases the nitrile served as the solvent.
[b] Isolated yield after column chromatographic purification.
[c] Yield was determined by ^1H NMR analysis of the crude reaction mixture.
[d] See Ref. 21b.

Table 2. $Cu(OTf)_2$ promoted [3+2] cycloaddition of *N*-tosylcyclohexeneaziridine with nitriles[a]

Entry	Aziridine **3**	Nitrile	Product **4**	Time (min)	Yield[b,d] (%)
1		CH_3CN	 **4a**	30	62 (93)[c]
2		PhCN	 **4b**	30	60
3			 **4c**	30	62

[a] In all cases the nitrile served as the solvent.
[b] Isolated yield after column chromatographic purification.
[c] Yield was determined by ^1H NMR analysis of the crude reaction mixture.
[d] See Ref. 21b.



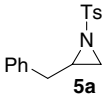
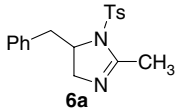
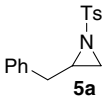
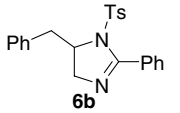
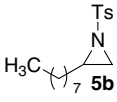
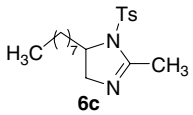
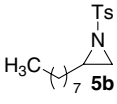
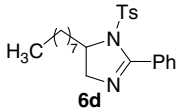
Scheme 3. Regioselective [3+2] cycloaddition of *N*-tosyl-2-alkylaziridines with nitriles.

ble mixture of regioisomers in a 2:1 ratio. In the case of *N*-tosyl-2-octylaziridine **5b**, the corresponding cycloadduct **6c** or **6d** was isolated as the only product using acetonitrile or benzonitrile (Scheme 3) as dipolarophiles (Table 3).

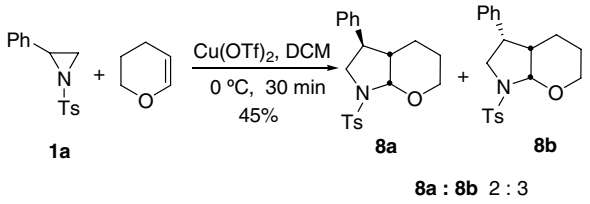
Finally, we explored the possibility of the [3+2] cycloaddition of *N*-tosylaziridine with other dipolarophiles in the presence of $Cu(OTf)_2$. We examined the cycloaddition reaction of **1a** with dihydropyran at 0 °C (Scheme 4). A mixture of *exo*/*endo* bicyclic pyrrolidine derivatives **8a** and **8b**, respectively, were obtained in a 2:3 ratio with an overall yield of 45%. Earlier the same reaction was reported in the presence of $BF_3{\cdot}OEt_2$ where the cycloadducts were obtained in a 1:1 ratio.[4c]

Formation of bicyclic imidazoline **4** with a trans ring junction as a single product from **3** suggested that the reaction proceeded through a S_N2 type pathway. Reaction of enantiomerically pure (*R*)-2-phenyl-1-(toluene-4-sulfonyl)aziridine **1a** with nitriles produced nonracemic imidazolines **2**: when R = CH_3, $[\alpha]_D^{25}$ −10 (*c* 1, $CHCl_3$) and when R = Ph, $[\alpha]_D^{25}$ −4.8 (*c* 0.8, $CHCl_3$). From these

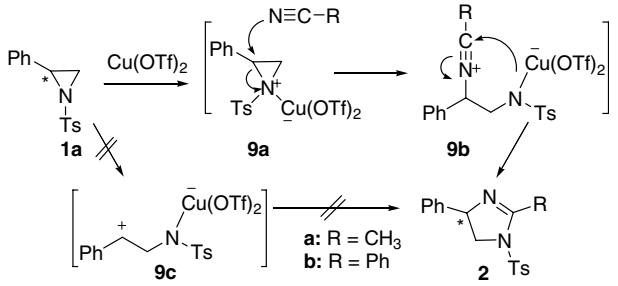
Table 3. $Cu(OTf)_2$ promoted [3+2] cycloaddition of alkylaziridines with nitriles[a]

Entry	Aziridine **5**	Nitrile	Product **6**	Time (h)	Yield[b,d] (%)	Ratio **6:7**
1	 **5a**	CH_3CN	 **6a**	2	52	2:1
2	 **5a**	PhCN	 **6b**	0.5	55 (70)[c]	4:1
3	 **5b**	CH_3CN	 **6c**	5	45 (54)[c]	>99:1
4	 **5b**	PhCN	 **6d**	2	54	>99:1

[a] In all cases the nitrile served as the solvent.
[b] Isolated yield after column chromatographic purification.
[c] Yield based on starting material recovery.
[d] See Ref. 21b.



Scheme 4. [3+2] Cycloaddition reaction of 2-phenyl-*N*-tosylaziridine with dihydropyran in the presence of $Cu(OTf)_2$.



Scheme 5. Proposed mechanism for the [3+2] cycloaddition reaction of 2-aryl-*N*-tosylaziridine with nitriles.

observations we believe that the reaction follows the same mechanism we proposed earlier for the $ZnBr_2$ mediated cycloaddition reaction.[13] The mechanism is illustrated in Scheme 5 where $Cu(OTf)_2$ is coordinated to the nitrogen atom of **1a** generating **9a**. Subsequent [3+2] cycloaddition leads to the formation of nonracemic imidazoline **2**. In recent work[12] by Wu et al. their cycloaddition reaction was also reported to follow our earlier proposed mechanism.[13]

In conclusion, we have developed a direct and efficient route to imidazoline and pyrrolidine derivatives using copper(II) triflate-mediated [3+2] cycloaddition of various aryl, alkyl and cycloalkyl *N*-tosylaziridines with nitriles and olefins as dipolarophiles. Moreover, our method successfully led to the formation of cycloadducts with simple alkylaziridines in moderate to good yields. We believe that the present reaction will be potentially useful for constructing biologically important imidazoline or pyrrolidine skeletons. Further study in this area is under investigation in our laboratory.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.05.059.

References and notes

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21. (a) A general experimental procedure: *N*-tosylaziridine (0.183 mmol) was dissolved in 1.0 ml of nitrile and was added to a suspension of $Cu(OTf)_2$(0.183 mmol) in nitrile under an argon atmosphere. The mixture was warmed to 65 °C for the appropriate time until complete consumption of the substrate (monitored by TLC). The reaction mixture was quenched with saturated $NaHCO_3$ solution (1.0 ml) and was extracted with ethyl acetate thrice. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent removed under vacuum. The crude product was purified by flash column chromatography on silica gel (230–400 mesh) using ethyl acetate in petroleum ether to provide the corresponding imidazoline derivatives. All products were characterized by ^{1}H NMR, ^{13}C NMR and mass spectral analysis.
In some cases where higher boiling nitriles were used, a modified purification method was followed. The reaction mixture was directly charged onto a deactivated basic alumina column (deactivated with 5% water) to remove copper salts. The column was washed first with petroleum ether to remove and recover excess nitriles. Pure compounds were obtained using ethyl acetate/petroleum ether (9–12%) as eluent.
Spectral data of **2c** (Ar = Ph; R = 4-EtC_6H_4): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, J = 7.6 Hz, 3H), 2.35 (s, 3H), 2.67 (q, J = 7.6 Hz, 2H), 3.81 (dd, J = 11.5, 7.8 Hz, 1H), 4.38 (dd, J = 11.5, 10.0 Hz, 1H), 4.89–4.93 (m, 1H), 6.89–6.92 (m, 2H), 7.09–7.34 (m, 9H), 7.66 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 21.6, 28.9, 56.9, 67.5, 126.3, 127.1, 127.2, 127.4, 127.6, 128.5, 129.7, 129.9, 134.3, 141.4, 144.6, 147.9, 160.2; MS (FAB) m/z 405 $[M+H]^+$, 389, 274, 249, 221, 145.
Spectral data of **4a** (R = Me): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15–1.33 (m, 3H), 1.54–1.64 (m, 1H), 1.74–1.85 (m, 2H), 2.19–2.22 (m, 1H), 2.29 (d, J = 2.2 Hz, 3H), 2.42 (s, 3H), 2.49–2.53 (m, 1H), 2.79–2.86 (m, 1H), 3.04–3.10 (m, 1H), 7.33 (d, J = 8.01 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.9, 21.6, 24.5, 24.9, 30.4, 30.5, 69.2, 70.1, 127.3, 130.0, 134.9, 144.5, 158.2; MS (FAB) m/z 293 $[M+H]^+$, 291, 252, 155, 137, 136, 97.
Spectral data of major regioisomer **6b** ($R^1 = CH_2Ph$; R = Ph): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24–2.30 (m, 1H), 2.36 (s, 3H), 2.89 (dd, J = 13.9, 5.1 Hz, 1H), 3.60–3.65 (m, 1H), 3.86 (dd, J = 11.2, 9.3 Hz, 1H), 4.10–4.18 (m, 1H), 7.02 (d, J = 6.8 Hz, 2H), 7.14–7.44 (m, 10H), 7.55–7.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 41.4, 53.5, 66.1, 126.6, 127.5, 127.6, 128.5, 129.2, 129.5, 129.7, 130.3, 134.7, 137.2, 144.5, 158.8; MS (FAB) m/z 391 $[M+H]^+$, 390 $[M]^+$, 257, 237, 217, 145, 91; Spectral data of minor regioisomer **7b** ($R^1 = CH_2Ph$; R = Ph): ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 2.86 (dd, J = 13.4, 9.2 Hz, 1H), 3.10–3.30 (m, 2H), 3.62 (dd, J = 15.9, 2.7 Hz, 1H), 4.42–4.45 (m, 1H), 7.15–7.65 (m, 12H), 7.66 (d, J = 7.1 Hz, 2H); MS (FAB) m/z 391 $[M+H]^+$, 302, 257, 145, 119.
Spectral data of **6c** ($R^1 = CH_3(CH_2)_7$; R = Me): ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.80 (t, J = 6.6 Hz, 3H), 1.16–1.21 (m, 14H), 2.21 (s, 3H), 2.38 (s, 3H), 3.26 (dd, J = 8.1, 5.8 Hz, 1H), 3.72–3.77 (m, 2H), 7.28 (d, J = 7.8 Hz, 2H), 7.67 (d, J = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 16.8, 21.5, 22.6, 25.6, 29.2, 29.3, 29.4, 31.8, 35.8, 53.1, 63.6, 127.1, 129.9, 135.4, 144.5, 154.8; MS (ESI) m/z 351 $[M+H]^+$.
(b) The decreased yield of isolated imidazolines was due to hydrolysis during column chromatographic purification which was necessary for preparing an analytical sample.