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Joint use of microwave and glycerol-zinc (II) acetate catalytic system in the synthesis of 2-pyridyl-2-oxazolines[1)]

Abstract: Glycerol combined with zinc (II) acetate catalyzed the reaction of 2-amino alcohols and 2-cyanopyridines under microwave irradiation, resulting in 2-pyridyl-2-oxazolines. Comparing the conversion to that obtained by conventional heating, a significant decrease in the reaction time was achieved. At the end of the reaction, the product was isolated and the glycerol-zinc (II) acetate catalytic system was recycled four times for the same transformation in reasonable to acceptable yields. The products were obtained in their pure form by simple filtration in a short pad of silica.

Keywords: 2-pyridyl-2-oxazoline; glycerol-zinc (II) acetate catalyst; microwave irradiation.

[1)]Supplementary material to this article can be found at: http://www.degruyter.com/view/j/gps.

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1 Introduction

The 2-oxazoline unit is present in a variety of biologically active compounds [1] and has received attention because of its applications in organic synthesis as a protecting group [2], a polymerization precursor [3–7] and particularly, as a catalyst for many transformations, including chirality induction/transference [8–13]. 2-Pyridyl-2-oxazolines are interesting ligands for metal complex precursors, which makes them good candidates for metal-catalyzed transformations. A myriad of well-established procedures for the preparation of optically active 2-oxazolines is known, however, many of the procedures are unappealing with regards to energy expenditure and reaction times [2, 14–21]. In 2009, Kempe and co-workers reported a clean zinc (II) acetate-catalyzed synthesis of 2-oxazolines from nitriles and 2-aminoethanol by conventional heating (130°C), using chlorobenzene as the solvent [22]. Although several nitriles were submitted to a reaction with 2-aminoethanol in the presence of various catalysts, only a few examples resulted in the product of interest. In addition, some cases required long reaction times to achieve the desired product in reasonable yields for preparative purposes. Recently, procedures involving the preparation of 2-oxazolines under microwave irradiation have been reported [23, 24].

Recently, glycerol is being produced in large quantities as a byproduct of the biodiesel industry, and traditional consumption of this commodity is not sufficient to uptake its surplus. Glycerol can be considered a green solvent, being found in many living organisms as triglycerides [25–34]. Because of the above-mentioned reasons, attention has been directed to new applications for glycerol, one of the most promising of which is its use as a green solvent. Considering that the transformation industry is deeply dependent on organic solvents, those based on renewable sources are the most attractive so far.

In this work we present our results concerning the association of glycerol and zinc (II) acetate as a renewable green reaction media for the preparation of 2-oxazolines under microwave irradiation in good yields and with short reaction times.

2 Experimental section

2.1 General information

Microwave reactions were performed with a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC, USA), with a continuous focused microwave power delivery system in a glass vessel (10 ml) sealed with a septum pierced by a needle (for the ammonia realizing), under magnetic stirring.

Nuclear magnetic resonance (NMR) spectra were recorded on a BRUKER AC 200 spectrometer operating at 200 MHz and 50 MHz for ^{1}H NMR and ^{13}C NMR, respectively (Bruker BioSpin GmbH, Rheinstetten, Baden-Württemberg, Germany). $CDCl_3$ was used as the solvent and as internal references, tetramethylsilane (TMS) for ^{1}H NMR and $CDCl_3$, for ^{13}C NMR, chemical shifts (δ) are given in parts per million and coupling constants (J) in hertz.

Gas chromatography analyses were performed on Shimadzu GC2014 devices (Shimadzu Corp., Nakagyo-ku, Kyoto, Japan), using a flame ionization detector (FID), N_2 as carrier gas and equipped with a DB-5-HT (5% – phenylmethylpolysiloxane) column with dimensions 30 m×0.32 mm×0.10 μm (Agilent Technologies, Inc., Santa Clara, CA, USA).

High performance liquid chromatography (HPLC) analyses were performed on a Shimadzu LC-30AD device equipped with a UV-Vis SPD-M20A detector, using a Chiralpak AD-H (Chiral Technologies Europe, Illkirch Graffenstaden, Bas Rhin, France) column with dimensions 4.6 mm×250 mm and hexane:isopropanol (9:1) as a mobile phase, with 1.0 ml/min flow.

Optical rotation analyses were performed on a Perkin-Elmer 241 polarimeter (PerkinElmer, Inc., Waltham, MA, USA) with a D ray sodium lamp.

All reagents are commercial grade and were pretreated before use, when needed (All reagents were purchased from Sigma-Aldrich Corporation, St. Louis, MO, USA).

2.2 Microwave-promoted synthesis of 2-pyridyl-2-oxazolines

2.2.1 General procedure

Appropriate amino alcohol (2 mmol), 2-cyanopyridine (1, 0.104 g, 0.096 ml, 1 mmol), zinc acetate dihydrate (0.004 g, 0.02 mmol, 2 mol%) and glycerol (1 ml) were mixed into a glass vessel sealed with a septum pierced by a needle. This reaction vessel was placed into the microwave reactor and heated at 110°C for 17 min under stirring. After cooling to room temperature, the product was extracted from the reaction mixture by washing with ethyl acetate (5×2 ml). The ethyl acetate phases were combined and washed with water (2×5 ml), then dried with Na_2SO_4. After filtration, the solvent was removed under reduced pressure. The crude product was filtered though a plug of silica gel, and the filter cake was washed with ethyl acetate (5×2 ml). After evaporation of the solvent, pure 2-pyridyl-2-oxazolines were obtained.

4,4-dimethyl-2-(pyridin-2-yl)-2-oxazoline (3)
CAS 109660-12-0
86% yield.

NMR ^{1}H (400 MHz, $CDCl_3$): δ 1.42 (s, 6H), 4.21 (s, 2H), 7.39 (ddd *J*1=7.7 Hz, *J*2=4.8 Hz, *J*3=1.2 Hz, 1H), 7.77 (td, *J1*=7.7 Hz, *J*2=1.8 Hz, 1H), 8.03 (dt, *J1*=7.7 Hz, *J*2=1.1 Hz, 1H), 8.71 (ddd, *J1*=4.8 Hz, *J*2=1.8 Hz, *J3*=1.0 Hz, 1H).

NMR ^{13}C (100 MHz, $CDCl_3$): δ 28.3, 67.7, 79.5, 123.7, 125.3, 136.4, 146.9, 149.6, 161.1.

4,4-dimethyl-2-(pyridin-2-ylmethyl)-2-oxazoline (5)
CAS 194096-82-7
63% yield.

NMR ^{1}H (200 MHz, $CDCl_3$): δ 1.30 (s, 6H), 3.82 (s, 2H), 3.95 (s, 2H), 7.19 (dddd, *J*1=7.7 Hz, *J*2=4.9 Hz, *J*3=1.0, *J*4=0.5 Hz, 1H), 7.29–7.35 (m, 1H), 7.66 (td, *J*1=7.7 Hz, *J*2=1.9 Hz, 1H), 8.56 (ddd, *J*1=4.9 Hz, *J*2=1.9 Hz, *J*3=1.0 Hz, 1H).

NMR ^{13}C (50 MHz, $CDCl_3$): δ 28.3 (2C), 37.6, 67.1, 79.3, 122.0, 123.0, 136.7, 149.4, 163.3.

(*S*)-4-*iso*butyl-2-(pyridin-2-yl)-2-oxazoline (6)
CAS 108915-07-7
78% yield.

NMR ^{1}H (400 MHz, $CDCl_3$): δ 0.97 (d, *J*1=6.6 Hz, 3H), 0.99 (d, *J*1=6.6 Hz, 3H), 1.41(dt, *J*1=13.4 Hz, *J*2=7.3 Hz, 1H), 1.76 (dt, *J*1=13.4 Hz, *J*2=6.9 Hz, 1H), 1.88 (non, *J*1=6.7 Hz, 1H), 4.07 (t, *J*1=8.2 Hz, 1H), 4.35–4.45 (m, 1H), 4.60 (dd, *J*1=9.5 Hz, *J*2=8.1 Hz, 1H), 7.38 (ddd, *J*1=7.6 Hz, *J*2=4.8 Hz, *J*3=1.2 Hz, 1H), 7.77 (td, *J1*=7.8 Hz, *J*2=1.8 Hz, 1H), 8.04 (dt, *J*1=7.9 Hz, *J*1=1.1 Hz, 1H), 8.71 (ddd, *J*1=4.8 Hz, *J*2=1.8 Hz, *J*3=0.9 Hz, 1H).

NMR ^{13}C (100 MHz, $CDCl_3$): δ 22.6 (2C), 25.2, 45.3, 65.2, 73.5, 123.7, 125.2, 136.4, 146.7, 149.5, 162.2.

(*S*)-4-(2-(methylthio)ethyl)-2-(pyridin-2-yl)-2-oxazoline (7)
CAS 108915-09-9
51% yield.

NMR ^{1}H (400 MHz, $CDCl_3$): δ 1.83–1.97 (m, 1H), 1.99–2.11 (m, 1H), 2.14 (s, 3H), 2.70 (ddd, *J*1=15.0 Hz, *J*2=8.3 Hz, *J*3=6.6 Hz, 1H), 2.73 (ddd, *J*1=15.0 Hz, *J*2=8.5 Hz, *J*3=6.1 Hz, 1H), 4.14 (t, *J*1=8.2 Hz, 1H), 4.44–4.55 (m, 1H), 4.63 (dd, *J*1=9.6 Hz, *J*2=8.3 Hz, 1H), 7.40 (ddd, *J*1=7.7 Hz, *J*2=4.8 Hz, *J*3=1.2 Hz, 1H), 7.87 (td, *J1*=7.8 Hz, *J*2=1.8 Hz, 1H), 8.03 (d, *J*1=7.8 Hz, 1H), 8.72 (ddd, *J*1=4.8 Hz, *J*2=1.7 Hz, *J*3=0.7 Hz, 1H).

NMR ^{13}C (100 MHz, $CDCl_3$): δ 15.5, 30.7, 35.2, 66.0, 72.9, 123.8, 125.5, 136.6, 146.6, 149.7, 162.8.

(*S*)-4-phenyl-2-(pyridin-2-yl)-2-oxazoline (8)
CAS 153880-57-0
60% yield.
$[\alpha]^{25}_{D}$ = –34° (C=2.045; toluene)

NMR ^{1}H (200 MHz, DMS): δ 4.40 (t, *J*=8.6 Hz, 1H), 4.91 (dd, *J*1=10.3 Hz, *J*2=8.6 Hz, 1H), 5.47 (dd, *J*1=10.3 Hz, *J*2=8.6 Hz, 1H), 7.55–7.28 (m, 6H), 7.82 (ddd, *J*1=7.7 Hz, *J*2=1.8 Hz, *J*3=0.9 Hz, 1H), 8.18 (dt, *J*1=7.7 Hz, *J*2=1.1 Hz, 1H), 8.75 (ddd, *J*1=4.8 Hz, *J*2=1.8 Hz, *J*3=0.9 Hz, 1H).

NMR ^{13}C (50 MHz, DMSO): δ 70.3, 75.3, 124.2, 125.8, 126.8 (2C), 127.7, 128.8 (2C), 136.7, 141.8, 149.8.

(*S*)-4-benzyl-2-(pyridin-2-yl)-2-oxazoline (9)
CAS 108915-08-8
89% yield.
$[\alpha]^{25}_{D}$=–52° (C=0.538; toluene)

NMR ^{1}H (400 MHz, $CDCl_3$): δ 2.77 (dd, *J*1=13.8 Hz, *J*2=9.0 Hz, 1H), 3.30 (dd, *J*1=13.8 Hz, *J*2=5.1 Hz, 1H), 4.23 (dd, *J*1=8.6 Hz, *J*2=7.7 Hz, 1H), 4.44 (dd, *J*1=9.4 Hz, *J*2=8.6 Hz, 1H), 4.66 (dddd, *J*1=9.4 Hz, *J*2=9.0 Hz, *J*3=7.7 Hz, *J*4=5.1 Hz, 1H), 7.20–7.33 (m, 5H), 7.39 (ddd, *J*1=7.6 Hz, *J*2=4.8 Hz, *J*3=1.2 Hz, 1H), 7.77 (ddd, *J*1=7.8 Hz, *J*2=7.7 Hz, *J*3=1.7 Hz, 1H), 8.06 (ddd, *J*1=7.8 Hz, *J*2=1.2 Hz, *J*3=0.9 Hz, 1H), 8.70 (ddd, *J*1=4.7 Hz, *J*2=1.7 Hz, *J*3=0.9 Hz, 1H).

NMR ^{13}C (100 MHz, $CDCl_3$): δ 41.5, 68.0, 72.3, 123.8, 125.4, 126.4, 128.4 (2C), 129.1 (2C), 136.5, 137.6, 146.6, 149.6, 163.0.

(*R*)-4-methyl-2-(pyridin-2-yl)-2-oxazoline (10)
CAS 242482-41-3
77% yield.

NMR ^{1}H (200 MHz, $CDCl_3$): δ 1.40 (d, *J*1=6.5 Hz, 3H), 4.05 (t, *J*1=7.77 Hz, 1H), 4.28–4.77 (m, 2H), 7.39 (ddd, *J*1=7.6 Hz, *J*2=4.8 Hz, *J*3=1.3 Hz, 1H), 7.78 (td, *J*1=7.8 Hz, *J*2=1.8 Hz, 1H), 7.96 (m, 1H), 8.71 (ddd, *J*1=4.9 Hz, *J*2=1.8 Hz, *J*3=1.0 Hz 1H).

NMR ^{13}C (50 MHz, $CDCl_3$): δ 21.1, 62.0, 74.4, 123.6, 125.3, 136.4, 146.5, 149.5, 162.4.

(*S*)-4-*iso*propyl-2-(pyridin-2-yl)-2-oxazoline (11)
CAS 108915-04-4
88% yield.
$[\alpha]^{25}_{D}$=–98° (C=0.506; toluene)

NMR ^{1}H (400 MHz, $CDCl_3$): δ 0.95 (d, *J*1=6.8 Hz, 3H), 1.06 (d, *J*1=6.8 Hz, 3H), 1.90 (oct, *J*1=6.8 Hz, 1H), 4.18 (dd, *J*1=16.0 Hz, *J*2=8.3 Hz, *J*3=6.3 Hz, 1H), 4.21 (dd, *J*1=16.0 Hz, *J*2=8.3 Hz, 1H), 4.51 (dd, *J*1=9.0 Hz, *J*2=7.6 Hz, 1H), 7.38 (ddd, *J*1=7.6 Hz, *J*2=4.8 Hz, *J*3=1.2 Hz, 1H), 7.77 (ddd, *J*1=7.8 Hz, *J*2=7.7 Hz, *J*3=1.7 Hz, 1H), 8.05 (ddd, *J*1=7.8, *J*2=1.2 Hz, *J*1=0.9 Hz, 1H), 8.71 (ddd, *J*1=4.8 Hz, *J*2=1.7 Hz, *J*3=0.9 Hz, 1H).

NMR ^{13}C (100 MHz, $CDCl_3$): δ 18.0, 18.9, 32.6, 70.6, 72.8, 123.7, 125.2, 136.4, 146.8, 149.5, 162.4.
(*S*)-4-((*R*)-*sec*-butyl)-2-(pyridin-2-yl)-2-oxazoline (12)
CAS 108915-03-3
92% yield.
$[\alpha]^{25}_{D}$=–75° (C=2.011; toluene)

NMR ^{1}H (400 MHz, $CDCl_3$): δ 0.89 (d, *J*1=6.7 Hz, 3H), 0.96 (t, *J*1=7.4 Hz, 3H), 1.12–1.37 (m, 1H), 1.57–1.88 (m, 2H), 4.22 (dd, *J*1=8.4 Hz, *J*2=7.7 Hz, 1H), 4,30 (ddd, *J*1=9,3 Hz, *J*2=8,4 Hz, *J*3=5,7 Hz, 1H), 4.50 (dd, *J*1=9.3 Hz, *J*2=7.8 Hz, 1H), 7.39 (ddd, *J*1=7.6 Hz, *J*2=4.8 Hz, *J*3=1.2 Hz, 1H), 7.77 (ddd, *J*1=9.6 Hz, *J*1=7.8 Hz, *J*2=1.8 Hz, 1H), 8.06 (dt, *J*1=7.9 Hz, *J*2=1.0 Hz, 1H), 8.71 (ddd, *J*1=4.8 Hz, *J*2=1.8 Hz, *J*3=1.0 Hz, 1H).

NMR ^{13}C (100 MHz, $CDCl_3$): δ 11.4, 14.3, 26.1, 39.0, 70.2, 71.4, 123.8, 125.3, 136.5, 146.8, 149.6, 162.4.

2-(5-bromopyridin-2-yl)-4,4-dimethyl-2-oxazoline (13)
51% yield.

NMR ^{1}H (200 MHz, $CDCl_3$): δ 1.41 (s, 6H), 4.21 (s, 2H), 7.91 (d, *J*1=1.5 Hz, 2H), 8.76 (t, *J1*=1.5 Hz, 1H).

NMR ^{13}C (50 MHz, $CDCl_3$): δ 28.3, 68.2, 79.8, 123.1, 124.9, 139.3, 145.3, 150.9.

IR (KBr): ν 3431, 3034, 2957, 2417, 2366, 2341, 1760, 1699, 1648, 1561, 1388, 1088, 991, 909, 879, 838, 680, 629.

MS (IES^{+}): calc for $C_{10}H_{11}BrN_2O$ [M+H] 255.0133, found 255.0130.

MP (°C): 96.5–98.9.

(*S*)-2-(5-ethynylpyridin-2-yl)-4-phenyl-2-oxazoline (14)
61% yield.
$[\alpha]^{25}_{D}$=–38° (C=1.125; chloroform)

NMR ^{1}H (200 MHz, $CDCl_3$): δ 3.36 (s, 1H), 4.40 (t, *J*1=8.6 Hz, 1H), 4.91(dd, *J*1=10.3 Hz, *J*2=8.6 Hz, 1H), 5.48 (dd, *J*1=10.3 Hz, *J*2=8.6 Hz, 1H), 7.29–7.41 (m, 5H), 7.88 (dd,

*J*1=8.2 Hz, *J*2=2.0 Hz, 1H), 8.14 (dd, *J*1=8.2 Hz, *J*2=0.8 Hz, 1H), 8.82 (dd, *J*1=2.0 Hz, *J*2=0.8 Hz, 1H).

NMR ^{13}C (50 MHz, $CDCl_3$): δ 70.4, 75.4, 79.9, 82.9, 121.4, 123.5, 126.7 (2C), 127.8, 128.8 (2C), 139.7, 141.5, 145.6, 152.6, 163.2.

IR (KBr): ν 3391, 2924, 2855, 2367, 2333, 1652, 1514, 1384, 1068, 1026, 827, 751, 696.

MS (IES$^+$): calc for $C_{16}H_{12}N_2O$ [M^{+H}] 249.1028, found 249.1026.
MP (°C): 136.6–139.1.

2-((1H-indol-3-yl)methyl)-4-(pyridin-2-yl)-2-oxazoline (15)
61% yield.
$[\alpha]^{25}_D$=+9° (C=0.320; chloroform)

NMR ^{1}H (200 MHz, $CDCl_3$): δ 2.92 (dd, *J*1=14.5 Hz, *J*2=9.1 Hz, 1H), 3.44 (ddd, *J*1=14.5 Hz, *J*2=4.7 Hz, *J*3=1.0 Hz 1H), 4.27 (dd, *J*1=8.6 Hz, *J*2=7.7 Hz, 1H), 4.45 (t, *J*1=9.1 Hz, 1H), 4.80 (tdd, *J*1=9.2 Hz, *J*2=7.6 Hz, *J*3=4.7 Hz 1H), 7.01–7.25 (m, 3H), 7.30–7.56 (m, 2H), 7.60–7.73 (m, 1H), 7.79 (td, *J*1=7.7 Hz, *J*2=1.8 Hz, 1H), 8.01–8.14 (m, 1H), 8.72 (ddd, *J*1=4.7 Hz, *J*2=1.8 Hz, *J*3=1.0 Hz 1H).

NMR ^{13}C (50 MHz, $CDCl_3$): δ 31.3, 67.2, 72.9, 111.2, 111.6, 118.7, 119.3, 122.0, 122.4, 123.9, 125.5, 127.5, 136.2, 146.7, 149.6, 163.0.

IR (KBr): ν 3201, 3184, 3105, 3043, 2983, 2900, 2883, 1647, 1384, 1361, 1323, 1274, 1249, 1101, 1085, 1037, 966, 744, 725.

MS (IES$^+$): calc for $C_{16}H_{12}N_2O$ [M^{+H}] 278.1293, found 278.1293.

MP (°C): 170.1–171.6.

4,4-dimethyl-2-phenyl-2-oxazoline (16)
CAS 19312-06-2
30% yield.

NMR ^{1}H (200 MHz, $CDCl_3$): δ 1.38 (s, 6H), 4.11 (s, 2H), 7.35–7.51 (m, 3H), 7.91–7.98 (m, 2H).

NMR ^{13}C (50 MHz, $CDCl_3$): δ 28.4 (2C), 67.5, 79.1, 128.0, 128.1 (2C), 128.2 (2C), 131.1, 162.0.

3 Results and discussion

In the course of exploring some enantioselective transformations based on chiral metal complexes, appealing and more environmentally friendly preparation procedures of 2-pyridyl-2-oxazolines were of interest in our research group. Herein, we report the associative utilization of glycerol and zinc (II) acetate as a catalyst system for the preparation of 2-pyridyl-2-oxazolines from 2-cyanopyridines and amino alcohols, under microwave irradiation. Glycerol was chosen as a solvent, because of its green aspects and also based on the premise that the product could be extracted from the reaction medium by washing with a glycerol-immiscible organic solvent. To test the feasibility of our proposition, 2-cyanopyridine (**1**) and 2-amino-2-methylpropanol (**2**, 2 eq) were subjected to a reaction in the presence of zinc (II) acetate (2 mol%) in glycerol, under conventional heating (Figure 1). Initial studies focused on the optimal temperature needed for maximum conversion into the corresponding 2-oxazoline (Table 1).

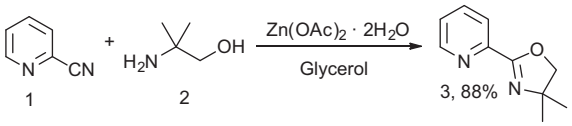


Figure 1 Oxazoline synthesis using glycerol as solvent.

Even after prolonged reaction times at 70°C or 90°C, low conversions were observed. On the other hand, at 110°C, the desired oxazoline was obtained in 88% yield within 2 h. On searching for a more efficient process and tapping into the microwave irradiation absorption properties of glycerol [35], we focused our attention in the application of this energy source.

A reaction time screening for the total conversion of 2-cyanopyridine (**1**) into the corresponding oxazoline, was carried out at 110°C and it was observed that within 17 min, total consumption of the starting material was achieved, leading to the oxazoline (**3**) in 86% isolated yield, as shown in Table 2.

Table 1 2-Pyridyl-2-oxazoline synthesis under conventional heating.

Entry	T (°C)	t (h)	Yield (%)[1,2]
1	70	20[3]	lc[4]
2	90	5[3]	lc[4]
3	110	2	88

Reactions were conducted using 1 mmol of the 2-cyanopyridine, 2 mmol of amino alcohol and 2 mol% of $Zn(AcO)_2$ in 1 ml of glycerol.
[1]Analyzed by GC.
[2]Isolated yield.
[3]Starting material was not totally consumed.
[4]Low conversions were observed.

Table 2 Microwave screening for the oxazoline synthesis.

Entry	t (min)	SM:P[1]	Yield (%)[2]
1	2	73:27	nd
2	5	36:64	nd
3	10	19:81	nd
4	12	2:98	nd
5	15	1:99	nd
6	17	0:100	86
7	20	Byproducts[3]	nd

Reactions were conducted using 1 mmol of the 2-cyanopyridine, 2 mmol of amino alcohol and 2 mol% of $Zn(AcO)_2$ in 1 ml of glycerol at 110°C.
nd, not determined; P, product (3, 2-oxazoline); SM, starting material (1, 2-cyanopyridine).
[1]Analyzed by GC.
[2]Isolated yield.
[3]Unidentified byproducts.

As can be observed, a progressively higher conversion was achieved as a function of time. Reaction times longer than 17 min resulted in the formation of unidentified byproducts (entry 7).

It is worth mentioning that the reaction was accompanied by color changes, resulting in a deep greenish-blue solution after 17 min of microwave irradiation (Figure 2). We have no explanation for this color change, since zinc glycerolate, which can be generated *in situ*, as well as ammonium acetate (another possible byproduct), are both white solids and their solutions are colorless [36].

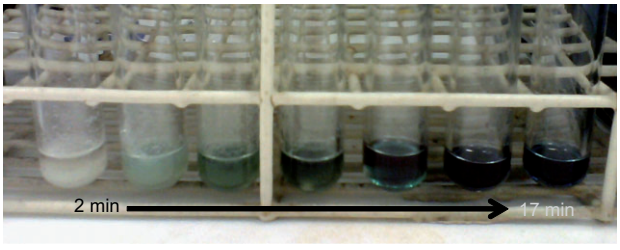


Figure 2 Color changes of the reaction media through time under microwave irradiation.

As was initially hypothesized, after completion of the reaction, removal of the product from the reaction media can be easily accomplished by extraction with ethyl acetate (immiscible in glycerol), leading to the nearly pure product after solvent evaporation. Following this procedure, a purification consisting of a simple filtration through a short pad of silica was necessary for preparative purposes. According to this result, we proposed that the glycerol-zinc (II) acetate catalytic system could be recycled for new reactions. Thus, after extraction of oxazoline (**3**) produced in the first cycle, stoichiometric amounts of (**1**) and (**2**) were added to the reaction media and submitted to another cycle of reaction in both conditions of conventional heating and microwave irradiation. The results are shown in the bar graphic in Figure 3.

Five cycles were conducted by sequential reaction/extraction procedures and a decrease in yield was observed for the two new cycles, with virtually the same results for conventional heating and microwave irradiation. Interestingly, under microwave irradiation, product (**3**) was isolated in almost the same yield from reactions of the 4th as well as the 5th cycles. By contrast, by conventional heating, the product yield was substantially diminished in the 4th cycle, and in the 5th cycle, no product was isolated under the same reaction conditions. Despite appreciable yield reduction after the 3rd cycle, it was demonstrated that the reaction media could be reused.

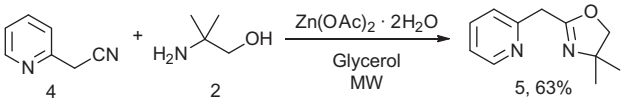


Figure 4 Oxazoline synthesis with 2-pyridylacetonitrile.

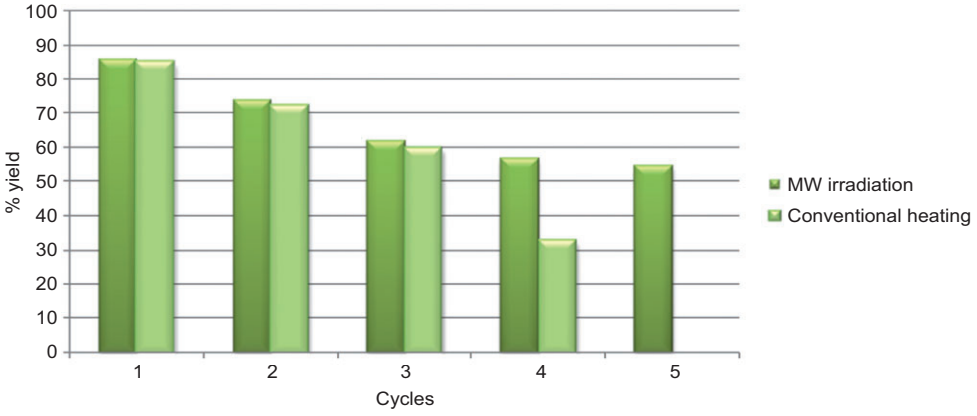


Figure 3 Recycling of the reaction media for new reactions.

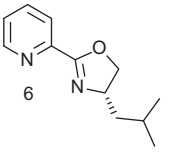
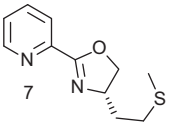
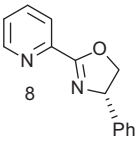
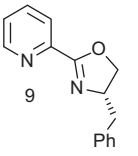
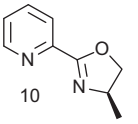
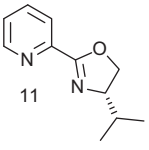
Table 3 Microwave screening for the reaction of 2-pyridylacetonitrile (**4**) with amino alcohol (**2**).

Entry	T (°C)	t (min)	SM:P[1]	Yield (%)
1	110	17	72:28	nd
2	110	34	51:49	nd
3	110	51	49:51	nd
4	140	30	26:74	nd
5	150	40	1:99	63[2]

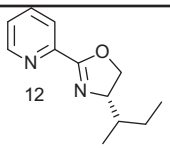
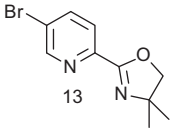
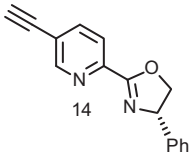
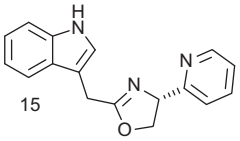
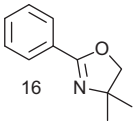
Reactions were conducted using 1 mmol of the 2-pyridylacetonitrile, 2 mmol of amino alcohol and 2 mol% of $Zn(AcO)_2$ in 1 ml of glycerol. nd, not determined; P, product (5, 2-oxazoline); SM, starting material (4, 2-pyridylacetonitrile).
[1]Analyzed by GC.
[2]Isolated yield.

2-Pyridylacetonitrile (**4**) was also submitted to reaction with amino alcohol (**2**) under several reaction conditions. No reaction was observed following the conditions reported by Kempe et al. [22], using chlorobenzene and zinc (II) acetate, or when testing different solvent-catalyst systems. However, using our reaction conditions, the expected oxazoline (**5**) was produced in 63% isolated yield after 40 min irradiation at 150°C (Figure 4). As presented in Table 3, progressively higher conversions were observed through time (GC analysis), but only at a higher temperature (150°C) was a nearly quantitative conversion achieved (entry 5), leading to the corresponding 2-oxazoline in 63% isolated yield.

Table 4 2-Pyridyl-2-oxazolines synthesized under microwave irradiation.

Entry	2-Oxazoline	Yield (%)[1]
1	 6	78
2	 7	51
3	 8	60
4	 9	89
5	 10	77
6	 11	88

(**Table 4** Continued)

Entry	2-Oxazoline	Yield (%)[1]
7	 12	92
8	 13	51
9	 14	61
11	 15	61
12	 16	30[2]

Reactions were conducted using 1 mmol of the 2-cyanopyridine, 2 mmol of amino alcohol and 2 mol% of $Zn(AcO)_2$ in 1 ml of glycerol at 110°C.
[1]Isolated yield.
[2]Non-optimized conditions. It was not possible to obtain this oxazoline using the procedure reported in reference 22.

In order to verify the scope and limitations of the protocol, other amino alcohols were submitted to a reaction with 2-cyanopyridine (**1**) under microwave irradiation.

In Table 4, the structure and isolated yields of the reaction of 2-cyanopyridine or benzonitrile and other amino alcohols are presented.

With the exception of 2-oxazoline (**16**) (entry 12), all other products were obtained in good to excellent yields, which suggests that benzonitrile is less reactive than the other nitriles used.

As enantiopure amino alcohols were used, the optical purity of the corresponding oxazolines was determined by chiral liquid chromatography. An artificially

enantioenriched mixture of (*R*)- and (*S*)-2-oxazoline (**8**) was prepared by mixing enantiopure (*R*)- and (*S*)-phenylglycinol and reacting this mixture with the corresponding nitrile. This oxazoline was chosen because the stereogenic center is a benzylic carbon, thus if some epimerization could occur during the synthesis, an enantiomeric mixture of oxazoline (**8**) would be produced. The artificial enantiomeric mixture and the enantiopure oxazolines were analyzed by chiral HPLC, confirming that no epimerization occurred during the reaction. The optical rotation of other oxazolines was measured and the results are in agreement with literature reported values [37].

In conclusion, we have developed a fast and green reaction procedure to prepare 2-pyridyl-2-oxazolines under microwave irradiation. Use of the glycerol-zinc (II) acetate system has proven to be very practical, considering that at the end of the reaction, the desired product can be easily extracted from the reaction media by washing with ethyl acetate, allowing reuse of the reaction media. Modest to good yields were achieved by recycling the solvent-catalyst system. As a rule, product purification required solely filtration in a short silica pad-column. No exogenous byproducts were observed under the optimal reaction conditions.

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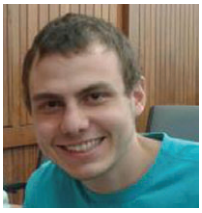

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