Efficient and One-Pot Catalytic Synthesis of 2-Imidazolines and Bis-Imidazolines with *p*-Toluenesulfonic Acid under Solvent Free Conditions

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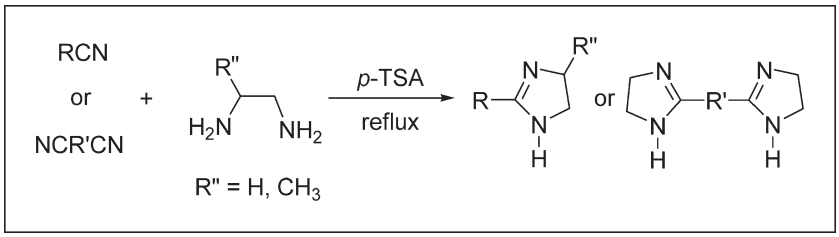
Received January 31, 2010
DOI 10.1002/jhet.516
Published online 18 November 2010 in Wiley Online Library (wileyonlinelibrary.com).



A practical, efficient, and inexpensive method for the synthesis of 2-imidazoline from the reaction of nitriles with ethylenediamine or 1,2-propanediamine using *p*-toluenesulfonic acid or pyridinium *p*-toluenesulfonate under reflux conditions is reported. This catalyst can be successfully applied for the chemoselective conversion of dicyanobenzenes to corresponding mono- and bis-imidazolines. The applications of these catalysts are feasible because of easy preparation, easy handling, stability, inexpensive, good activity, and eco-friendly.

J. Heterocyclic Chem., **48**, 249 (2011).

INTRODUCTION

2-Imidazolines are very important moieties because of their extensive utilities in chemistry, biochemistry, and pharmacology [1]. These heterocycles exhibit several pharmaceutical activities such as antidiabetic [2], antihypertensive [3], antidepressive [4], anticancer [5], anti HIV-1 [6], antitumor [7], and anti-Alzheimer [8] activities. These compounds are also used as catalysts [9] and synthetic intermediates [10]. Various reaction conditions including homogeneous and/or heterogeneous catalysts have been used for this purpose. Several publications have been described for the preparation of 2-substituted imidazolines from different precursors such as carboxylic acids [11], esters [12], nitriles [13], amides [14], aziridines [15], aldehydes [16], orthoesters [17], hydroximoylchlorides [18], hydroxy amides [19], mono- or disubstituted (chlorodicyanovinyl)benzene [20], and *N-tert*-butoxycarbonyl-protected α-amino acids [21]. However, many of the synthetic protocols reported have certain limitations, such as needing anhydrous conditions, the applications of stoichiometric amounts of catalysts, organic solvents and metals and expensive reagents, harsh reaction conditions and prolonged reaction times. Therefore, the development of an efficient, simple and environmentally benign catalytic procedure for the synthesis of these heterocycles is still in high demand.

The application of 1,2-diamines is the first class synthesis methods of imidazolines. The highlighted advantage of this method is the easy introduction of chirality by using enantiopure 1,2-diamines [22]. A good source of C-1 for preparation of imidazolines is nitriles. Some novel conditions have been developed for this reaction, using Lewis acids, Brönsted acids, or other small molecules as catalysts, such as HCl [13d], CuCl [13e], thioacetamide [23], sulfur [13i], $ZrOCl_2$ [13j], silica sulfuric acid [24], 12-tungstophosphoric acid [25], and carbon disulfide [13k].

We have found that *p*-toluenesulfonic acid (*p*-TSA) and pyridinium *p*-toluenesulfonate (PPTS) as inexpensive and common organic chemicals are efficient catalysts for the synthesis of 2-imidazolines and bis-imidazolines.

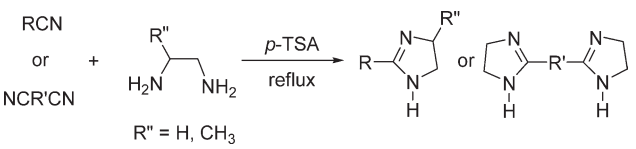
Crystalline pyridinium *p*-toluenesulfonate can easily be prepared from pyridine and *p*-toluenesulfonic acid monohydrate [26]. It is soluble in methylene chloride, chloroform, ethanol, and acetone, and slightly soluble in benzene but insoluble in ether. It is noteworthy that pyridinium *p*-toluenesulfonate is a weaker acid (pH 3.0 in 1.0*M* aqueous solution) than acetic acid (pH 2.4 in 1.0*M* aqueous solution). Consequently, this catalyst is mild enough to be used on complex systems containing sensitive polyfunctional groups.

In this work, we wish to report an efficient synthesis of imidazolines and bisimidazolines using catalytic amounts of a Brønsted acid, such as *p*-toluenesulfonic acid or pyridinium *p*-toluenesulfonate.

RESULTS AND DISCUSSION

In this article, we describe an efficient method for the synthesis of 2-imidazolines and bis-imidazolines by the

Scheme 1



reaction of ethylenediamine or 1,2-propanediamine with nitriles in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TSA) or pyridinium *p*-toluenesulfonate (PPTS) under reflux condition (Scheme 1).

Synthesis of 2-imidazolines catalyzed by *p*-toluenesulfonic acid. The results from the reaction of ethylenediamine or 1,2-propanediamine and various nitriles in the presence of optimized amount of *p*-toluenesulfonic acid are shown in Table 1. As shown in entries 1–17, the reactions using various aromatic nitriles proceeded well to give the corresponding 2-imidazolines and bis-imidazolines in good to excellent yields.

Typically, benzonitrile (**4**), ethylenediamine, and *p*-TSA were mixed and exposed to heating for 35 min. Cold water was added and the mixture was extracted by $CHCl_3$. Removal of the solvent and recrystallization of the crude product from cyclohexane gave the corresponding 2-imidazoline in 92% yield.

Surprisingly, it was observed that both mono- and bis-imidazolines can be obtained by this catalytic system. As shown in Table 1, mono-imidazolines were produced from dinitriles in 90–92% yields with shorter reaction times (50–60 min). Increasing of the reaction times to 100–110 min, produced bis-imidazolines in 85–87% yields. The preparation of mono-imidazolines from dinitrile compounds is of great interest because the remaining nitrile group can be converted to other functional groups [28].

As it has been reported, catalytic synthesis of bis-imidazolines from the reaction of dinitriles with ethylenediamine in the presence of supported tungstophosphoric was not successful [25], whereas in the presence of *p*-TSA, the corresponding bis-imidazolines were synthesized from dinitriles in the good yields (entries 11, 13; Table 1).

One advantage of this method is large scale applicability so that imidazolines and bis-imidazolines were prepared on a 100 mmol scale, and the results were comparable with the small scale experiments.

A plausible mechanism is shown in Scheme 2. The nitrile is first activated by the catalyst to give **1** then ethylenediamine attacks **1** to produce **2** and in final cyclization of **2** gives product and releases of the catalyst for the next catalytic cycle.

Synthesis of 2-imidazolines catalyzed by pyridinium *p*-toluenesulfonate. As shown in Table 2, in the presence of pyridinium *p*-toluenesulfonate, the synthesis of 2-imidazoline was performed in longer time with slightly reduced yields in comparison with *p*-TSA. For example, in the presence of *p*-TSA, the reaction of benzonitrile was completed in 35 min, whereas PPTS catalyst carried out the reaction in 85 min with 85% yield. These results show that PPTS probably can be used in the synthesis of imidazolines containing sensitive groups.

CONCLUSIONS

A simple and efficient procedure for the synthesis of 2-imidazolines and bis-imidazolines has been developed. Mild reaction conditions, absence of solvent, moderate reaction times, easy and quick isolation of the products, good to excellent yields (75–92%), inexpensive and easily preparation of the catalyst, and large scale applicability are the main advantages.

EXPERIMENTAL

Chemicals were purchased from Merck, Fluka, and Aldrich chemical companies. All of the products were identified by comparison of their physical and spectral data with those of authentic samples. IR spectra were recorded on a Jasco IR-680 spectrophotometer. ^{1}H NMR spectra were obtained with a Bruker-Arance AQS 300 MHz or a Bruker 400 Ultrasheilld (400 MHz) spectrometers.

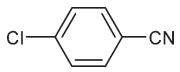
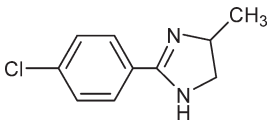
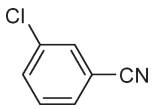
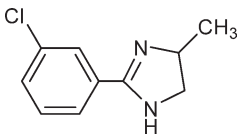
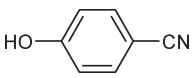
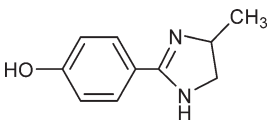
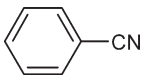
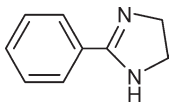
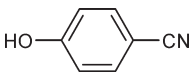
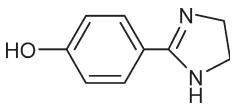
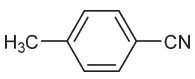
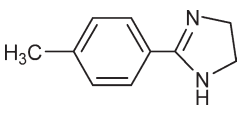
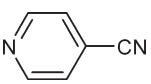
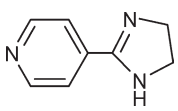
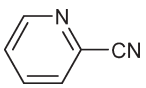
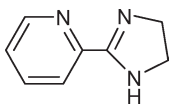
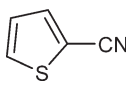
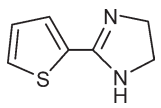
General procedure for the preparation of 2-imidazolines and bis-imidazolines. A mixture of nitrile (10 mmol), ethylenediamine or 1,2-propanediamine (40 mmol), and *p*-toluenesulfonic acid (3 mmol) or pyridinium *p*-toluenesulfonate (4 mmol) was heated under reflux for 45–220 min. After completion of the reaction as indicated by TLC (eluent:EtOAc/MeOH, 4:1), cold water was then added after the reaction mixture cooled down to room temperature. After stirred, the mixture was extracted by 15 mL (3×5) $CHCl_3$ and solvent evaporated. The crude products were recrystallized from suitable solvents (**4** was recrystalised from cyclohexane; **12** and **14** were recrystallized from methanol and others were recrystallized from *n*-hexane) gave the pure products in 75–95% yields based on the starting nitrile (Table 1). Spectroscopic data of new compounds:

2-(4-Chlorophenyl)-4,5-dihydro-4-methyl-1H-imidazole (Table 3, entry 1). Mp:150–152°C; $R_f = 0.464$ (ethyl acetate:methanol = 9:1); IR (KBr) ν(cm^{-1}): 3100 (NH), 2953, 1600, 1583, 1479, 1368, 1331, 831; ^{1}H NMR (400 MHz, DMSO) δ(ppm) : 1.27 (d, 3H, CH_3), 3.33 (m, 2H, CH_2), 3.92 (m, 1H, CH), 4.25 (s, 1H, NH), 7.55–7.85 (dd, 4H, ArH). ^{13}C NMR (400 MHz, DMSO) δ(ppm): 22.23, 56.47, 57.34, 126.92, 128.77, 129.6, 138.55, 162.06. Anal. Calcd. for $C_{10}H_{11}ClN_2$: C 61.70, H 5.70, N 14.39; found: C 61.6, H 5.8, N 14.3.

2-(3-Chlorophenyl)-4,5-dihydro-4-methyl-1H-imidazole (Table 3, entry 2). Mp:147–149°C; $R_f = 0.500$ (ethyl acetate:methanol = 9:1); IR (KBr) ν(cm^{-1}): 3120 (NH), 2962, 1592, 1542, 1490; ^{1}H NMR (400 MHz, DMSO) δ(ppm): 1.14 (d, 3H, CH_3), 3.18 (t, 1H, CH_2), 3.37 (s, 1H, NH), 3.75 (t, 1H, CH_2), 3.97 (m, 1H, CH), 7.43–7.91 (m, 4H, ArH). ^{13}C NMR (400

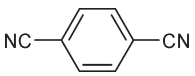
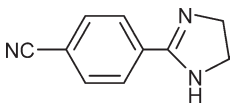
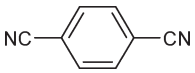
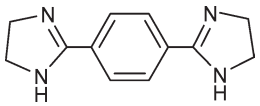
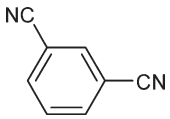
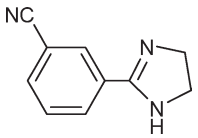
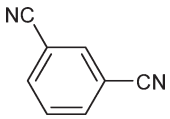
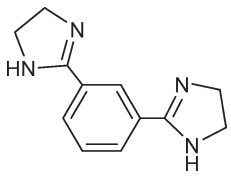
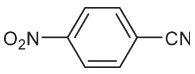
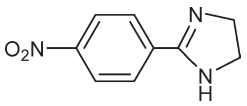
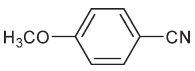
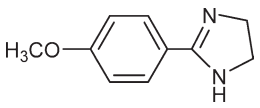
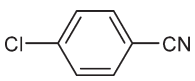
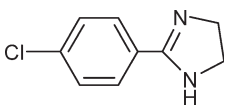
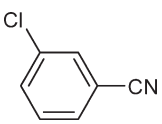
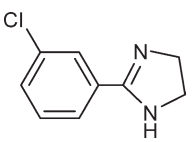
Table 1

Synthesis of imidazolines and bis-imidazolines in the presence of *p*-TSA.

Entry	Substrate	R''	Product[a]	Time (min)	Yield[b] (%)	Mp (°C) found	Mp (°C) reported
1		CH_3		90	75	150–152	–
2		CH_3		30	90	147–149	–
3		CH_3		75	80	148–150	–
4		H		35	92	100–101	101–102
5		H		60	92	300–302	–
6		H		75	92	177–179	175–176
7		H		100	85	134–135	136–137
8		H		140	85	101–102	94
9		H		105	90	175–178	178

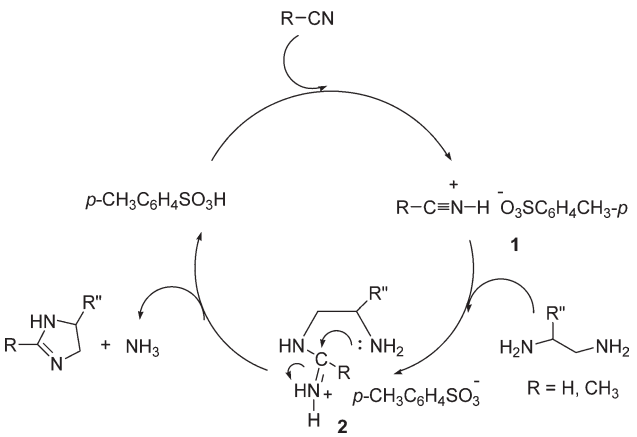
(*Continued*)

Table 1
(*Continued*)

Entry	Substrate	R''	Product[a]	Time (min)	Yield[b] (%)	Mp (°C) found	Mp (°C) reported
10		H		50	92	204–205	202
11		H		100	85	312–314	318
12		H		60	90	132–134	133–134
13		H		110	87	242–243	244
14		H		180	72	230–232	231
15		H		80	80	139–140	138–140
16		H		50	87	186–188	185–187
17		H		25	92	136–137	134–136

[a] Characterized by spectral analysis and comparison with these reported in the literature [13, 16, 25, 27].
[b] Yields refer to isolated and purified products.

Scheme 2



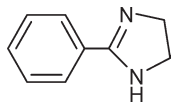
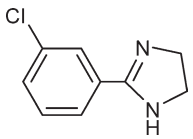
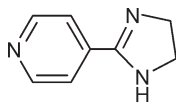
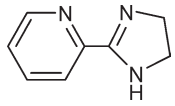
MHz, DMSO) δ(ppm): 22.11, 56.75, 57.99, 123.36, 124.47, 125.82, 127.29, 130.36, 133.20, 161.42. Anal. Calcd. for $C_{10}H_{11}ClN_2$: C 61.70, H 5.70, N 14.39; found: C 61.8, H 5.8, N 14.5.

2-(4-Hydroxyphenyl)-4,5-dihydro-4-methyl-1H-imidazole (Table 3, entry 3). Mp:148–150°C; R_f = 0.587 (ethyl acetate:methanol = 9:1); IR (KBr) ν(cm^{-1}): 3350 (b, OH), 3188 (NH), 2998, 1591, 1184, 856; ^{1}H NMR (400 MHz, DMSO) δ(ppm): 1.19 (d, 3H, CH_3), 3.23 (dd, 1H,CH_2), 3.80 (t, 1H, CH_2), 4.23(m, 1H, CH), 4.42 (s, 1H, NH), 4.72 (s, 1H, OH), 6.70 (d, 2H, ArH), 7.64 (d, 2H, ArH). ^{13}C NMR (400 MHz, DMSO) δ(ppm): 21.81, 53.42, 54.67, 114.25, 116.72, 130.20, 163.20, 165.57. Anal. Calcd. for $C_{10}H_{12}N_2O$: C 68.16, H 6.86, N 15.90; found: C 68.2, H 6.8, N 15.8.

2-(4-Hydroxyphenyl)-4,5-dihydro-1H-imidazole (Table 1, entry 5). Mp:300–302°C; R_f = 0.536 (ethyl acetate:methanol = 9:1); IR (KBr) ν(cm^{-1}): 3323 (b, OH), 3201 (NH), 1613, 1592, 1503, 1186, 853; ^{1}H NMR (400 MHz, DMSO) δ(ppm) : 3.55 (s, 4H, $2CH_2$), 3.40 (s, 1H, NH), 6.70 (d, 2H, ArH), 7.61 (d, 2H, ArH), 8.31 (s, 1H, OH). Anal. Calcd. for $C_9H_{10}N_2O$: C 66.65, H 6.21, N 17.27; found: C 66.5, H 6.3, N 17.2.

Table 2

Synthesis of some imidazolines in the presence of pyridinium *p*-toluenesulfonate.

		PPTS		*P*-TSA	
Entry	Product	Time (min)	Yield (%)	Time (min)	Yield (%)
1		85	85	35	90
2		80	78	25	92
3		270	80	100	85
4		360	82	140	85

Acknowledgment. The partial support of this work by Yasouj University is acknowledged.

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