



Efficacious and rapid metal- and solvent-free synthesis of enantiopure oxazolines



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ABSTRACT

A rapid and efficient synthesis of oxazolines was performed starting from various nitriles using microwave irradiation combined to metal- and solvent-free conditions to afford high to quantitative yields of the targeted heterocycles.

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1. Introduction

Optically active oxazoline derivatives have attracted a great deal of attention due to their high efficiency and versatility as protecting groups,^{1,2} chiral auxiliaries,³ and ligands for asymmetric catalysis.⁴ The latter area has witnessed an exponential development due to the first independent reports by Corey and Evans in 1991.⁵ Since then, mono or bisoxazolines have appeared as privileged ligands in the expanding field of enantioselective transformations⁶ that not only generated progresses in mechanistic aspects but also extensive efforts of the scientific community to design new oxazoline-based catalytic systems and facilitate the preparation of this key heterocycle.

In addition, the development of catalytic enantioselective transformations paved the way for the preparation of enantiopure oxazoline derivatives. Therefore, various procedures have been reported in order to synthesize oxazoline derivatives from carboxaldehydes,⁷ carboxylic acid derivatives,^{8,9} or nitrile precursors.^{10–13} In spite of the potential utility of the aforementioned routes, many of these methods involve expensive or metallic reagents, strongly acidic or harsh conditions, require long reaction times, and need a large amount of organic solvents. Such parameters appear nowadays as severe drawbacks. Therefore, to avoid these limitations, the development of new and efficient alternatives combining high yields, short reaction times, and green conditions (mild, practical, metal-free, solvent free, and non-conventional activation methods) is highly desirable.

During our studies devoted to the incorporation of nitriles in various molecular architectures and their reactivity toward nucleophiles,¹⁴ we became interested in the preparation of oxazolines

from nitriles. In this context, oxazolines can be obtained by Witte and Seeliger's¹⁵ procedure involving nitriles and aminoalcohols in the presence of catalytic amounts of metal salts. Most commonly, oxazolines are obtained through either a two-step condensation/cyclization sequence starting from nitriles in the presence of metal salts,^{16–18} or strong Brønsted acids¹⁹ or by stepwise formation of the corresponding imidates²⁰ followed by cyclization. Initially limited to mononitrile substrates, this methodology has been since revisited by several groups in order to improve the efficiency of the transformation. Indeed, catalytic amounts of ZnCl₂ or Zn(OTf)₂ in refluxing chlorobenzene or toluene under anhydrous conditions,¹⁶ Cd(OAc)₂-mediated condensation of a large excess of aminoalcohols for prolonged reaction times (4–5 days in refluxing chlorobenzene),²¹ account for the optimum experimental conditions. Several heterogeneous or biopolymer-based catalysts such as Dowex-50W-hydrogen ion exchange resin,²² natural Kaolinitic Clay,²³ silica sulfuric acid (SSA) under ultrasonic irradiation or refluxing conditions,²⁴ tungstophosphoric acid (H₃PW₁₂O₄₀),²⁵ cellulose sulfuric acid (CSA),²⁶ and trichloroisocyanuric acid (TCCA)²⁷ and more recently, Fe₃O₄ supported Pd(0) nanoparticles (Pd/Fe₃O₄)²⁸ and S/Co(NO₃)₂ under thermal or MW conditions,²⁹ have been also reported.

Herein we report the one pot preparation of 2-oxazolines starting from nitriles using an equimolar amount of various aminoalcohols under microwave, metal-free, and solvent-free reaction conditions.

2. Results and discussion

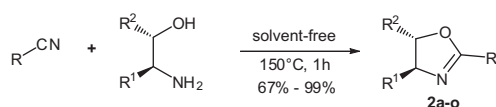
In continuation of our studies concerning the application of useful synthetic microwave methods,³⁰ we describe herein a simple, efficient, and high-yielding microwave-mediated procedure for the synthesis of 2-oxazoline derivatives by the reaction of nitriles

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with 2-aminoalcohols. In order to find the optimum reaction conditions, we screened different molar ratios of substrates and catalyst, at various temperatures and in different polar and non-polar solvents. It is noteworthy that solvent-free conditions were not only beneficial in reagents' cost but also more efficient than conditions including a solvent.

Using microwave irradiation at 150 °C in the absence of any catalyst and any solvent, the reaction was completed in only 1 h affording the expected oxazoline. From both an economical and efficiency point of view, to the best of our knowledge, our method afforded a better overall compromise by comparison with known reported procedures. To further investigate the beneficial effect of the microwave-assisted construction of oxazolines the following series of condensations were performed using various aminoalcohols. In order to extend the scope of our methodology, we focused on the preparation of oxazoline derivatives from various aromatic and heterocyclic nitriles. Seventeen enantiopure oxazolines were prepared using different 2-aminoalcohols under microwave, solvent-free conditions as shown in Scheme 1.



Scheme 1.

In the azine series, pyrazin-, pyridine-, and quinoline-2-carbonitriles were subjected to the aforementioned conditions. Various aminoalcohols including L-phenylalaninol, L-phenylglycinol, L-valinol, L-alaninol, and 1-amino-2-propanol afforded the corresponding oxazolines **2a–g** in yields ranging from 73% to 98%. These reaction conditions were also successfully applied to 5-chlorothiophene-2-carbonitrile which could be converted into the corresponding oxazolines **2h** and **2i** in 95–98% yields.

These reactants were successfully used in our earlier work devoted to the synthesis of oxazolines. The synthesis of oxazolines **2** was accomplished by using an alternate method. All targeted oxazolines were characterized by TOF-MS and NMR techniques. Most importantly, the specific rotation and HPLC data of these products confirmed full conservation of stereochemical information, thus evidencing the presence of one single enantiomer. The enantiomeric purity was unequivocally established by HPLC using a chiral OJ-H column (heptane/2-propanol, 95:5, 1.0 mL/min, 30 °C).

The reaction of 2-cyanoquinoline with (L)-valinol gave the (S)-(–)-4-isopropyl-2-(2-quinoline)oxazoline **2g** with an enantiomeric purity of >99% as determined by comparison of the specific rotation with a literature value.³¹ The oxazoline **2g** was obtained in 73% yield and high purity (ee >99% at t_R = 14.245 min starting from (D)-valinol; ee >99% at t_R = 12.865 min starting from (L)-valinol and for racemic valinol area = 49.57% at t_R = 12.933 min and area = 50.43% at t_R = 14.250 min). This sequence has been proven to be highly amenable to parallel, semi-automated methods of synthesis.

We next moved from heterocyclic substrates to benzo- and naphtho-nitrile starting materials. As shown in Figure 1, our method was again successful within this series. We were thus able to prepare the corresponding (S)-4-benzyl-2-(naphthalen-1-yl)-4,5-dihydrooxazole **2m** and (S)-4-isopropyl-2-(naphthalen-1-yl)-4,5-dihydrooxazole **2n** in 76% and 70% yields, respectively, from naphthalenecarbonitrile under microwave activation at 240 °C for 100 min. Some derivatives such as chloro- and fluorobenzene were also tested. In these cases, an increase of the temperature from 210 °C to 240 °C for 4-chlorobenzonitrile and from 180 °C to 240 °C for 4-fluorobenzonitrile respectively ensured complete conversion of the starting material leading to high yields of **2q** and **2o**. In both cases, our method was again superior to the literature reported procedures in terms of yields, number of steps, and convenience.^{32,33} Finally, cyclopropylcarbonitrile and pyruvonitrile were tested in order to extend our methodology to chiral

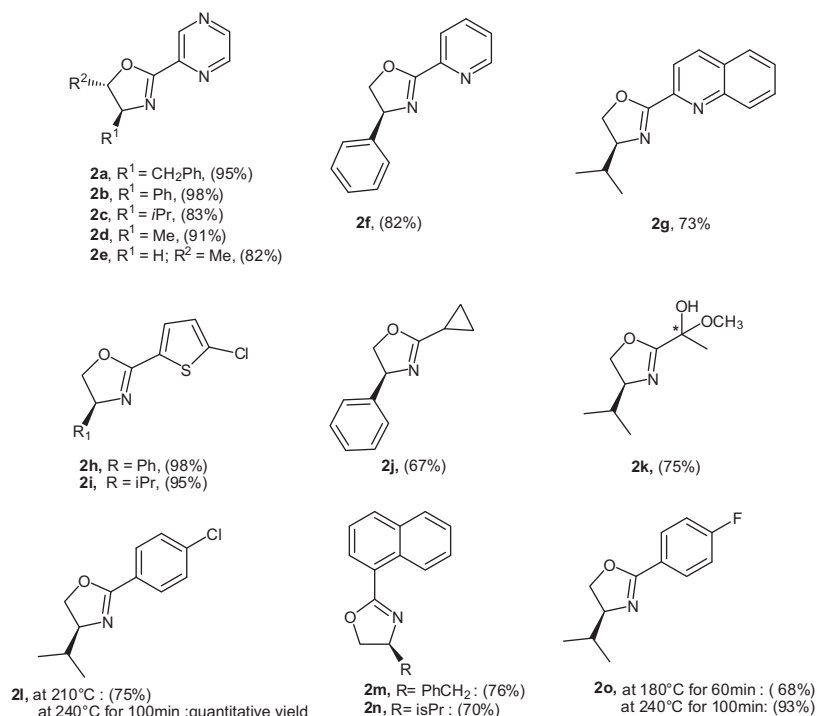


Figure 1. General conditions: nitrile substrate (1 equiv), aminoalcohol (1.1 equiv), solvent-free conditions, MW. 150 °C and 1 h except for oxazolines **2l**, **2m**, **2n**, **2o** that require 240 °C for 100 min.

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