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Rapid and efficient synthesis of 2-imidazolines and bis-imidazolines under ultrasonic irradiation

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Abstract—Rapid and efficient preparation of 2-imidazolines and bis-imidazolines by reaction of ethylenediamine with nitriles in the presence of catalytic amounts of sulfur under ultrasonic irradiation is reported. The advantages of this system are short reaction times, high yields and the ability to carry out large scale reactions.

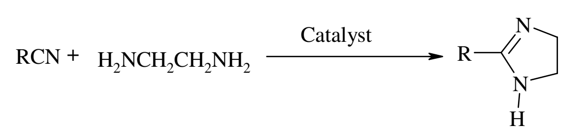
Imidazoline derivatives are of great importance because they exhibit significant biological and pharmacological activities including antihypertensive,[1,2] antihyperglycemic,[3–7] antidepressive,[8] antihypercholesterolemic[9] and antiinflammatory.[10] These compounds are also used as catalysts[11] and synthetic intermediates.[12]

There are several methods for the synthesis of 2-imidazolines from carboxylic acids,[13] esters,[14] nitriles,[15] orthoesters,[16] hydroximoylchlorides,[17] hydroxy amides[18] and mono- or disubstituted (chlorodicyanovinyl)benzene.[19] However, some of these methods suffer from disadvantages such as long reaction times, low yields, difficulty in preparation of starting materials and tedious work-up. Due to these problems, there is still scope to find new methods for the synthesis of imidazolines and bis-imidazolines. The synthesis of 2-imidazolines by the reaction of ethylenediamine (EDA) with nitriles using different reaction conditions has been reported previously. These methods have some disadvantages which are summarized in Table 1.

The application of ultrasonic irradiation in reactions using heterogeneous catalyst is a promising technique. The advantages of ultrasound procedures, such as good yields, short reaction times and mild reaction conditions, are well documented.[20–22] Ultrasonic irradiation can also be used to influence selectivity and yields of reactions. In this letter, we describe an efficient method for the synthesis of 2-imidazolines and bis-imidazolines by the reaction of ethylenediamine (EDA) with nitriles in the presence of catalytic amounts of sulfur under ultrasonic irradiation (Scheme 1).

Typically, benzonitrile **1a**, ethylenediamine and sulfur were mixed and exposed to ultrasonic irradiation for

Table 1. Methods for synthesis of 2-imidazolines by the reaction of ethylenediamine (EDA) to nitriles and their disadvantages



Entry	Catalyst	Disadvantage
1	No catalyst[15c]	High temperature
2	H_2S[15b]	Long reaction times (4 days)
3	HCl/EtOH[15d]	Low product yield Long reaction times (12–24 h) Needs multi-step synthesis
4	CuCl/MeOH[15e]	Low product yield Long reaction times Needs high quantity of catalyst
5	$La(OTf)_3$[15f]	High temperature Long reaction times (24 h)
6	CS_2[15g]	Low product yield High temperature

Keywords: Nitrile; Imidazoline; Ultrasonic irradiation; Ethylenediamine.

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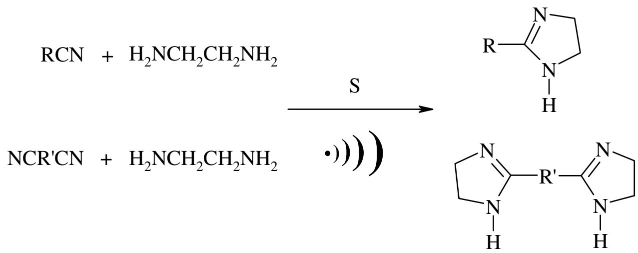


Scheme 1.

5 min. Cold water was added and the mixture was extracted with chloroform. Removal of the solvent and recrystallization of the crude product from cyclohexane gave the corresponding 2-imidazoline **2a** in 90% yield. The effect of ultrasonic irradiation intensity on this reaction was also investigated. The results show that the highest yield of compound **2a** was obtained at 100% intensity. Under the same reaction conditions, a variety of nitriles were cleanly and rapidly converted to their corresponding 2-imidazolines and bis-imidazolines in 84–95% yields within 5–30 min.[23] When *N*-methylethylenediamine was used instead of ethylenediamine, in the reaction with 4-chlorobenzonitrile under the same reaction conditions, the corresponding N-substituted 2-imidazoline **2l** was obtained in high yield (Table 2). The presence of sulfur was shown to be necessary by blank experiments in the absence of sulfur, but with ultrasonic irradiation, which showed that the reaction did not proceed at all. The exact mechanism of the reaction is not clear at this time. However, a plausible explanation is that sulfur reacts with the nitrile grove to produce a thioamide. The thioamide reacts with ethylenediamine, which upon elimination of hydrogen sulfide and ammonia, produces the 2-imidazoline.[15b] Evolution of hydrogen sulfide evidence for the above statement. Reaction of benzonitrile with a monoamine such as *n*-butylamine gave corresponding thiobenzamide, which provided further evidence for the suggested mechanism. On the other hand, 2-imidazoline can be synthesized by reaction of thioamides and ethylenediamine.[24]

When sulfur was replaced with selenium, no product was detected in the reaction of nitriles and ethylenediamine under ultrasonic irradiation.

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

In conclusion, a simple and efficient procedure for the synthesis of 2-imidazolines and bis-imidazolines has been developed. Mild reaction conditions, absence of solvent, short reaction times, easy and quick isolation of the products, excellent yields and large scale applicability are the main advantages.

Compound **2a**: Mp 100–101 °C (lit.[16] 101–102 °C). ^{1}H NMR ($CDCl_3$):[15b] $\delta = 3.75$ (s, 4H, $2CH_2$), 4.8 (s, 1H, NH), 7.30–7.40 (m, 2H, ArH), 7.70–7.81 (m, 3H, ArH); IR (KBr): 3190 (NH), 1598 (C=N) cm^{-1}.

Compound **2b**: Mp 177–179 °C (lit.[15] 175–176 °C). ^{1}H NMR ($CDCl_3$):[15b] $\delta = 2.38$ (s, 3H, CH_3), 3.75 (s, 4H, $2CH_2$), 4.45 (s, 1H, NH), 7.15 (d, 2H, $J =$ ArH), 7.63 (d, 2H, $J =$ ArH). IR (KBr): 3130 (NH), 1598 (C=N) cm^{-1}.

Compound **2c**: Mp 186–188 °C (lit.[16] 185–187 °C). ^{1}H NMR ($CDCl_3$):[25] $\delta = 3.75$ (s, 4H, $2CH_2$), 4.22 (s, 1H, NH), 7.30 (d, 2H, $J =$ ArH), 7.93 (d, 2H, $J =$ ArH). IR (KBr) 3140 (NH), 1590 (C=N) cm^{-1}.

Compound **2d**: Mp 133–135 °C. ^{1}H NMR ($CDCl_3$):[26] $\delta = 3.76$ (s, 4H, $2CH_2$), 4.25 (s, 1H, NH), 7.22–7.75 (m, 4H, ArH). IR (KBr): 3140 (NH), 1595 (C=N) cm^{-1}.

Compound **2e**: Mp 134–135 °C (lit.[14] 136–137 °C). ^{1}H NMR ($CDCl_3$):[27] $\delta = 3.79$ (s, 4H, $2CH_2$), 4.30 (s, 1H, NH), 7.61 (d, 2H, $J =$ ArH), 8.65 (d, 2H, $J =$ ArH). IR (KBr): 3180 (NH), 1594 (C=N) cm^{-1}.

Compound **2f**: Mp 111–113 °C (lit.[14] 106–107 °C). ^{1}H NMR ($CDCl_3$):[27] $\delta = 3.78$ (s, 4H, $2CH_2$), 4.54 (s, 1H, NH), 7.20–7.38 (m, 1H, ArH), 8.02–8.15 (m, 1H, ArH), 8.60–8.67 (m, 1H, ArH), 8.92 (s, 1H, ArH). IR (KBr): 3150 (NH), 1586 (C=N) cm^{-1}.

Compound **2g**: Mp 101–102 °C. ^{1}H NMR ($CDCl_3$):[28] $\delta = 3.81$(s, 4H, $2CH_2$), 5.38 (s, 1H, NH), 7.22–7.38 (m, 1H, ArH), 7.62–7.85 (m, 1H, ArH), 8.12 (d, 1H, $J =$ ArH), 8.55 (d, 1H, $J =$ ArH). IR (KBr): 3240 (NH), 1594 (C=N) cm^{-1}.

Compound **2h**: Mp 139–140 °C (lit.[16] 138–140 °C). ^{1}H NMR ($CDCl_3$):[4] $\delta = 3.74$ (s, 4H, $2CH_2$), 3.81 (s, 3H, CH_3), 4.42 (s, 1H, NH), 6.87 (d, 2H, $J =$ ArH), 8.70 (d, 2H, $J =$ ArH). IR (KBr): 3170 (NH), 1605 (C=N) cm^{-1}.

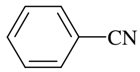
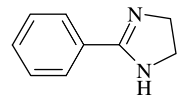
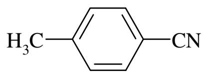
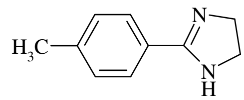
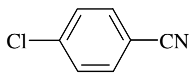
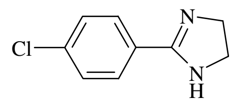
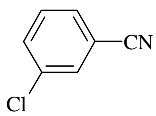
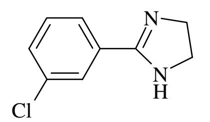
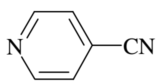
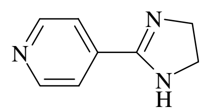
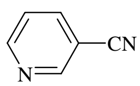
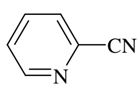
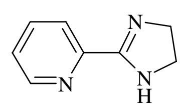
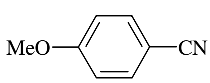
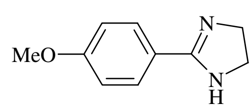
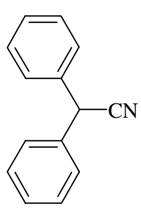
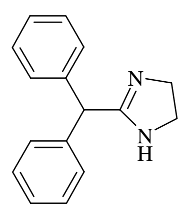
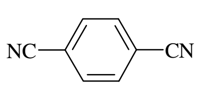
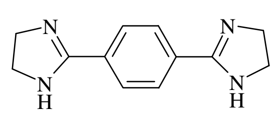
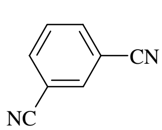
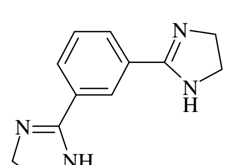
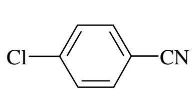
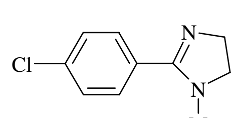
Compound **2i**: Mp 156–157 °C. ^{1}H NMR ($CDCl_3$): $\delta = 3.00$ (s, 1H, NH), 3.59 (s, 4H, $2CH_2$), 5.05 (s, 1H, CH), 7.25–7.30 (m, 10H, ArH). IR (KBr): 3180 (NH), 1594 (C=N) cm^{-1}. Elemental analysis calculated for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85%. Found: C, 81.21; H, 6.91; N, 11.71%.

Compound **2j**: Mp 312 °C (lit.[15] 318 °C). ^{1}H NMR (DMSO-d_6):[15b] $\delta = 3.60$ (s, 8H, $2CH_2$), 6.94 (s, 2H, NH), 7.83 (s, 4H, ArH). IR (KBr): 3180 (NH), 1576 (C=N) cm^{-1}.

Compound **2k**: Mp 242 °C (lit.[15] 244 °C). ^{1}H NMR (DMSO-d_6):[15b] $\delta = 3.60$ (s, 8H, $2CH_2$), 6.88 (s, 2H, NH), 7.45 (m, 1H, ArH), 7.86 (d, 2H, $J =$ ArH), 8.29 (s, 1H, ArH). IR (KBr): 3150 (NH), 1565 (C=N) cm^{-1}.

Compound **2l**: Oily yellow compound. ^{1}H NMR ($CDCl_3$): $\delta = 2.66$ (s, 3H, CH_3), 3.36 (t, 2H, $J = CH_2$), 3.71 (t, 2H, $J = CH_2$), 7.25 (d, 2H, $J =$ ArH), 7.43 (d, 2H, $J =$ ArH). IR: 1318 (N–CH_3), 1603 (C=N) cm^{-1}. Elemental analysis calculated for $C_{10}H_{11}ClN_2$: C, 61.70; H, 5.70; N, 14.39%. Found: C, 61.65; H, 5.78; N, 14.21%.

Table 2. Synthesis of imidazolines and bis-imidazolines under ultrasonic irradiation[a]

Entry	Substrate		Product	Time (min)	Yield[b] (%)
1a		**2a**		5	90
1b		**2b**		15	89
1c		**2c**		7	88
1d		**2d**		7	89
1e		**2e**		5	95
1f		**2f**		5	93
1g		**2g**		7	90
1h		**2h**		20	89
1i		**2i**		15	92
1j		**2j**		5	85
1k		**2k**		5	84
1l		**2l**		30	90[c]

[a] Reaction conditions: nitrile (10 mmol), EDA (40 mmol) and sulfur (2.5 mmol).
[b] Isolated yields.
[c] *N*-Methylethylenediamine was used instead of ethylenediamine.

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23. *General procedure for the preparation of 2-imidazolines and bis-imidazolines under ultrasonic irradiation:* All reactions were carried out at room temperature in a 40 mL glass reactor. A UP 400S ultrasonic processor equipped with a 3 mm wide and 140 mm long probe, which was immersed directly into the reaction mixture, was used for sonication ^{1}H NMR spectra were recorded on a Bruker-Arance AQS 300 MHz. A mixture of nitrile (10 mmol), ethylenediamine (40 mmol) and sulfur (2.5 mmol) was irradiated with ultrasonic waves for 5–30 min. After completion of the reaction as indicated by TLC (eluent: EtOAc/MeOH, 4:1), cold water was added and the mixture extracted with chloroform. The organic layer was dried (Na_2SO_4) and evaporated. Recrystallization of the crude product (**2a** was recrystallized from cyclohexane, **2b**–**i** were recrystallized from *n*-hexane and, **2j** and **2k** were recrystallized from methanol) gave the pure product in 84–95% yields based on the starting nitrile (Table 2).
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