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Preparation of imidazolines from aziridines and nitriles *via* TfOH promoted Ritter process

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ABSTRACT

An efficient preparation of imidazolines from nitriles and aziridines in the presence of TfOH *via* Ritter reaction is described. It indicates that different kinds of nitriles can undergo the process. Among the nitriles, pivalonitrile is proven to be better than acetonitrile. The reaction is performed at room temperature and the yields are excellent.

1. Introduction

The preparation of imidazolines analogs has attracted considerable interest [1] due to their potential biological activities [2] and applications in organocatalysis [3]. The Ritter reaction provides an important route to generate amides *via* stabilized carbocations. Originally, the carbocations employed are generated from alkenes [4] and alcohols [5] in the presence of Brønsted acids. Recently, epoxides [6] and aziridines [7], as available carbonium ion sources, have been employed and proven successful in the Ritter process. Utilizing the Ritter reaction, the products from epoxides and aziridines are dihydrooxazoles and imidazolines, respectively, followed with ring closure (Scheme 1). Although several groups have reported that the combination of nitriles and aziridines with the promotion of a Lewis acid can give imidazolines [7], however, the deficiencies of the reported procedures, including expensive reagents [7e,7f], high temperature [7a,7d,7e] and unsatisfied yields [7a,7b,7d–7g], tended to limit their applications. The reported yields are generally from 60% to 80% and some use lanthanide triflates [7e] as the promoter for this conversion. To our surprise, with aziridines and epoxides only Lewis acids have been reported to be successful, and the most widely referenced one is $BF_3{\cdot}OEt_2$. The Lewis acids employed in the process are (frequently) moisture sensitive, and moreover, some Lewis acids result in undesired products, since the halide anion from the promoter can act as a nucleophile to attack the aziridine ring, or the intermediate. For example in reference [7f], $InCl_3$, $ErCl_3$ and $YbCl_3$ do not give any Ritter products, but deliver chlorinated compounds as the major product, while Et_3OBF_4 results in some fluorinated product [7b] accompanied with the imidazoline. Furthermore, the imidazolines could be easily hydrolyzed to diamine derivatives with the promotion of HCl in EtOH in very high yield [8]. Considering the important application of diamines, the efficient preparation of imidazolines is of potential and high demand. Herein, we describe a practical preparation of imidazolines in excellent yields from aziridines and nitriles at room temperature.

2. Experimental

As mentioned above, we focused our attention on the use of Brønsted acids for the Ritter transformation. Aziridine **1a** and acetonitrile **2a** were selected for the model reaction because of their frequent appearance in other reported experiments. Initially, we applied 1 equiv. of Brønsted acid as the promoter (Table 1, entries 1–6), while $BF_3{\cdot}OEt_2$ was used as comparison. Among the Brønsted acids, H_2SO_4, aqueous HCl, TFA, $HClO_4$ and trifluoromethanesulfonic acid (TfOH) were screened, but TfOH was demonstrated the most efficient and gave the corresponding

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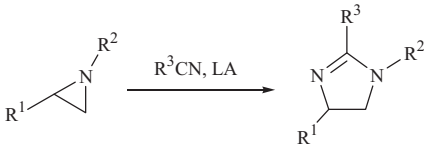
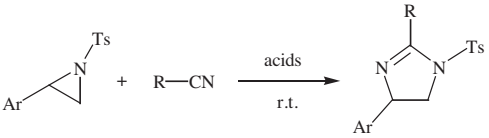


Scheme 1. Representative Ritter process of nitrile and aziridine.

imidazoline **3a** in 72% yield, as the control subject, and in contrast, $BF_3{\cdot}OEt_2$ delivered **3a** in 60% yield.

After TfOH was identified as the promoter, we switched our attention to the nitriles, since acetonitrile was widely used in the literature. Apart from it, aliphatic nitriles, including propiononitrile and isobutyronitrile, were expanded, and gave the corresponding imidazolines in similar yields to that of acetonitrile [7b,7g]. There are a variable number of protons at the position α to the nitrile group, and we reasoned that these protons could probably affect the process. To the best of our knowledge, pivalonitrile **2b** was not reported for this transformation. We conducted the experiment with pivalonitrile **2b** and aziridine **1a** in the presence of 1 equiv. of TfOH for 24 h and obtained the imidazoline **3b** in 84% yield (Table 1, entry 7). This indicated that

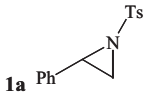
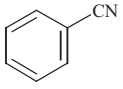
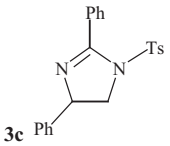
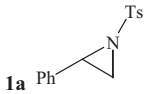
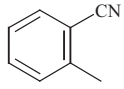
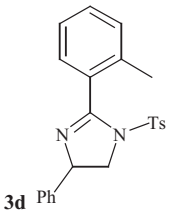
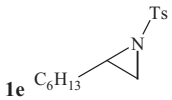
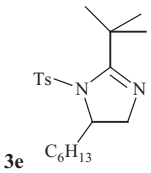
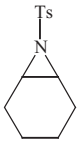
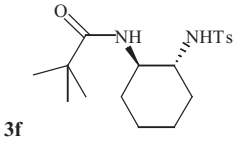
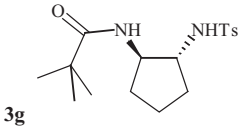
Table 1
Screening of acids for reaction of **1a** and acetonirile.[a]



Entry	Nitriles	Acids (equiv.)	Time (h)	Yield (%)[b]
1	CH_3CN (**2a**)	HCl (1.0)	24	20
2	CH_3CN (**2a**)	H_2SO_4 (1.0)	24	38
3	CH_3CN (**2a**)	$HClO_4$ (1.0)	24	48[c]
4	CH_3CN (**2a**)	TFA (1.0)	24	42
5	CH_3CN (**2a**)	$BF_3{\cdot}OEt_2$ (1.0)	24	60
6	CH_3CN (**2a**)	TfOH (1.0)	24	72
7	*t*-BuCN (**2b**)	TfOH (1.0)	24	84
8	*t*-BuCN (**2b**)	TfOH (1.2)	24	92
9	*t*-BuCN (**2b**)	TfOH (1.5)	24	95
10	*t*-BuCN (**2b**)	TfOH (2.0)	6	96
11	CH_3CN (**2a**)	TfOH (2.0)	6	89
12	CH_3CN (**2a**)	TfOH (2.5)	0.7	95

[a] Combination of 1 equiv. of aziridine **1a** with the corresponding equiv. of TfOH in nitrile for the required duration.
[b] Isolated yield after column chromatography.
[c] Accompanied with some unknown compound.

Table 2
TfOH promoted Ritter reaction of alkylaziridines and nitriles.[a]

Entry	Aziridines **1**	Nitriles **2**	Products **3**	Time (h)	Yield[b] (%)
1	 **1a**	 **2c**	 **3c**	6	80[c] (90[d])
2	 **1a**	 **2d**	 **3d**	12	80[c] (91[d])
3	 **1e**	 **2b**	 **3e**	12	90
4	 **1f**	 **2b**	 **3f**	6	86
5	 **1g**	 **2b**	 **3g**	6	85

[a] 2.0 equiv. of TfOH used as the promoter.
[b] Isolated yield after column chromatography.
[c] Average yield based on three runs.
[d] The best yield of three runs.

nitrile **2b** would be better than acetonitrile **2a** (Table 1, entry 7 *vs.* entry 6). In order to achieve a higher yield, we increased TfOH from 1 equiv. to 1.2 equiv. and 1.5 equiv., the yield of **3b** was improved to 92% and 95%, while the reaction time remained at 24 h (Table 1, entry 8 and entry 9). Then 2.0 equiv. of TfOH was attempted, **3b** was obtained in 96% yield, and the reaction time was shortened to 6 h (Table 1, entry 10). The acetonitrile **2a** was also reacted with aziridine **1a** under the above conditions, and **3a** was generated in 89% yield (Table 1, entry 11). The reaction conditions were optimized as follows: Treatment of 1 equiv. of the aziridine with 2.0 equiv. of TfOH in nitrile at room temperature for the required time. Furthermore, the imidazoline **3a** could be obtained in 95% yield in 0.7 h by slightly increasing the amount of the promoter to 2.5 equiv. (Table 1, entry 12), which was the best yield with the same substrates in the reports, and the common yield was only around 70% [7].

A represent procedure for preparation of imidazoline **3**: To a stirred solution of **1a** (272 mg, 1.0 mmol) in pivalonitrile **2b** (2 mL) was added TfOH (300 mg, 2.0 mmol). After stirring at room temperature for an additional 6 h, the mixture was concentrated and the residue was chromatographed to afford imidazoline **3b** as a yellow oil (342 mg, 96% yield from **1a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 9 H), 2.42 (s, 3 H), 3.59 (dd, 1H, J = 8.2 Hz and 10.8 Hz), 4.13 (dd, 1H, J = 9.6 Hz and 10.8 Hz), 4.78 (t, 1H, J = 9.2 Hz), 7.06–7.08 (m, 2 H), 7.24–7.29 (m, 5 H), 7.74 (d, 2H, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 29.4 (3), 36.7, 58.4, 66.3, 126.4 (2), 127.2 (2), 127.4, 128.6 (2), 129.9 (2), 136.5, 141.5, 144.3, 167.7; IR (film, cm^{-1}): 2962, 1617, 1351, 1169, 1003, 668; MS (EI): m/z 341, 291, 200, 173, 117, 98, 91; HRMS (ESI) calcd. for $C_{20}H_{25}N_2O_2S$ (M^++H): 357.1631, found: 357.1625.

The analytical data for all the other products and copies of ^{1}H NMR and ^{13}C NMR spectra can be found in Supporting information.

3. Results and discussion

To further demonstrate the efficiency of the reaction, a series of substrates were investigated (Table 2). Besides the aliphatic nitriles, the aromatic nitrile PhCN **2c** was examined (Table 2, entry 1), it proceeded well with aziridine **1a** and gave the imidazoline **3c** in 80% yield. Increasing the hindrance by introducing a methyl group to the *o*-position of aromatic ring in the nitrile did not decrease the yield (Table 2, entry 2), the yield of the transformation remained at 80% but required a longer time (12 h *vs.* 6 h). Aliphatic substituted aziridine **1e** was also reacted with **2b** and gave the imidazoline **3e** in 90% yield (Table 2, entry 3). It should be noted that the regioselectivity was altered mainly due to the reaction proceeding *via* SN2 mode where the attack took place at the less hindered site. The structure of imidazoline **3e** was assigned by comparison to the similar compound reported [7g]. Cycloalkyl aziridines **1f** and **1g** could also be successfully transformed to the bicyclic imidazolines in high yields, but we were unable to separate them from the reaction mixtures. After column chromatographic purification, the hydrolyzed products **3f** and **3g** were obtained in 86% and 85% yield (Table 2, entries 4 and 5).

4. Conclusion

In conclusion, we have developed an efficient procedure for the preparation of imidazolines from aziridines and nitriles. The procedure employed the Brønsted acid TfOH as the promoter, and it indicated that pivalonitrile was better than acetonitrile. The imidazoline could be obtained in 80%–96% yield. Furthermore, even the acetonitrile could deliver the imidazoline in excellent yield by slightly increasing the amount of TfOH. The reaction was performed at room temperature and no expensive promoters were used, and the yields were much better than those of the reported procedures.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2014.01.020.

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