

# Dowex-50W-Promoted Synthesis of Oxazoline, Imidazoline and Thiazoline Derivatives

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**Abstract:** Dowex-50W-hydrogen ion exchange resin was used as a reusable catalyst for the synthesis of oxazoline, imidazoline and thiazoline derivatives through condensation reaction between aryl nitriles and 2-aminoalcohol, ethylenediamine or 2-aminoethanethiol. This process provides several advantages such as excellent yields of the products, simple operation, convenient separation and inexpensive and recyclable catalyst.

**Keywords:** Dowex-50W, oxazoline, imidazoline, thiazoline, recyclable catalyst.

## 1. INTRODUCTION

One of the main themes of contemporary synthetic organic chemistry is the development of atom-economic and environmentally benign catalytic systems [1]. In this context, the development of heterogeneous catalysis is of prime importance not only from the economic point of view, but also due to the easy work-up procedures involved in the separation of the catalyst products from reactions mixture. Accordingly, various solid acids such as zeolites, clays, alumina, heteropolyacids, and acidic resins have been tested in heterogeneous system [2-5]. Each catalyst has its own advantages and disadvantages. It is always interesting to develop a new environmental benign catalyst for organic transformations.

On the other hand, heterocyclic compounds occur very widely in nature and are essential to life. Nitrogen-containing heterocyclic molecules constitute the largest portion of chemical entities, which are part of many natural products, fine chemicals, and biologically active pharmaceuticals vital for enhancing the quality of life [6]. Among a large variety of nitrogen-containing heterocyclic compounds, heterocycles containing an oxazoline, imidazoline and thiazoline moiety are of interest because they constitute an important class of natural and synthetic products, many of which exhibit useful biological activities and clinical applications [7-11]. Furthermore, these compounds, have recently received great attention because of their wide range of therapeutic and biological properties, such as antihypertensive [12], antidiabetic [13], anticancer [14, 15] and antialzheimer [16] activities. They are also known as important intermediates in organic transformations [17].

Various procedures have been disclosed in order to synthesize oxazoline, imidazoline and thiazoline derivatives by employing precursors such as aldehydes [18], amides [19], esters [20], aziridines [21], and nitriles [22-26]. In spite

of potential utility of aforementioned routes for the synthesis of oxazoline, imidazoline and thiazoline derivatives, many of these methods involve expensive reagents, strong acidic conditions, long reaction times, low yields and use of toxic organic solvents. Therefore, to avoid these limitations, the discovery of a new and efficient catalyst with high catalytic activity, short reaction time, recyclability and simple work-up for the preparation of these compounds under neutral, mild and practical conditions is of prime interest. The aim of this study is to utilize the Dowex-50W ion exchange resin as catalyst for the synthesis of oxazoline, imidazoline and thiazoline derivatives.

## 2. EXPERIMENTAL

Melting points were measured on an Electrothermal 9200 apparatus and are uncorrected. IR spectra were recorded on FT-IR 102MB BOMEM apparatus.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were determined on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Dowex-50W-hydrogen ion exchange resin was purchased from Aldrich and used as received.

### 2.1. General Procedure for the Preparation of Oxazolines, Thiazolines and Imidazolines (3)

A mixture of nitrile (1 mmol), 2-aminoalcohol, ethylenediamine or 2-aminoethanethiol (2 mmol) and resin (0.2 g) was heated at 80 °C for an appropriate time. The reaction monitored TLC. After cooling to r.t., reaction mixture was washed with EtOH (10 mL) and catalyst was filtered off. The solvent was evaporated and the crude product was purified by recrystallization in n-hexane or by column chromatography.

All the products are known compounds and were characterized by IR and NMR spectroscopic data and their melting points are compared with the reported values [22-26].

*2-phenyl-4,5-dihydro-1H-imidazole (7a)*: mp 99-101 °C; IR (KBr) ( $\nu_{\text{max}}$ ,  $\text{cm}^{-1}$ ): 3210, 1603;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  3.74 (4H, s, 2CH<sub>2</sub>), 4.95 (1H, s, NH), 7.32-7.71 (5H, m, H-Arom.);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  50.5, 115.2, 128.5, 133.3, 135.2, 165.7. MS ( $m/z$ , %): 146 ( $\text{M}^+$ , 15), 144 (35), 77 (100).

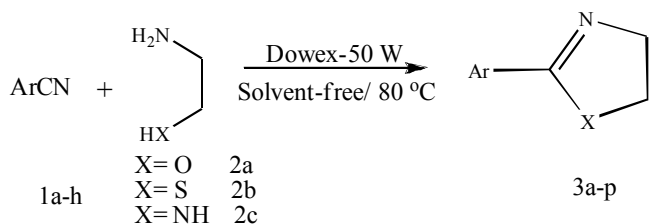
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2-(pyridin-4-yl)-4,5-dihydrothiazole (**5d**): m.p. 75-77 °C; IR (KBr) ( $\nu_{\max}$ ,  $\text{cm}^{-1}$ ): 3007, 1598  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{H}}$  3.46 (2H, t,  $J = 8.8$  Hz,  $\text{CH}_2\text{S}$ ), 4.49 (2H, t,  $J = 8.7$  Hz,  $\text{CH}_2\text{N}$ ), 7.70-8.67 (4H, m, H-Arom.);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta_{\text{C}}$  33.4, 51.6, 124.1, 142.6, 149.0, 159.9; MS ( $m/z$ , %): 165 ( $M^+ + 1$ , 20), 136 (45), 78 (100).

### 3. RESULTS AND DISCUSSION

Considering the above reports and in continuation of our previous works on the application of heterogeneous catalysts for development of useful synthetic methodology [27-30], we wish to report a simple, efficient and practical approach for the synthesis of oxazoline, imidazoline and thiazoline derivatives using Dowex-50W ion exchange resin as eco-friendly catalysts with high catalytic activity under solvent-free conditions.

The reaction conditions were optimized by examining the amount of catalyst for the reaction involving 4-chlorobenzonitrile (**1b**) (1 mmol) and 2-aminoalcohol (**2a**) (2 mmol) to afford the product (**3b**) under solvent-free conditions at 80 °C (Scheme 1). The best results was obtained with a 0.2 g catalyst under solvent-free conditions and gave 2-(4-chlorophenyl)-4,5-dihydrooxazole (**3b**) in high yield.



**Scheme 1.** Preparation of oxazolines, imidazolines and thiazolines catalyzed by Dowex-50.

Dowex-50W ion exchange resin catalyzed the condensation of 2-aminoalcohol (**2a**) or 2-aminoethanethiol (**2b**) or ethylenediamine (**2c**) and a wide range of aromatic nitriles (**1**) under solvent-free conditions at 80 °C. As indicated in Table 1, in all cases the reaction gives the products in good yields and prevents problems which many associate with solvent use such as cost, handling, safety and pollution. In these experiments, the isolation of the catalyst from reaction mixture could be easily performed by its suspension in EtOH. The used catalyst was dried at 50 °C for 1h and then reloaded with fresh reagents for further runs. Apparently, recycling of catalyst is possible for four successive times without significant loss of activity (Table 1, entries **2b**, **2g** and **2m**). Finally, it should be mentioned when reactions were carried out in the absence of catalyst for long period of time (12 h.) and in solvent-free conditions at 80 °C the yields of products were low (< 40%).

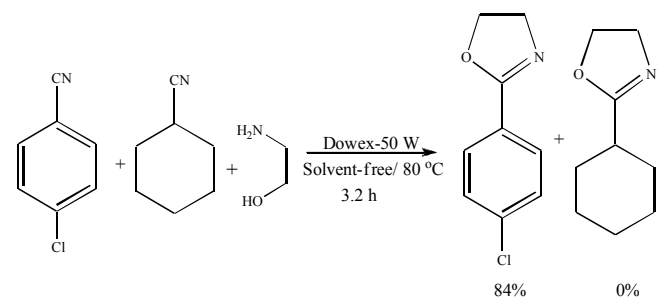
Under the same conditions, this reaction almost could not be observed when the alkylnitrile was used as a starting material. Therefore, the chemoselectivity of this method was demonstrated using equimolar mixture of aryl nitrile and alkylnitrile. Smooth conversion of the aryl nitrile to the corresponding oxazoline was observed while the alkylnitrile remained unaffected (Scheme 2).

**Table 1.** Preparation of Product 3 Using Dowex-50W Ion Exchange Resin

Product 3	Ar	X	Time (h)	Yield (%) <sup>a</sup>
a	C <sub>6</sub> H <sub>5</sub>	O	3.5	85
b	4-Cl-C <sub>6</sub> H <sub>4</sub>	O	3.2	87 (86,87,85) <sup>b</sup>
c	3-Cl-C <sub>6</sub> H <sub>4</sub>	O	3.5	85
d	4-Me-C <sub>6</sub> H <sub>4</sub>	O	4	81
e	4-CN-C <sub>6</sub> H <sub>4</sub>	O	3	86
f	C <sub>6</sub> H <sub>5</sub>	S	0.3	91
g	4-Cl-C <sub>6</sub> H <sub>4</sub>	S	0.3	93 (93,91,92) <sup>c</sup>
h	4-Me-C <sub>6</sub> H <sub>4</sub>	S	0.3	90
i	4-CN-C <sub>6</sub> H <sub>4</sub>	S	0.3	91
j	4-MeO-C <sub>6</sub> H <sub>4</sub>	S	0.5	88
k	4-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	S	0.3	91
l	C <sub>6</sub> H <sub>5</sub>	NH	3	74
m	4-Cl-C <sub>6</sub> H <sub>4</sub>	NH	3.5	90 (89,90,88) <sup>c</sup>
n	4-Me-C <sub>6</sub> H <sub>4</sub>	NH	5	75
o	4-CN-C <sub>6</sub> H <sub>4</sub>	NH	3.3	86
p	4-MeO-C <sub>6</sub> H <sub>4</sub>	NH	6	74

<sup>a</sup>Isolated yields.

<sup>b</sup>Isolated yield after recycling of catalyst.



**Scheme 2.** Chemoselective synthesis of aryl oxazolines vs alkyl oxazolines.

### 4. CONCLUSION

In conclusion, we have developed a simple, efficient and green protocol for the synthesis of oxazoline, imidazoline and thiazoline derivatives using Dowex-50W under solvent-free conditions. The simple work-up, a good yield, mild reaction conditions and recyclability of catalyst are features of this new procedure.

### ACKNOWLEDGMENTS

We gratefully acknowledge the financial support from the Research Council of Shahid Beheshti University and CCE (Catalyst Center of Excellence).

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Received: June 29, 2009

Revised: August 25, 2009

Accepted: August 26, 2009

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