

# One-pot synthesis of imidazolines from aldehydes: detailed study about solvents and substrates

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**Abstract**—Imidazolines were prepared in one-pot operation from aldehydes and diamines through oxidation of aminal intermediates by NBS. This method could be applied to various aromatic and aliphatic aldehydes and *N*-nonsubstituted and *N*-monosubstituted 1,2-diamines. Furthermore, it was found that CH<sub>2</sub>Cl<sub>2</sub> could be altered to TBME, a more environmentally friendly solvent, in the reaction using *N*-nonsubstituted 1,2-diamines. The reaction conditions were very mild and chemoselective.

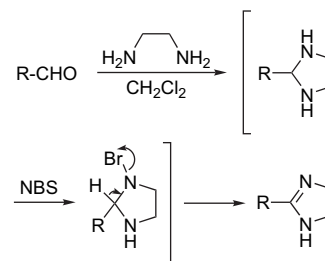
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## 1. Introduction

The importance of imidazolines in biochemistry has recently increased, since they are found in many biologically active compounds.<sup>1</sup> They are also used in organic synthesis as synthetic intermediates,<sup>2</sup> chiral ligands,<sup>3</sup> chiral auxiliaries,<sup>4</sup> and so on. Furthermore, many oxidizing methods of imidazolines to imidazoles, which are also found in many biological compounds, have been reported.<sup>5</sup> Development of an efficient method to synthesize imidazolines is a very important issue in the synthetic organic field. Many methodologies have been developed so far. Most of them are the methods using nitriles<sup>6</sup> and esters<sup>7</sup> as starting materials. However, these previous methods have several drawbacks. They need a high reaction temperature or acidic conditions. Furthermore, in the case of nitrile compounds, the use of highly toxic cyanide is necessary for their preparation. Although several new methods have recently been reported<sup>8</sup> to overcome these drawbacks, they must use special starting materials such as azalactones,<sup>8a</sup> 2-aryl-1,1-dibromoethanes,<sup>5c</sup> and amino amides.<sup>8b</sup> The development of simple methods that overcome the previous drawbacks is strongly desirable.

We recently communicated an efficient one-pot synthesis of imidazolines.<sup>9</sup> Thus, the first condensation of aldehydes and diamines forms aminals without any catalyst in CH<sub>2</sub>Cl<sub>2</sub>. Next, the addition of *N*-bromosuccinimide (NBS) oxidizes them to afford imidazolines in the one-pot operation (Scheme 1). This reaction is the first method to prepare imidazolines from aldehydes and has several advantages, such

as mild reaction conditions, low reaction temperature (0 °C–rt), and the use of an almost neutral reagent (NBS). After our study, several methods to prepare imidazolines from aldehydes were reported.<sup>5g,10</sup>



Scheme 1.

On the other hand, from the point of green chemistry, it is desirable not to use the halogen containing solvents. However, our reported method used CH<sub>2</sub>Cl<sub>2</sub>. We then tried to use other solvents, which do not contain halogen atoms, in our method. We discovered that the *tert*-butyl methyl ether (TBME) is as effective as CH<sub>2</sub>Cl<sub>2</sub>.

Herein, we report the improvement of our imidazoline synthetic method by altering the solvent for an environmentally friendly reaction and the generality of the reaction using aromatic and aliphatic aldehydes and *N*-nonsubstituted and *N*-substituted diamines.

## 2. Results and discussion

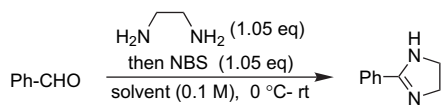
First, we examined the reaction in various solvents using benzaldehyde and ethylenediamine (Table 1). The reaction in CH<sub>2</sub>Cl<sub>2</sub> proceeded in excellent yield (entry 1). On the

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Table 1



Entry	Solvent	Yield (%)
1	CH <sub>2</sub> Cl <sub>2</sub>	99
2	AcOEt	73
3	THF	76
4	Toluene	75
5	TBME	99

other hand, the reactions in AcOEt, THF, and toluene resulted in moderate and insufficient yields (entries 2–4). However, the reaction in TBME proceeded similar to that in CH<sub>2</sub>Cl<sub>2</sub> (entry 5). Here, we have improved our reaction to an environmentally friendly one. We then examined the generality of the reaction in CH<sub>2</sub>Cl<sub>2</sub> and TBME.

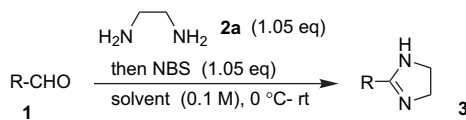
The results from the reactions of ethylenediamine and various aldehydes in both CH<sub>2</sub>Cl<sub>2</sub> and TBME are shown in Table 2. As shown in entries 1–8, the reactions using various aromatic aldehydes having electron donating groups (entries 2 and 6) or electron withdrawing groups (entries 3, 4, and 7) and pyridine aldehyde (entry 8) proceeded well to give the corresponding imidazolines in good yields. It is noteworthy that aldehydes having a nitrile or an ester were selectively converted to imidazolines without affecting the functional groups (entries 3 and 4), although such functional groups were used as starting materials in the previous methods. The

reactions of aliphatic aldehydes, the primary one (entry 9), the unsaturated one (entry 10), the primary one with benzoate ester (entry 11), and the secondary one (entry 12), also proceeded well. Most of the aldehydes gave almost the same results in CH<sub>2</sub>Cl<sub>2</sub> and TBME, whereas in some cases, the yields of the products in TBME tend to be decreased probably due to the lower solubility of the aminor intermediates in the solvent (entries 3, 4, 9, and 10).

Table 3 shows the results of the reactions of various typical aldehydes and (*dl*)-*trans*-1,2-diphenylethylene-1,2-diamine. Since the studies about asymmetric reactions using chiral imidazolines as chiral ligands are increasing,<sup>3</sup> diphenylethylenediamine is a very popular chiral diamine.<sup>11</sup> In these cases, the reactions of both the aromatic and aliphatic aldehydes proceeded in high yields regardless of the solvent.

Lastly, we studied the reactions using some *N*-monosubstituted diamines (Table 4). The reactions of *N*-benzyl ethylenediamine **2c** with both aromatic and aliphatic aldehydes resulted in moderate yields both in CH<sub>2</sub>Cl<sub>2</sub> and TBME (entries 1 and 2). The *N*-benzyl ethylenediamine decreased the yields more than ethylenediamine (Table 2, entries 1 and 9). This is probably because the formation of the intermediates, aminorals, is difficult due to the *N*-substituent. We also studied the reactions of the diamines **2d** and **2e** prepared from phenylalanine. Various *N*-monosubstituted diamines such as **2d** and **2e** are easily prepared from amino acids. The *N*-benzyl substituted diamine **2d** resulted in good yields in CH<sub>2</sub>Cl<sub>2</sub>, whereas the yields of the imidazolines in TBME are not good (entries 3 and 4). The results in entries 1–4 show

Table 2



Entry	R-CHO	Product yield in CH <sub>2</sub> Cl <sub>2</sub> , TBME (%)	Entry	R-CHO	Product yield in CH <sub>2</sub> Cl <sub>2</sub> , TBME (%)
1		<b>3a</b> (99, 99)	7		<b>3g</b> (83, 85)
2		<b>3b</b> (94, 96)	8		<b>3h</b> (100, 99)
3		<b>3c</b> (95, 80)	9		<b>3i</b> (96, 77)
4		<b>3d</b> (94, 76)	10		<b>3j</b> (87, 73)
5		<b>3e</b> (96, 98)	11		<b>3k</b> (98, 98)
6		<b>3f</b> (83, 84)	12		<b>3l</b> (85, 81)

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